Ketanserin and hypertension in cardiac surgery

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Ketanserin and hypertension in cardiac surgery

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Proefschrift

ter verkrijging van de graad van doctor in de geneeskunde aan de
Rijksuniversiteit Limburg te Maastricht, op gezag van de
Rector Magnificus Prof. Dr. F.I.M. Bonke, volgens het besluit van het
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26 februari 1988 om vier uur

door

Pieter Jacobus Adriaan van der Starre

geboren te Tegal in Indonesië

Promotor : Prof. Dr. R.S. Reneman
Referenten : Prof. Dr. J.G. Bovill
Prof. Dr. S. de Lange

To the memory of Christine

To my parents

To Annèt, Daniël, Hergen and Taco

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Chapter 1

General introduction

1.1 Hypertension

One of the most important problems the anesthesiologist is confronted with during cardiac surgery, particularly coronary artery bypass surgery, is the prevention and treatment of systemic hypertension. In general, patients who are suffering from coronary artery occlusive disease, are treated with beta-blocking agents, calcium entry blockers and nitrates, but nevertheless systemic hypertension frequently occurs during the surgical procedure. Not only in patients with coronary artery disease, but also in patients with congestive heart failure due to progressive valvular disease, like aortic valve stenosis and mitral valve insufficiency, hypertension may lead to increased oxygen demands of the already compromised myocardium, occasionally resulting in myocardial ischemia and infarction (Moffitt et al.1985, Moffitt and Sethna 1986, Merin et al.1986, Slogoff and Keats 1986).

The most threatening moments are intubation (Forbes and Dally 1970, Wycoff 1960, Fox et al.1977), sternotomy and sternal spread (Low et al.1986). The cause of the hypertensive episodes at these moments is stimulation of the sympathetic nervous system, causing an increase in the levels of circulating catecholamines (noradrenaline and adrenaline) and, as a consequence, elevated blood pressure associated with an increase in systemic and pulmonary vascular resistance and heart rate (Roberts et al.1977, Wallach et al.1980, Balasaraswathi et al.1978,1982, Kim et al.1981, Estafanous and Tarazi 1980, Estafanous et al.1984, Low et al.1986). Increased plasma renin activity and angiotensin-II-levels have been reported to contribute as well. Because of the fact that most of the patients receive beta blocking agents preoperatively, heart rate does not change as often as blood pressure (Sill et al.1984).

In the course of cardiopulmonary bypass the levels of circulating catecholamines increase, causing an increase in systemic vascular resistance (Engelman et al.1983, Reves et al.1982). The levels of renin and angiotensin II increase as well (Townsend et al.1984), in spite of the use of pulsatile flow (Taylor et al.1979, Salerno et al.1981, Azariades et al.1986, Anton et al.1964). Others investigators have reported increases in vasopressin-levels (Hawkins et al.1986,1983, Knight et al. 1986, Chambers et al.1984). The mechanisms involved in the increases in plasma levels of circulating catecholamines and renin-angiotensin during cardiopulmonary bypass are speculative: hemodilution (Hine et al.1976), initial hypotension, hypothermia (Chernow et al.1983, Arnett and Watts 1960), non-pulsatile flow, decreased levels of beta-blocking agents (Cooper et al.1985, Bolling et al.1984) and a chemoreceptor reflex (Brown 1979) have been proposed. In the early postbypass period hypertension does not frequently occur,

since the heart has to recover from the effects of the cardioplegic solution and the ischemic episode during aortic cross-clamping. In addition a low systemic vascular resistance is observed following termination of cardiopulmonary bypass. The often observed drop in blood pressure during transportation to the Intensive Care Unit (ICU) (Ivanov et al.1984), as caused by acute movements of patients in a relatively unstable condition, contributes to the delay of the onset of hypertension in the immediate postoperative period (Insel et al.1986).

In the following hours in the ICU hypertension has been reported in 40-60% of the patients following coronary artery bypass surgery, depending on the criteria applied and the actual condition of the patient (Estafanous et al.1973, 1978, Viljoen and Estafanous 1976). Apart from the factors, which are also responsible for the development of prebypass hypertension, the type of narcotic agents used might also contribute to the development of hypertension in the postoperative phase (Hardy et al.1983). Recently the contribution of the renin-angiotensin system for the development of postoperative hypertension was questioned (Weinstein et al.1987). Additional factors like hypothermia, resulting in peripheral vasoconstriction and shivering, arousal, intolerance to endotracheal intubation, hypercapnia, hypoxia and pain, may cause hypertension and tachycardia.

Hypertension should not only be prevented because of the risk of myocardial damage, but also because neurologic complications may occur (Sotaniemi 1980), which are often difficult to detect during general anesthesia and in the early postoperative period (Fremes et al.1983, Ivanov et al.1983, Kolkka and Hilberman 1980). Surgery can be complicated by an increase in blood loss because of hypertension, since the patients are heparinized. Even so it has been suggested that early hypertension is one of the causes of premature graft closure and accelerated atherosclerosis of saphenous vein grafts due to intimal damage (Brody et al.1972).

Serious bleeding, leading to a reintervention, is reported in 2 to 10 % of the cases (Bachmann et al.1975), peri-operative myocardial infarction in 5 to 15% of the cases (Kirklin et al.1979) and neurologic deficit following cardiac surgery, mainly attributed to particulate matter (aggregates) and unstable blood pressure, has been reported in 1 to 31% of the cases, depending on the applied criteria (Slogoff et al.1982, Gonzales-Scarano and Hurting 1981, Utley and Stephens 1986). Studies on the causal relations, if any, between per and postoperative hypertension on the one hand and neurologic complications on the other still have to be performed.

During and following cardiac surgery systemic hypertension is routinely treated with a variety of compounds, mainly vasodilating agents. These antihypertensive drugs will be briefly discussed in the next section. Per-

operatively inhalation anesthetics like halothane (Kien et al.1986, Cork et al.1985), enflurane (Heikkila et al.1985) or isoflurane (Fisherstrom et al.1985, Gunnicker et al.1986), have been applied to treat hypertension because of their vasodilating properties. Stellate ganglion blockade (Bidwai and Rogers 1979) or epidural anesthesia (Hoar et al.1976) have been advocated as preventive measures as well.

1.2 Agents for acute treatment of hypertension

Sodium nitroprusside is a potent, non-specific arterial and a moderate venous vasodilator, causing primarily a decrease in systemic vascular resistance and an increase in venous capacitance (Tinker and Michenfelder 1976, Kaplan et al.1980, Gustafson 1984, Gerson et al.1982). When hypovolemia is avoided, cardiac output will be enhanced. As an autonomic reflex heart rate increases, particularly at higher doses (Yaster et al.1986, Kaplan et al.1980). Some authors have reported unchanged cardiac output (Adams et al.1974, Stoelting et al.1977, Styles et al.1973) and unaffected stroke volume after the administration of nitroprusside (Wildsmith et al.1973, Rowe et al.1962). The main side effects are thiocyanate toxicity (Arnold et al.1984, Moore et al.1985b, Bloor et al.1985, Patel et al.1986), particularly in patients treated longer than 72 hours at high dose levels, and an increase in pulmonary shunting, possibly leading to hypoxemia (D'Oliveira et al.1981, Saarnivaara et al.1984, Seltzer et al.1976). In the case of coronary artery disease, reports on the development of a coronary steal-phenomenon during the administration of nitroprusside have been published (Hickey et al.1983). Recently nitroprusside was reported to cause an increase in plasma levels of circulating catecholamines and renin-angiotensin-activity (Knight et al.1983, Lagerkranser et al.1985).

Nitroglycerin, administered as a continuous infusion, is an effective antihypertensive compound (Thys et al.1985, Gallagher et al.1986, Gerson et al.1982, Cattaneo and Leier 1982), although failure to prevent intraoperative myocardial ischemia has been reported (Thomson et al.1984). This agent causes mainly venous vasodilatation (Coriat 1986, Moffitt et al.1983), which is an advantage in patients undergoing cardiac surgery, because venous vasoconstriction often occurs during cardiopulmonary bypass. At higher dose levels nitroglycerin also causes arterial vasodilatation. Side effects are reflex tachycardia (Kaplan et al.1980), an increase in intrapulmonary shunting, although less pronounced than with nitroprusside (Berthelsen et al.1986, Flaherty et al.1982, Kopman et al.1978), acute methemoglobinemia (Zurick et al.1984, Robiczek 1985), and a dose-related prolongation of the bleeding time (Lichtenthal et al.1985). In

coronary artery disease nitroglycerin improves coronary collateral flow without causing a steal phenomenon (Coriat et al.1984).

Of the ganglionic blocking agents trimetaphan has been studied best (Shell and Sobel 1974). Apart from the ganglionic blockade, this agent has direct vasodilating properties, and in higher concentrations an alpha-adrenergic blocking action (Harioka et al.1984). It produces an increase in cardiac output and heart rate, probably as a consequence of parasympathetic ganglionic blockade. Histamine release and tachyphylaxis are important side-effect. Because of the ganglionic blockade no changes are observed in the plasma levels of catecholamines, renin and angiotensin (Fahmy and Soter 1985, Knight et al.1983). Chlorpromazine has a hemodynamic pattern similar to that of trimetaphan (Stinson et al.1975), but is generally intermittently administered.

Phentolamine, an α_1 - and α_2 -adrenergic receptor blocking agent, reduces arteriolar resistance and, to a lesser degree, increases venous capacitance (Champoux and Gauthier 1984, El-Etr and Glisson 1978). Side effects are an increase in the levels of circulating catecholamines, tachycardia (Hoffman and Lefkowitz 1980), vomiting, diarrhoea, and sometimes exacerbation of peptic ulcer disease (Gould and Reddy 1976).

Phenoxybenzamine, a pure α_1 -adrenergic receptor antagonist, shows a similar pattern of action and has the same side-effects as phentolamine, but its duration of action is much longer (El-Etr and Glisson 1978).

Dehydrobenzperidol (droperidol), a butyrophenon derivate, has α_1 -adrenergic receptor blocking properties (Whitwam and Russell 1971, Van Nueten et al.1977), but is mostly used as a neuroleptic agent in combination with a narcotic analgesic compound like fentanyl (Fox et al. 1967, Graves et al.1975). The main side effects are reflex tachycardia and increased plasma levels of catecholamines (Radnay et al.1977, Ferrari et al.1974).

Hydralazine is mainly an arteriolar vasodilator with little effect on the venous capacitance vessels (Koch-Weser 1976), and with a slow onset of action, which makes it less suitable for anesthetic purposes. Systemic and pulmonary vascular resistance are lowered, associated with an increase in cardiac output (Bishop and Cheney 1986, Sandoval et al.1986). Common side effect are reflex tachycardia (Metha et al.1978) and an increase in pulmonary shunting (Bishop and Cheney 1986, Sandoval et al.1986, Seoane and Lupi-Herrera 1986).

Clonidine is a specific α_2 -adrenergic agonist, reducing centrally mediated sympathetic outflow . It causes a decrease in systemic vascular resistance, cardiac output and heart rate (Ghignone et al.1986, Pettinger 1975, Niarchos 1978). Its main disadvantages are the rather unpredict-

able mode and duration of action, and a well known rebound hypertension when treatment is abruptly stopped (O'Connor 1981).

Among the calcium entry blockers the antihypertensive activity of nifedipine has been studied best (Van Wezel et al.1986, Franklin et al.1986). It causes arterial vasodilatation (Hess and Meyer 1986) and a decrease in coronary arteriolar resistance. The main side effects are reflex tachycardia and an increase in intrapulmonary shunting (Casthely et al.1985).

Labetolol has both alpha- and beta-adrenergic receptor blocking properties (Richards 1976, Farmer et al.1972, Morel et al.1982). It reduces arterial blood pressure by reducing systemic vascular resistance without reflex increases in heart rate. Predictable side effects are bradycardia, bronchoconstriction and decreased stroke volume (Brown et al.1977). The reduction in both heart rate and stroke volume leads to a decrease in cardiac output (Kaulman 1979). Its relatively long duration of action (4-18h) implies careful monitoring of blood volume because, due to the beta-adrenergic receptor blockade, compensatory mechanisms against hypovolemia may be attenuated.

Adenosine and adenine nucleotides possess vasodilator properties and have been recently studied to treat hypertension or to induce controlled hypotension (Bloor et al.1985, Torsell et al.1986, Sollevi et al.1984). They mainly cause arteriolar dilatation with a slight increase in cardiac output, but without reflex tachycardia, implicating an increase in stroke volume (Bloor et al.1985, Newberg et al.1985, Lagerkranser et al.1984, Van Aken et al.1984a). Some authors have reported a decrease in heart rate at high dose levels (Fukunaga et al.1981). The main side effect is vasoconstriction of the renal arteries (Kassel et al.1983).

Recently urapidil was introduced as antihypertensive agent (Lehmann and Heimig 1985, Puchstein et al.1984, Williams et al.1985). This compound shows α_1 - and weak β_1 -adrenergic receptor blocking properties and causes a decrease in systemic and pulmonary vascular resistance without reflex tachycardia. It also displays a significant centrally mediated hypotensive activity (Van Zwieten et al.1985).

From this brief survey of the mode of action of the vasodilating agents commonly used in the treatment of hypertension during and after cardiac surgery it can be concluded that there is a need for compounds with comparable efficacy, a short duration of action, a non-toxic profile, but devoid of the side effects described. In earlier studies in patients with essential hypertension ketanserin, a specific S_2 -serotonergic receptor antagonist with α_1 -adrenergic receptor blocking properties, was found to be an effective antihypertensive agent, devoid of reflex tachycardia (De Cree et al.1981c). It was considered to be appropriate to evaluate the efficacy of ketanserin in the treatment of hypertension during and following cardiac

surgery, especially since previous reports indicated that serotonin may be released during cardiac surgery (Replogle et al.1962, Ilcin et al.1972, Sarajas et al.1959).

1.3 Serotonin

Serotonin (fig. 1.3.1) was discovered by Rapport, Green and Page (1948), and found to be present in chromaffin cells in the gastro-intestinal tract (Erspamer and Asero 1952), platelets, the pineal glands, and the central and peripheral nervous system (Garratini and Valzelli 1965). It is synthesized from tryptophan and metabolized to 5-hydroxyindolaceticacid (5-HIAA) in the liver (Drapanas and McDonald 1963). The remaining free fraction of serotonin is rapidly taken up in the endothelial cells of capillaries and small vessels, especially in the lung (Gillis and Pitt 1982, Axelrod and Inscoe 1963).

Fig.1.3.1. Chemical and tridimensional crystal structure of serotonin.

When the uptake function of the lung is diminished, like in hypertension (Vanhoutte et al.1983a), embolization (Rosoff et al.1971) and endotoxic shock (Stein and Thomas 1967), substantial increases in arterial plasma levels of serotonin are observed.

It has been reported that platelets are activated and damaged during cardiopulmonary bypass mainly due to suction (Boonstra et al.1985, De Jong et al.1980), but also as a result of blood-gas interaction in the oxygenator and contact of blood with artificial surfaces in the extracorporeal circuit (Van den Dungen et al.1982, Schmid-Schonbein 1979, Bick et al.1976, Eika 1972, Anderson et al.1978, Brown et al.1975, Barrer and Ellison 1977, Friedman et al.1970, Mohr et al.1986). Platelet aggregation is also induced by heparin (Heiden et al.1977, Eika 1972, Bell et al.1976, Wurzinger et al.1979, Thomson et al.1973, Zucker 1974, Abela et

al.1986) and protamine (Eika 1972, Velders et al.1980, Ellison et al.1978). When platelets are activated serotonin is released from the granules causing platelet aggregation and shape changes (De Clerck and Herman 1983). This process is regulated by a surface membrane S_2 -serotonergic receptor, in both animals and man (De Clerck et al.1984b). Apart from the release from platelets serotonin may originate from tissues around the ascending aorta and the main left coronary artery, as has been suggested by James et al.(1975), who suggested the presence of a so-called cardiogenic hypertensive reflex. In a previous study the suggestion was made that cardiopulmonary bypass alters the process of serotonin and noradrenaline extraction by human lungs (Gillis et al.1972).

In a variety of studies serotonin was found to be involved in the central and peripheral regulation of blood pressure. For example, the intracerebral administration of serotonin produces an increase in arterial blood pressure (Kuhn et al.1980), mediated by enhanced sympathetic activity. This pressor response mainly originates from the anterior part of the hypothalamus (Robinson 1982, Smits and Struycker-Boudier 1976, Wolf et al.1981). Serotonergic neurons are also involved in the transmission of baroreflex activity, impairing vagal responses (Head and Korner 1982).

Serotonin causes contraction of most isolated arteries and veins, but differences in sensitivity have been reported (Van Nueten et al.1981b, Feniuk et al.1983). Serotonin is a potent direct vasoconstrictor of coronary, cerebral, umbilical and pulmonary arteries (Cohen et al.1983b, Van Nueten et al.1981a,1983a, 1983c, Bentley and Henry 1981). This effect is mediated by S_2 -serotonergic receptors, but in a number of cutaneous arteries and in certain veins serotonin interacts with alpha-adrenergic receptors (Curro et al.1978, Laysen 1983, Van Nueten et al.1986). Serotonin also potentiates the vasoconstrictive response to angiotensin II, noradrenaline, prostaglandin $F2\alpha$, thromboxane A_2 and fibrin degradation products (FDP) (Van Nueten et al.1982,1983a, Forster et al.1980, Mullane et al.1982). On the other hand serotonin causes relaxation of arterioles in the splanchnic, coronary and cerebral vascular beds (Oxdemir et al.1972), and veins (Van Nueten et al.1983a, Cohen et al.1983b). It is postulated that these effects are mediated by S_1 -serotonergic receptors (Cohen et al.1983a,1983b, Houston et al.1984, Van Nueten et al.1981a), located in the endothelial cells and adrenergic nerve endings (Tuncer et al.1985, Van Nueten et al.1981a, Vanhoutte 1983b). This action is likely to be mediated by the release of endothelium-derived relaxing factors (EDRF)(Cohen et al.1983a,1983b). In this way a balance exists between the S_2 -serotonergic receptor mediated vasoconstricting effect and the S_1 -serotonergic receptor mediated, endothelium dependent, relaxing effect of serotonin. Serotonin has also been reported to be involved in the platelet mediated in-

crease in vascular permeability (De Clerck et al.1984a,1984c).

1.4 The aim of the thesis

It was the aim of the present thesis to investigate:

- the efficacy of ketanserin to prevent systemic arterial hypertension and the effect of the compound on the humoral responses during and following coronary artery bypass surgery (chapter 4)
- the efficacy of ketanserin to treat postoperative hypertension following coronary artery bypass surgery (chapters 5 and 6)
- the differences in systemic and pulmonary hemodynamic responses between ketanserin and sodium nitroprusside in the treatment of postoperative hypertension following coronary artery bypass surgery (chapter 7)
- the differences between ketanserin and sodium nitroprusside in the treatment of pulmonary hypertension following valvular surgery (chapter 8)
- the underlying mechanism of the blood pressure lowering effect of ketanserin in man (chapter 9)
- the differences in peripheral vascular effects between ketanserin and nifedipine during cardiopulmonary bypass (chapter 10)

These chapters are preceded by a brief survey of the pharmacology of ketanserin (chapter 2) as well as a description of the anesthetic and surgical techniques used, and the postoperative management (chapter 3). The thesis ends with a general discussion of the findings in the various studies (chapter 11).

Chapter 2

The pharmacology of ketanserin

The pharmacology of ketanserin

Ketanserin is a quinazoline-derivative (fig. 2.1), which selectively blocks S_2 -serotonergic receptors. The compound is devoid of serotonin agonistic properties, in contrast with for example methylsergide (Van Nueten 1981a,1983b, Leysen et al.1981). In higher concentrations ketanserin also binds to α_1 -adrenergic and H_1 -histaminergic receptors (Leysen et al.1981,1982).

Fig.2.1. Chemical and tridimensional crystal structure of ketanserin

Pharmacokinetic studies performed after an intravenous injection of 10 mg, revealed that the elimination of ketanserin could be described by an open three compartment model. Total clearance was found to be 0.39 l/kg/h and the volume of distribution 3.3 l/kg. Terminal half-life was calculated to be 15.6 h. After an oral administration of 20 mg terminal half-life was found to be 18.5 h and the bioavailability 51% (Reimann et al.1983b, Trenk et al.1983, Heykants et al.1986).

Ketanserin is almost exclusively metabolized in the liver, the metabolites being excreted in the urine (68%) and the faeces (24%) (Meuldermans et al. 1984). In elderly hypertensive patients (De Cree et al.1985), the bioavailability of orally administered ketanserin is higher due to reduced hepatic elimination. In patients with renal insufficiency adaption of the doses is not necessary because only 0.7% of the parent compound is excreted in the urine and the metabolites, mainly ketanserin-ol, have negligible pharmacological activity (Heykants et al.1986).

With respect to its effect on arteries ketanserin inhibits S_2 -serotonergic receptor mediated contractions of the caudal artery in the rat, the femoral and pulmonary arteries in the rabbit, the basilar, internal carotid, coronary

and gastrosplenic arteries in the dog, and the coronary arteries in cattle (Van Nueten et al.1982, Kaumann 1983, Frenken and Kaumann 1984, Brazenor and Angus 1982).

Ketanserin also blocks the S_2 -serotonergic receptor mediated contractions of large veins in dogs and rats (Van Nueten et al. 1982, Cohen et al.1981). Ketanserin inhibits the S_2 -serotonergic receptor mediated contractions of isolated blood vessels, induced by serotonin released from aggregating platelets (Cohen et al.1983a, Vanhoutte 1983b, Van Nueten 1983a). It does not prevent endothelium dependent S_1 -serotonergic receptor mediated relaxation induced by serotonin or aggregating platelets (Cohen et al.1983a,1983b).

In concentrations 6-90 times higher than those required to inhibit S_2 -serotonergic receptor mediated effects ketanserin inhibits contractions induced by noradrenaline and histamine in isolated blood vessels from various species, including rat, rabbit, dog and man (Van Nueten et al.1982,1981b,1981c). The amplifying effect of serotonin on various agents like noradrenaline, histamine, angiotensin and prostaglandin $F_2 \alpha$ is inhibited by ketanserin, without depressing the contractile response to the administration of the respective agonists (Van Nueten et al.1982). In vitro ketanserin prevents the S_2 -serotonergic receptor mediated aggregation of blood platelets induced by serotonin in platelet rich plasma of rat, cat and man (De Clerck et al.1982a,1982b). Under these circumstances ketanserin prevents the amplifying effect of serotonin on the aggregation of platelets, as induced by noradrenaline, ADP or collagen (Bevan and Heptinstall 1983).

In normotensive rats at low doses ketanserin antagonizes the pressor effect of serotonin and at higher doses also blocks the pressor effects of noradrenaline and phenylephrine (Kalkman et al.1982, Fozard 1982, Persson et al.1982). In conscious, anesthetized, spontaneously hypertensive rats and other species ketanserin lowers systolic and diastolic blood pressure, which was attributed to the α_1 -adrenergic receptor blocking properties of the compound (Kalkman et al.1982, Fozard 1982, Petterson et al.1985b, Nelson et al.1984, Bolt and Saxena 1985).

In a study on closed-chest dogs ketanserin blocked the serotonin induced pulmonary hypertension and bronchoconstriction (Van de Water et al.1985).

In man ketanserin has been mainly studied with respect to its blood pressure lowering effects (Vanhoutte et al.1983a, De Cree et al.1981c). In patients with essential hypertension, intravenously and orally administered ketanserin decreases blood pressure, without causing reflex tachycardia (De Cree et al.1981a,1981b, Wenting et al.1982a,1982b, Wing et al.1984, McGourty et al.1984, Murphy et al.1985).

Ketanserin has not only been evaluated in essential hypertension but also in other forms of hypertension, like preeclamptic hypertension (Weiner et al.1984a,1984b,), per- and postoperative hypertension (Nalda et al.1985, Anger et al.1985, Rucquoi et al.1985, Griffith and Whitwam 1986a,1986b, Cashman et al.1986), and neurogenic hypertension (Van Aken et al.1984b, Thomson et al.1984) and appeared to be effective in approximately 75% of the patients. Recently ketanserin was reported to be effective in the perioperative control of blood pressure in patients with carcinoid syndrome (Casthely et al.1986, Houghton and Carte 1986).

Among the mechanisms underlying the blood pressure lowering effect of ketanserin several possibilities have been postulated: merely α_1 -adrenergic receptor blocking activity, (Reimann and Frohlich 1983a, Petterson et al.1985b, Zabudowski et al.1985, Gasic et al.1985), mainly S_2 -serotonergic blockade (Wenting et al.1984), centrally mediated inhibition of sympathetic vascular tone (Phillips et al.1985, McCall and Schuette 1984, Petterson et al.1984, Lakoski et al.1985, Mylechrane et al.1985, Copeland and Bentley 1985), and a miscellaneous mode of action, incorporating these mechanisms (Vanhoutte 1985). It has been suggested that an interaction between blockade of S_2 -serotonergic and α_1 -adrenergic receptors plays a role in the antihypertensive action of ketanserin (Van Nueten et al.1986).

Studies on the effect of ketanserin on myocardial contractility show that the compound does not impair myocardial function and even might be beneficial, since it prevents arrhythmias in ischemic conditions (Saman et al.1985). Ketanserin does not affect heart rate (Walker et al.1984). The latter phenomenon might indicate that ketanserin blocks the sympathetic outflow of catecholamines by its inhibitory action on central α_1 -adrenergic receptors.

The effect of ketanserin on the pulmonary circulation includes a reduction of pulmonary vascular resistance, particularly in conditions like pulmonary embolization, endotoxic shock and adult respiratory distress syndrome (Meuleman et al.1983, Huval et al.1983, Vincent et al.1984, Koyama et al.1985, Hechtman and Sherpo 1984, Breuer et al.1986).

In normotensive man the effects of ketanserin on the humoral system include an increase in renin activity and angiotensin II-levels. The compound has minimal effect on plasma aldosterone, cortisol and noradrenaline levels (Zoccali et al.1983, Fagard et al.1984b, Reimann et al.1985). In patients with essential hypertension ketanserin causes a slight rise in plasma levels of aldosterone and noradrenaline and a decrease in renin activity and plasma levels of angiotensin II (Zabudowski et al.1984, Fagard et al.1984a), presumably due to increased renal cortical blood flow. The reported side effects after intravenous injection are sleepiness, light-

headedness and hypotension (Amery et al.1985, Murphy et al.1985, Jennings and Opie 1987).

Chapter 3

Anesthetic and surgical techniques, and postoperative management

3.1 Anesthetic technique and monitoring

All patients undergoing coronary artery bypass surgery included in the studies on systemic arterial hypertension had a normal left ventricular function, as evaluated by ejection fraction, left ventricular end-diastolic pressure and wall motion descriptions at preoperative left ventricular angiography. All patients had chronic therapy with beta-blocking agents (propranolol, metoprolol), calcium entry blockers (nifedipine) and nitrates, received their medication up to 6-8 hrs before induction of anesthesia. None of the patients had concomitant renal, hepatic or pulmonary disease or had received anticoagulant medication preoperatively.

The patients who suffered from valvular heart disease also had their cardiac medication continued until 6-8 hrs before surgery, but long-acting coumadines were stopped 3-4 days preoperatively and replaced by intravenous heparin.

The patients were premedicated with scopolamine 0.005 mg/kg and morphine 0.15 mg/kg between 45 and 60 minutes before induction of anesthesia. In the operating room an intravenous (peripheral) and intra-arterial (radial artery) catheter were inserted, E.C.G. electrodes were placed (lead II and V5), and induction was started by means of fentanyl 30 µg/kg, pancuronium bromide 0.1 mg/kg and etomidate 0.2 mg/kg. During the pre-bypass procedure the lungs of the patients were ventilated with 100% oxygen in the following studies: the comparison between nitroprusside and ketanserin in the treatment of postoperative hypertension following coronary artery bypass grafting (CABG) and in the treatment of pulmonary hypertension following valvular surgery. They were ventilated with 50% O₂/50% N₂O in the remaining studies. However, in the early post-bypass period the patients were ventilated with 100% oxygen in all the studies. Anesthesia was maintained by means of the intermittent administration of fentanyl (maximum 75 µg/kg), pancuronium (maximum 0.2 mg/kg) and midazolam (0.15 mg/kg). After endotracheal intubation a nasogastric tube was inserted and then nasopharyngeal and rectal temperature probes were placed. A Swan Ganz thermodilution pulmonary artery catheter (Edwards) (Swan et al.1970) was inserted through an internal jugular or a subclavian vein via an introducer system (Argon) to measure central venous pressure (CVP), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP). Cardiac output (CO) was determined by means of the thermodilution method (Edwards). All measurements were made in triplicate during the same phase of respiration. Systemic (SVR) and pulmonary (PVR) vascular resistance were calculated by means of standard equations. In the studies described in chapters 4 and 8 the pulmonary artery catheter was inserted under local anesthe-

sia before induction of general anesthesia in order to obtain control values in the awake patient (Damen and Bolton 1986). In all patients a catheter was inserted into the bladder after induction of anesthesia.

During the pre-bypass period 10 ml/kg Ringer's lactate with 5% glucose was infused in order to maintain a CVP between 5 and 8 mmHg and a PCWP between 8 and 10 mmHg. If the colloid osmotic pressure (COD), measured with a membrane-transducer oncometer, was lower than 18 mmHg, 100 ml albumin 20% solution was slowly administered.

The anesthesia technique was associated with a 10-15% decrease of mean arterial blood pressure during induction and an elevation of systolic arterial blood pressure up to 130 mmHg during intubation, a level maintained during the prebypass period. If this intravenous, balanced anesthesia technique (Milocco et al.1985) failed to prevent hypertension, vasodilatation with a continuous infusion of nitroglycerin was applied (Stengert et al.1978). Inhalation anesthetics, specifically halothane, were avoided to prevent dysrhythmias in the presence of elevated levels of catecholamines (Spiss et al.1984, Brown and Gandolfi 1987, Halsey 1987, Sorensen et al.1986, Turner et al.1986, Hess et al.1983). In addition recent data suggest that isoflurane may cause a "steal phenomenon" in patients with ischemic heart disease (Reiz and Ostman 1985, Gelman et al. 1984).

The fentanyl dose used (30 µg/kg at induction, augmented to 75 µg/kg at sternotomy) is considered to be a moderate analgesic dosage (Bailey et al.1985), but in combination with hypnotic and relaxant agents it has been reported to be sufficient to overcome stressful events in the prebypass period (Murphy et al.1983). We did not choose for a mono anesthetic high dose fentanyl-technique (100 µg/kg) in the coronary artery bypass surgery patients (Yrjola 1983, Murkin et al.1985, Moffitt et al.1984, Bazaral et al.1985), because it excessively prolongs extubation time postoperatively and because of other reported complications like perioperative awareness, postoperative muscle rigidity and respiratory depression (Hardy et al.1983, Sanford et al.1986, Sebel et al.1982a, Peters et al.1979). In the group of patients undergoing surgery for valvular disease (chapter 8), a high dose fentanyl technique (100 µg/kg) was preferred because of the favorable influence on the cardiovascular system of these high-risk patients during induction (Bovill et al. 1984a,1984b, Wynands et al.1983), the reduction of the stress response during surgery and because a longer duration of mechanical ventilation postoperatively is required in these patients when compared to patients undergoing coronary artery bypass surgery (Howie et al.1985).

Etomidate was administered as hypnotic agent because of its minimal effects on the cardiovascular system (Reneman et al.1974, Xhonneux et al.1974, Spiss et al.1984, Nimmo and Miller 1983, Giese et al.1985,

McCollum and Dundee 1986, Sear 1987). Although recent reports suggest a depression of the adrenal-cortical system (Metha et al.1985, Wanscher et al.1985, Wagner and White 1984, Fragen et al.1984, Moore et al.1985a) during the administration of etomidate, in our department the drug is considered to be the best possible choice for these high-risk patients.

Pancuronium bromide as non-depolarizing muscle relaxant may cause tachycardia, mainly because of its vagolytic properties (Saxena and Bonta 1970), but possibly also by facilitating noradrenaline release (Bowman 1980). In the presence of fentanyl, with its vagomimetic properties, tachycardia is seldom seen, particularly in patients who received beta-blocking agents preoperatively (Crul 1982, Miller 1982, Slogoff et al.1978).

Midazolam (0.15 mg/kg) was administered 10-15 min after the etomidate dose during maintenance of anesthesia because of its minimal influence on the cardiovascular system and its advantages over diazepam, particularly with respect to the difference in metabolism (Marty et al.1986a,1986b, Greenblatt et al.1984, Reves et al.1985).

When the pericardium was opened heparin 3 mg/kg was injected through the introducer side-port. When the activated clotting time (ACT), which indicates the degree of heparinization of the patient, was longer than 400 sec the ascending aorta was cannulated. When the patient was weaned from cardiopulmonary bypass and no serious bleeding was present, protamine sulphate was slowly injected intravenously in a dose equal to the heparin dose. The residual priming solution from the extra-corporeal circuit was infused postoperatively, together with a slow infusion of 100 mg of protamine sulphate for every 1000 ml prime. In this period the activated clotting time was considered to be normal when it remained below 140 sec.

Just before the start of cardiopulmonary bypass etomidate 0.2 mg/kg was injected intravenously, because the very first episode of cardiopulmonary bypass represents the most dangerous period with respect to the cerebral function of the patient and etomidate might act as a cerebral protective agent (Wauquier et al.1981, Hempelman et al.1982, Newberg Milde and Milde 1986), comparable with the cerebral protection by barbiturates (Nussmeier et al.1986).

Occasionally pancuronium bromide and fentanyl were injected during cardiopulmonary bypass in incremental doses, especially when this period lasted longer than 60 minutes, to stabilize the patient particularly during the rewarming phase and to guarantee adequate muscle relaxation during the often required defibrillation before weaning from cardiopulmonary bypass. In most cases midazolam 0.1 mg/kg was administered after the end of the surgical procedure just before leaving the operating

room (Lowry et al.1985), to ensure adequate sedation before installation in the ICU.

3.2 Surgical technique

The surgical technique in the patients undergoing coronary artery bypass surgery was standardized. After heparinization, an arterial and venous cannula were inserted into the aorta and the right atrium, respectively, whereafter cardiopulmonary bypass was slowly started. A venting system was inserted into the aortic root and connected to a roller pump to evacuate blood from the left ventricle. The patient was first cooled to a nasopharyngeal temperature of 32°C and the definitive locations for the venous grafts on the coronary arteries were determined. The aorta was cross-clamped followed by the infusion of 10 ml/kg of a hyperkalemic cardioplegic solution at 4°C into the aortic root. The patient was then further cooled to approximately 28°C. The heart was simultaneously cooled externally by flushing the pericardial cavity with 2 litres of cold saline (4°C).

First the distal anastomoses were made whereafter the aorta was de-clamped. Generally so-called jump grafts were constructed, which means that only one or two proximal anastomoses had to be made. When the patient was rewarmed to 36.5°C nasopharyngeally and 34.5°C rectally, weaning from cardiopulmonary bypass was started, followed by decannulation when the hemodynamic status of the patient was considered to be adequate. The sternum was closed by means of sternal wires. Usually one mediastinal drain was used, except when the pleura was accidentally opened, in which case a pleural drain was also inserted.

In valvular surgery two venous cannulas were inserted through the right atrium into the superior and inferior caval vein respectively, and the left ventricle was temporarily vented through a cannula, inserted via a pulmonary vein. In patients with aortic insufficiency, the cardioplegic solution was administered by means of two separate cannulas in the ostia of the left and right coronary arteries. External temporary pacing wires were sutured to the epicardium before weaning from cardiopulmonary bypass.

3.3 Cardiopulmonary bypass technique

Cardiopulmonary bypass was achieved by means of a heart-lung machine (Sarns) with four roller pumps. The extracorporeal circuit consisted of PVC-tubing, including a cardiotomy reservoir, and a bubble oxygenator (Harvey, Bentley) connected to a heater-cooler system (Sarns).

The priming solution of the extracorporeal circuit consisted of 20 ml/kg Ringer's lactate with 5% dextrose, 100 ml NaHCO_3 8.4% and 100 ml albumin 20%. If the hematocrit, measured after 5 minutes of cardiopulmonary bypass, was lower than 20 %, one unit of red blood cell concentrate was added. When during cardiopulmonary bypass the colloid osmotic pressure was lower than 10 mmHg, 100 ml albumin 20% was added.

The flow was calculated with the use of a flow rate computer (Sarns) and kept as close as possible to 50 ml/kg/min. Mean arterial pressure was adjusted between 50 and 80 mmHg by administering either phenylephrine, an alpha-adrenergic vasoconstricting agent, to increase blood pressure, or vasodilators, like nitroglycerin, nitroprusside or chlorpromazine, to decrease blood pressure.

Anticoagulation was monitored by intermittent measurements of activated clotting time (ACT) which was kept above 400 sec. If lower heparin was administered in incremental bolus doses of 50 mg.

The temperature of the patient, measured by means of nasopharyngeal and rectal temperature probes, was kept at approximately 28°C nasopharyngeally. Rewarming was started just after the last distal anastomosis was completed, and terminated when the temperature had reached 36.5°C nasopharyngeally and 34.5°C rectally.

In the patients who received coronary artery bypass grafts weaning from cardiopulmonary bypass was routinely managed without the administration of inotropic agents, like dopamine or dobutamine. But in most patients calcium chloride was injected to increase temporarily myocardial contractility during weaning. In the patients undergoing valvular surgery, inotropic agents were routinely administered during and after weaning from cardiopulmonary bypass to improve myocardial contractility. A combination of dopamine and dobutamine was used in order to improve myocardial performance as well as renal and systemic perfusion. After weaning from cardiopulmonary bypass the residual priming solution in the oxygenator was transferred to a plastic infusion bag for re-infusion during the early postoperative period.

3.4 General postoperative management

In the Intensive Care Unit (ICU) the patient was mechanically ventilated (Siemens Servo ventilator), keeping the PaCO_2 between 35 and 45 mmHg and the PaO_2 between 80 and 150 mmHg. Positive end-expiratory pressure (PEEP) was not used routinely (Marvel et al.1986, Good et al.1979), as long as the blood gas criteria were fulfilled by means of con-

ventional intermittent positive pressure ventilation (IPPV).

During the study periods the patients were sedated with midazolam and muscle relaxation was maintained with pancuronium or vecuronium to eliminate influences of wakening and intolerance to the endotracheal tube. Postoperatively ECG (lead II and V5), heart rate (HR), arterial blood pressure (AP), central venous pressure (CVP), pulmonary artery pressure (PAP) and pulmonary capillary wedge pressure (PCWP) were continuously monitored, and cardiac output, systemic and pulmonary vascular resistance intermittently determined.

In the patients undergoing coronary artery bypass grafting the fluid regimen consisted of 1 ml/kg/hour Ringer's lactate with 5% dextrose. If the colloid osmotic pressure was lower than 18 mmHg, 100 ml albumin 20% was infused. During the first hour the infusion mainly consisted of the residual priming solution from the extracorporeal circuit. During infusion of this priming substance 100 mg protamine/1000 ml infusion fluid was slowly administered, to neutralize the residual amount of heparin. Drainage through the chest tube was maintained at a suction pressure of 12 cm H₂O. Blood loss was considered to be normal if less than an average of 100 ml/hr in the first three hours. If this was exceeded the patient was excluded from the study.

Diuresis was normally high in the first few hours (more than 100 ml/h) due to the residual hemodilution, as indicated by a hematocrit between 24 and 28% when the patient entered the ICU.

A patient undergoing coronary artery bypass grafting was excluded from the study if he or she did not have a normal sinus rhythm with a heart rate between 70 and 110/min or developed low cardiac output during the study period which needed treatment with inotropic agents like dopamine and dobutamine.

Antibiotic prophylaxis was 15 mg/kg cefamandole given 6 hourly for 24 hours.

In the patients undergoing valvular surgery, the infusion regimen was different: 1.5 ml/kg/hour Ringer's lactate with 5% dextrose was administered after the infusion of the residual priming solution.

In this group of patients PEEP had to be applied because of increased pulmonary water content causing diminished pulmonary function (Boldt et al.1985). Inotropic agents were necessary in all patients to increase cardiac output. This therapy consisted of dopamine, dobutamine or a combination of these agents, and was started during weaning from cardiopulmonary bypass (see section 3.3). Since dysrhythmias, including heart block, were frequently observed during the first postoperative hours following valvular surgery, temporary pacing was used in most of the patients.

Many of the valvular patients had an abnormal clotting profile due to the preoperative use of coumadine derivatives, congestive heart failure with liver insufficiency and/or prolonged periods of cardiopulmonary bypass. Fresh frozen plasma and platelet concentrate were infused when indicated by laboratory tests, i.e. activated partial thromboplastin time, prothrombine time, thrombotest and platelet count. The criteria for blood loss were the same as in the group undergoing coronary artery bypass grafting. In the patients undergoing valvular surgery the prophylactic antibiotic regimen consisted of cefamandole (15 mg/kg given 6 hourly) and gentamycin, both drugs given for 24 hours and the dosage of the latter drug adjusted to body weight and renal function.

Chapter 4

Ketanserin during and following coronary artery bypass grafting: hemodynamic and humoral responses

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Anesthesiology (submitted)

Introduction

Hypertension during and following coronary artery bypass grafting (CABG) is a major clinical problem (Estafanous et al.1973, Estafanous and Tarazi 1980, Roberts et al.1977, Wallach et al.1980), since it may cause myocardial ischemia, bleeding and neurological complications (Moffitt et al.1985, Merin 1980, Slogoff and Keats 1986). Increased levels of circulating catecholamines (Roberts et al.1977, Balasarawathi et al 1978, Low et al.1986), attributed to pressor reflexes from the heart, the great vessels and the coronary arteries, and increased concentrations of renin and angiotensin (Bailey et al.1975, Taylor et al.1979) due to the use of hemodilution (Hine et al.1976) and hypothermia (Arnett and Watts 1960, Chernow et al.1983) during cardiopulmonary bypass (CPB) have been considered to contribute to the development of perioperative hypertension. Serotonin (Replogle et al.1962, James et al.1975, Swank et al.1964, Ilcin et al.1972), for example released during the activation and aggregation of platelets (Wenzel et al.1979), might play a role as well. Hemodynamic studies revealed that perioperative hypertension is associated with an increase in systemic vascular resistance without a significant change in cardiac performance (Kim et al.1981, Estafanous et al.1984).

The treatment of perioperative hypertension generally consists of lowering arterial blood pressure by means of vasodilating agents, like sodium nitroprusside (Kaplan and Jones 1979, Tinker and Michenfelder 1976), nitroglycerin (Gallagher et al.1986, Gerson et al.1982), hydralazine (Koch-Weser 1976), trimetaphan (Stinson et al.1975) and calcium entry blockers (Van Wezel et al.1986, Franklin et al.1986). Blockade of the stellate ganglion (Fouad et al.1978, Bidwai and Rogers 1979) and epidural anesthesia (Hoar et al.1976) also have been advocated. Anesthesia techniques with the use of high doses of narcotic compounds, like fentanyl (De Lange et al.1982, Sebel et al.1982) and sufentanil (Howie et al.1985, Sebel and Bovill 1982, Rosow et al.1984), have been used to prevent hypertensive responses during induction and surgery, but side-effects, like rigidity and prolonged postoperative respiratory depression, are a major concern (Sebel and Bovill 1982, Hardy et al.1983, Sanford et al 1986).

Ketanserin, a specific S_2 -serotonergic receptor blocking agent (Van Nueten et al.1981, Van Nueten 1983) with α_1 -adrenergic receptor blocking properties (Gasic et al.1985, Petterson et al.1985, Reimann and Frohlich 1983) has been used in the treatment of postoperative hypertension following CABG and appeared to be effective in lowering arterial blood pressure in the majority of the patients (Van der Starre et al.1983). In in vitro studies the compound also prevented serotonin induced aggregation of

platelets (De Clerck and Van Nueten 1982, De Clerck et al.1982).

In the present prospective double-blind study we investigated whether a continuous infusion of ketanserin during and after CABG could modulate the pressor responses, the plasma levels of vasoactive hormones, like catecholamines, renin and angiotensin, the dose of fentanyl used and the number of nitroglycerin administrations required to treat hypertensive episodes. Since pressor reflexes may influence renal blood flow, diuresis was intermittently recorded. Plasma levels of beta-thromboglobulin, platelet factor-4 and serotonin also were measured to obtain information about possible platelet activation.

Methods and materials

The prospective double-blind study was performed in 2 groups of 12 patients undergoing CABG. The patients had a normal myocardial function and no concomitant diseases. All patients gave informed consent and the protocol was approved by the Hospital Ethics Committee. Premedication consisted of 0.005 mg/kg scopolamine IM and 0.15 mg/kg morphine IM, administered 45-60 min before induction of anesthesia. After arrival in the operating room ECG monitoring was started (lead II and V₅), and a peripheral venous and a radial artery cannula were inserted. Before induction of anesthesia a Swan-Ganz thermodilution catheter was inserted into the pulmonary artery via an internal jugular vein. Heart rate (HR, as assessed from the ECG), systolic (SBP), diastolic (DBP), and mean (MAP) arterial blood pressure, mean pulmonary artery pressure (MPAP), central venous pressure (CVP), and pulmonary capillary wedge pressure (PCWP) were measured. The pressures were measured with external transducers (Bentley). Cardiac output (CO) was determined by means of thermodilution (Edwards), using 10 ml of saline at room temperature. The average of three measurements, made during the same phase of respiration, was taken as the actual value. Systemic (SVR) and pulmonary (PVR) vascular resistance were calculated using standard formulas. Nasopharyngeal and peripheral (skin) temperatures were continuously monitored and recorded (Philips thermistor probes). Anesthesia was induced with fentanyl 50 µg/kg, pancuronium bromide 0.1 mg/kg and etomidate 0.2 mg/kg. Midazolam 0.2 mg/kg was administered 15-20 minutes after induction and in the early post-bypass period. The patients were ventilated with 100% O₂ during surgery and with 50% O₂/50% air in the first postoperative hours. Ventilation was adjusted to maintain a PaCO₂ between 35 and 45 mmHg.

Immediately after intubation of the trachea a continuous infusion of

either 0.1 mg/kg/hr ketanserin (group K) or the solvent of ketanserin (group S) was started. The patients were randomly allocated to either group. If the patient developed hypertension in the pre-bypass period during surgery (SBP higher than 130 mmHg), fentanyl was administered in incremental doses of 0.5 mg, up to a total dose of 75 µg/kg. If this was not sufficient to normalize arterial blood pressure, a continuous infusion of nitroglycerin was started. During cardiopulmonary bypass (CPB) flow rate was set at 50 to 60 ml/kg and MAP was kept between 40 and 60 mmHg. The initial priming solution of the extracorporeal circuit consisted of 20 ml/kg Ringer's lactate with 5% dextrose. If during CPB the colloid osmotic pressure (COP), as determined with a membrane-transducer osmometer (Barclay and Bennett 1987), was lower than 10 mmHg, 100 ml albumin 20% was added. None of the patients received any other blood product during and following surgery. During CPB the patients were cooled to 28-30°C nasopharyngeal temperature and the heart was arrested by means of a cold potassium cardioplegic solution. To prevent a prolonged period of hypotension, the infusion of ketanserin, and hence solvent, was stopped just before the initiation of CPB. The infusion was started again when MAP was higher than 50 mmHg. After termination of CPB and in the following postoperative period the infusion of ketanserin or solvent was continued for at least 3 hrs. When hypertension (SBP higher than 150 mmHg) developed, a nitroglycerin infusion was started. The above mentioned variables were recorded and calculated before induction (1, control values), before thoracic skin incision (2), during sternotomy (3), just after the administration of heparin (4), 15 (5) and 45 min (6) after the start of CPB, at the end of CPB (7), 15 min after termination of CPB (8), at arrival in the ICU (9), and 60 (10), 120 (11) and 180 min (12) after arrival in the ICU. Arterial blood samples for determination of the plasma concentrations of circulating adrenaline, noradrenaline, dopamine, plasma renin and angiotensin II were obtained before induction (1), before sternal skin incision (2), during sternotomy (3), 15 (5) and 45 min (7) after the start of CPB, immediately after termination of CPB (8) and 120 min after arrival in the ICU (11). Plasma levels of platelet factor-4, beta-thromboglobulin, plasma serotonin and platelet-bound serotonin were determined and platelets were counted before induction (1), after termination of CPB (8), and 120 (11) and 180 min (12) after arrival in the ICU. The dose of fentanyl administered in the pre-bypass period and the necessity to infuse nitroglycerin in the pre-bypass and postoperative ICU-periods were recorded. Pre-, per- and post-bypass diuresis was also recorded.

Radioimmunoassay techniques were used to determine plasma levels of adrenaline, noradrenaline, dopamine, renin, angiotensin II (De Leeuw et

al.1983), and platelet factor-4 and beta-thromboglobulin plasma levels (De Clerck et al.1982). Plasma-serotonin and platelet-bound serotonin were determined by fluorimetric methods as described by Drummond (Drummond and Gordon 1974). The total number of platelets was determined with a Coulter-Counter technique.

Changes within the groups were evaluated for statistical significance with the use of the Wilcoxon signed-rank test, two tailed probability, and differences between the groups by applying the Mann-Whitney U-test. Differences in the number of nitroglycerin administrations in the pre-bypass and postoperative period, and the demographic data were evaluated by Fisher's exact test. Differences were considered to be significant in case of a probability value $p < 0.05$. The data are presented as mean $\pm$ SEM.

Results

There were no significant differences between the groups with respect to age, sex, weight, number of bypass grafts, aortic clamp time and CPB-time (table 1). No patient in either group needed inotropic support during the study period.

Table 4.1. Demographic data of the patients in both groups

	Ketanserin	Solvent
number	12	12
age (yrs)	56 $\pm$ 2.5	57 $\pm$ 1.2
sex (M/F)	10/2	12/0
weight (kg)	82 $\pm$ 2.1	80 $\pm$ 1.9
AoC (min)	39 $\pm$ 3.7	48 $\pm$ 5.3
CPB (min)	64 $\pm$ 4.9	73 $\pm$ 6.1
ACB (n)	4 $\pm$ 0.4	5 $\pm$ 0.2

Values are presented as mean $\pm$ SEM.
 AoC= Aortic clamp time; CPB= Cardiopulmonary bypass time; ACB= number of venous bypass grafts

In both groups SBP (fig 1) significantly decreased after induction of anesthesia, increased to the pre-induction value during sternotomy and in group K significantly decreased again in the period preceding CPB. Imme-

Fig. 4.1.

diately following CPB, SBP was significantly lower than the control value (before induction) in both groups. In the ICU SBP remained lower than the control value in group K till 60 min.

In both groups DBP (not depicted) significantly decreased after induction of anesthesia, and increased to the pre-induction value in the remaining pre-bypass period. After CPB DBP values were similar to the pre-induction values in both groups. Between the groups there were no significant differences in DBP during the complete study period.

In both groups MAP (fig 1) followed the same pattern as SBP in the pre-bypass and in the early post-bypass period. In both groups MAP was significantly lower during CPB than in the control period. During the first hour in the ICU MAP was significantly lower in group K than in group S.

In group S MPAP (fig 1) decreased following induction of anesthesia and remained lower than the control value until the start of CPB. In group K MPAP was lower than the control value only just before CPB. After CPB MPAP was lower than in the control period in both groups. In group K the decrease in MPAP was more pronounced and MPAP remained lower for a longer period of time. During the first hour in the ICU MPAP was significantly lower in group K than in group S.

In group S HR (fig 2) was significantly higher than in the control period at sternotomy, in the remaining pre-bypass period, in the whole post-bypass period and in the ICU. In group K HR was significantly higher than in the control period during the whole post-bypass and ICU-periods. At sternotomy and from 60 min after arrival in the ICU HR was significantly lower in group K than in group S.

In group S CO (fig 2) was significantly lower than in the control period at sternotomy, in the remaining pre-bypass period and in the early post-by-

Fig.4.1.

Systolic (SBP) and mean (MAP) arterial pressure, and mean pulmonary artery pressure (MPAP) in the solvent (....) and ketanserin (—) groups during and following surgery (mean $\pm$ SEM).

1= before induction (control value); 2= before sternal skin incision; 3= during sternotomy; 4= after the administration of heparin; 5= at 15 min on CPB; 6= at 45 min on CPB; 7= at the end of CPB; 8= 15 min after CPB; 9= at arrival in the ICU; 10= 60 min after arrival in ICU; 11= 120 min after arrival in ICU; 12= 180 min after arrival in ICU.

BYPASS = cardiopulmonary bypass.

* = significantly different from control value ($p < 0.05$)

+ = significant difference between the groups ($p < 0.05$)

Fig. 4.2.

pass period until 60 min after arrival in the ICU. In group K CO was lower than in the control period immediately before CPB and after CPB from the moment of arrival in the ICU. In group K CO was significantly lower than in group S immediately before CPB and 60 and 120 min after arrival in the ICU.

In group S SVR (fig 2) was significantly higher than in the control period after induction of anesthesia, at sternotomy and during the first 60 min in the ICU. In group K SVR was higher than in the control period at sternotomy, at arrival and 120 min after arrival in the ICU. SVR was significantly higher in group K than in group S before induction of anesthesia and from 60 min after arrival in the ICU.

The nasopharyngeal temperature (fig 3) changed equally in both groups during and following the investigation, but the peripheral (skin) temperature (fig 3) was significantly higher in group K than in group S from the end of CPB up to 120 min after arrival in the ICU. In group S skin temperature was significantly lower during the post-bypass period, as compared with the control value.

Catecholamine-levels (fig 4) increased significantly in both groups from the initiation of CPB and remained higher than the control value during the residual study period. In group K the adrenaline-levels were significantly lower than in group S 180 min after arrival in the ICU. The plasma levels of noradrenaline tended to be lower 120 and 180 min after arrival in the ICU in group K, but this difference did not reach the level of significance. The changes in dopamine-levels (fig 4) were similar to those observed in the other catecholamine-levels and were not significantly different in both groups. The renin- and angiotensin II-levels (fig 4) significantly increased in both groups from the moment of sternotomy and remained significantly elevated during the complete study period. The renin and angiotensin II-levels tended to be lower in group K, but the difference only reached the level of significance 180 min after arrival in the ICU. In both groups the plasma levels of beta-thromboglobulin and platelet factor-4 were significantly higher after termination of CPB and in the postoperative period as compared with the control values. Plasma-serotonin and plate-

Fig.4.2.

Heart rate (HR), cardiac output (CO) and systemic vascular resistance (SVR) in the solvent (....) and ketanserin (—) groups during and following surgery (mean $\pm$ SEM). For explanation of recording moments and abbreviations see Fig. 4.1.

* = significantly different from control value ($p < 0.05$)

+ = significant difference between the groups ($p < 0.05$)

Fig. 4.3.

let-bound serotonin tended to increase during CPB, but these changes did not reach the level of significance. The platelet count significantly decreased during CPB. The changes in the platelet parameters between the two groups were not significantly different (table 2).

Table 4.2.

Platelet count and plasma levels of beta-thromboglobulin, platelet factor-4, serotonin and platelet bound serotonin in both groups during and following surgery.

	T	Platelet count ($\times 10^3$)	bTG (ng/ml)	PF-4 (ng/ml)	Ser (ng/ml)	PI-ser (ng/ 10^3 pl)
Ketanserin	1	186 + 22*	47 + 4.2	26 + 5.1	58 + 4.2	60 + 8.7
	8	78 + 31*	175 + 12.6*	52 + 10.2*	75 + 5.8	61 + 12.6
	11	95 + 19*	105 + 8.4*	23 + 4.7	64 + 4.7	56 + 5.7
	12	105 + 22*	96 + 11.8*	19 + 6.4	66 + 3.7	52 + 8.4
Solvent	1	193 + 30	52 + 8.5	28 + 3.4	51 + 4.9	51 + 7.9
	8	86 + 21*	186 + 15.8*	46 + 7.4*	69 + 6.8	56 + 9.2
	11	105 + 26*	104 + 11.6*	25 + 4.5	49 + 5.1	52 + 6.8
	12	109 + 17*	84 + 9.5*	21 + 3.5	42 + 3.5	51 + 7.4

Values are presented as mean $\pm$ SEM.

bTG= beta-thromboglobulin; PF-4= platelet factor-4; Ser= plasma-serotonin;

PI-ser= platelet-bound serotonin; pl= platelets; T= sample moments, for explanation of T=1,8,11,12 see Fig.1

* = significantly different from control value T=1 ($p < 0.05$)

Fig.4.3.

Nasopharyngeal (NPh) and peripheral (skin) temperature (mean $\pm$ SEM) in the solvent (....) and ketanserin (—) groups during and following surgery. For explanation of recording moments and abbreviations see Fig.4.1.

* = significantly different from control value ($p < 0.05$)

+ = significant difference between the groups ($p < 0.05$)

Fig. 4.4.

The dose of fentanyl administered to treat hypertensive episodes in the pre-bypass period was significantly lower in group K ($0.28 \pm 0.03 \mu\text{g/kg/min}$) than in group S ($0.36 \pm 0.02 \mu\text{g/kg/min}$). In this period nitroglycerin was administered to 2 patients in group K and in all the patients in group S, a significant difference ($p < 0.01$). In the ICU nitroglycerin was administered because of hypertension in 2 patients in group K and in 10 patients in group S. This difference was also statistically significant ($p < 0.01$).

In the period prior to CPB and during CPB diuresis (fig 6) was significantly higher ($p < 0.01$ and $p < 0.05$, respectively) in group K than in group S, but in the post-CPB period there was no significant difference between the two groups anymore.

Discussion

The findings in the study show that, as compared with the solvent, the continuous infusion of ketanserin is associated with significantly lower arterial blood pressure, heart rate and cardiac output values in patients undergoing coronary artery bypass grafting, particularly in the post-bypass period. Systemic vascular resistance is slightly, but significantly higher in the corresponding periods. Ketanserin induces a lower pulmonary artery pressure in the early postoperative period and a higher peripheral skin temperature during and following cardiopulmonary bypass. Ketanserin also causes a better diuresis before and during bypass. During the continuous infusion of ketanserin the need for the administration of fentanyl and nitroglycerin to treat hypertensive reflexes is significantly less than during solvent infusion. The higher heart rate values in the solvent-group can possibly be explained by more frequent administrations of nitroglycerin, which may cause reflex tachycardia (Kaplan et al.1980). In a previous study comparing ketanserin and sodium nitroprusside in the treatment of postoperative hypertension following coronary artery bypass grafting (Van der Starre and Reneman 1986), ketanserin, in contrast to nitroprusside, lowered arterial blood pressure without changing heart rate. Since myocardial

Fig.4.4.

Plasma levels (mean $\pm$ SEM) of adrenaline (top), noradrenaline (middle) and dopamine (below) in the solvent (....) and ketanserin (—) groups during and following surgery. For explanation of sampling moments and abbreviations see Fig.4.1.

* = significantly different from control value ($p < 0.05$)

+ = significant difference between the groups ($p < 0.05$)

Fig 4.5.

oxygen demand is mainly determined by heart rate and systolic arterial blood pressure (Braunwald 1971, Hoffman and Buckberg 1978), ketanserin potentially improves the balance between oxygen demand and supply.

The slightly lower systemic vascular resistance in the solvent group during the intensive care period may also be explained by the more frequent administrations of nitroglycerin to treat hypertensive episodes in this group. The significantly higher peripheral temperature in the ketanserin group during corresponding periods might be explained by a specific dilating effect of the compound on cutaneous blood vessels. The antihypertensive activity of ketanserin was recently attributed to an interaction between S_2 -serotonergic and α_1 -adrenergic receptor blockade, since S_2 -serotonergic receptor blockade alone does not change arterial blood pressure (Van der Starre and Reneman 1988, Van Nueten et al.1986).

In both groups the plasma levels of adrenaline, noradrenaline and dopamine remained stable during the pre-bypass period, but increased during cardiopulmonary bypass, whereas the plasma levels of renin and angiotensin already increased in the pre-bypass period. These humoral responses are in agreement with previous findings (Roberts et al.1977, Balasarawahti et al.1978, Low et al.1986, Bailey et al.1975, Taylor et al.1979) and are probably caused by the use of hemodilution (Hine et al.1976), hypothermia (Arnett and Watts 1960, Chernow et al.1983) and non-pulsatile flow (Landymore et al.1979). The findings in the solvent group confirm previous observations that during anesthesia with moderate doses of opioids (up to 75 $\mu\text{g/kg}$ fentanyl), muscle relaxants and hypnotic agents a vasodilating compound like nitroglycerin has to be administered to modulate extreme pressor responses (Dahlgren and Messeter 1981, Bovill et al.1984, Bedford and Marshall 1984, Kay et al.1985, Mofitt 1978). The lower dose of fentanyl administered in the ketanserin-group might be beneficial because of a shorter postoperative recovery time, although this was not recorded in the present study.

The observation that before and during cardiopulmonary bypass diuresis is significantly better during the infusion of ketanserin than during the

Fig.4.5.

Plasmalevels (mean $\pm$ SEM) of renin (top) and angiotensin II (below) in the solvent (....) and ketanserin (—) groups during and following surgery. For explanation of sampling moments and abbreviations see Fig.4.1.

* = significantly different from control value ($p < 0.05$)

+ = significant difference between the groups ($p < 0.05$)

infusion of solvent might be explained by the finding that ketanserin blocks the serotonin induced constriction of renal arteries in animals (Garattini and Valzelli 1965, Blackshear et al.1986, Page and McCubbin 1953).

In both groups activation and aggregation of platelets occurred during cardiopulmonary bypass, as indicated by the significant increase of plasma levels of beta-thromboglobulin and platelet factor-4. This is in agreement with earlier observations (Kobinia et al.1986, Faymonville et al.1986, Solis et al.1975). It has been suggested (Replogle et al.1962, Swank et al.1964, Ilicin et al.1972) that serotonin released from platelets activated during cardiopulmonary bypass might contribute to the vaso-

Fig.4.6.

Diuresis (mean $\pm$ SEM) pre-CPB, during CPB and post-CPB in the solvent ( ) and ketanserin ( ) groups. CPB= cardiopulmonary bypass.

* = significant difference between the groups ($p < 0.05$)

** = significant difference between the groups ($p < 0.01$)

pressor response. However, elevations of plasma levels of serotonin are not uniformly detected (Anger et al.1985, this study) suggesting that circulating platelets in patients during cardiopulmonary bypass are activated through a process involving release from α -granules (beta-thromboglobulin, platelet factor-4) but not of dense granule constituents (serotonin)(Harker et al.1980). However, the failure to demonstrate increased plasma levels of serotonin may also be due to the particular kinetic behaviour of the mono-amine in the circulation and does not necessarily exclude a serotonergic contribution to the hypertension observed during and following surgery. Indeed, release of serotonin by the platelets and re-uptake of the mono-amine by these activated cells, as well as the endothelial lining of the vessel wall, are time-sharing processes (Costa and Murphy 1977, Reimers et al.1973). Low-grade release from platelets thus may provide serotonin to act in concert with other vasopressors (Van Nueten et al.1982), while concomitant re-uptake yields apparently normal plasma and platelet levels.

In conclusion a continuous infusion of ketanserin during and following coronary artery bypass grafting significantly lowers arterial blood pressure, heart rate and cardiac output per-and postoperatively as opposed to its solvent. The administration of ketanserin reduces the need for opioids and nitroglycerin to treat hypertensive episodes, which might be beneficial in preventing side-effects like rigidity, postoperative respiratory depression and tachycardia. Diuresis is significantly better during the administration of ketanserin than of its solvent. Although platelet counts and plasma levels of serotonin did not significantly change, a substantial role of serotonin in the genesis of perioperative hypertension cannot be excluded.

Summary

In a prospective double-blind study in patients undergoing coronary artery bypass grafting (CABG), the effects of a continuous infusion of ketanserin 0.1 mg/kg/hr, a S_2 -serotonergic receptor blocking compound with α_1 -adrennergic receptor blocking properties, were compared with those induced by the infusion of the solvent of ketanserin. Both infusions were started immediately after intubation. The solvent and the ketanserin group each consisted of 12 patients. A comparison was made between the effects on systemic and pulmonary hemodynamics, plasma levels of circulating adrenaline, noradrenaline, dopamine, renin, angiotensin II, serotonin, beta-thromboglobulin and platelet factor-4, diuresis, and the dose of fentanyl and the number of nitroglycerin administrations required to treat hypertensive episodes during and following surgery. In the treated group arterial

blood pressure, heart rate and cardiac output were significantly lower ($p < 0.05$), mainly in the post-bypass period, whereas skin temperature and systemic vascular resistance were significantly higher ($p < 0.05$) at corresponding moments. Before ($p < 0.01$) and during cardiopulmonary bypass ($p < 0.05$), diuresis was significantly higher whereas the dose of fentanyl and the number of nitroglycerin administrations required were significantly lower ($p < 0.05$ and $p < 0.01$, respectively). It is concluded that the continuous infusion of ketanserin leads to a more stable condition with less hypertensive episodes during and after CABG, which may benefit patients at risk.

Chapter 5

The use of ketanserin, a S₂-serotonergic receptor antagonist, for treatment of postoperative hypertension following coronary artery bypass surgery

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Introduction

Hypertension following coronary artery bypass surgery occurs in 30-60% of patients during the first few postoperative hours (Estafanous et al.1973,Estafanous and Tarazi 1980,Roberts et al. 1977, Salerno et al.1981). Several factors may contribute to the development of this postoperative hypertension including arousal, nasopharyngeal and tracheal stimulation, and pain. Increased levels of circulating catecholamines, renin, angiotensin, and/or serotonin may be involved in the development of hypertension (Balasaraswathi et al.1978, Wallach et al.1980,Taylor et al.1977,Frick 1960, Replogle et al.1962). Serotonin may either be released from platelets activated during the extracorporeal circulation or gradually released from e.g. the spleen in the postoperative period (Wenzel et al.1979). Whether serotonin-induced cardiogenic hypertension reflex (James et al.1975) plays a role in this type of postoperative hypertension is unknown.

Methods

Of 82 NYHA category II/III patients, not in heart failure and undergoing elective coronary artery bypass surgery, 40 patients (49%) developing hypertension during the early postoperative period (110-180 min after the end of surgery; median 132 min), were studied. In all patients with arteriographically confirmed coronary artery bypass disease, the coronary lesions were bypassed by saphenous vein grafts. Preoperative management, the anesthetic and surgical technique and postoperative care were standardized (chapter 5). All patients gave informed consent; the study was approved by the ethics committee of the hospital.

Preoperative therapy consisting usually of beta-adrenergic antagonists, long-acting nitrates, and calcium-antagonists was continued during hospitalization until the night before surgery. Patients were not given anti-coagulants either before or after surgery.

Premedication with 0.005 mg/kg scopolamin and 0.125 mg/kg morphine was administered intramuscularly 45 min before induction of anesthesia.

Anesthesia was induced intravenously with 0.3 mg/kg etomidate, 0.5 mg fentanyl, and 0.15 mg/kg pancuronium; the patients were mechanically ventilated with a mixture of 50% nitrous oxide and 50% oxygen. Ventilation was governed by the capnographically determined CO₂ concentration in expired air (Mijnhardt) and by serial measurements of arterial blood gas tensions. Incremental doses of 0.25-0.5 mg of fentanyl

and 0.1 mg/kg of pancuronium were given intravenously before median sternotomy, during cardiopulmonary bypass, and before closure of the sternum. Anesthesia was adjusted according to response of the electroencephalogram (EEG) as well as changes in blood pressure, heart rate, and peripheral circulation. Incidental hypertension during the surgical procedure was treated with intravenous injections of nitroglycerin.

Heparin (3 mg/kg) was administered intravenously before extracorporeal circuit (ECC), which consisted of an arterial and a venous roller pump (Sarns), and a bubble oxygenator (Bentley, Harvey). The calculated flow was 50 ml/kg. The priming solution consisted of 5% dextrose in Ringer's lactate solution, 20 ml/kg, with 50 meq bicarbonate and 50 mg heparin/L of the priming solution. Mean arterial pressure during ECC was kept at 50 mmHg, regulated by vasodilating drugs like trimethaphan and nitroglycerin. The patients were cooled to a nasopharyngeal temperature of 28°C with a heat exchanger. The heart was stopped by ventricular fibrillation or by a cardioplegic solution containing 30 meq potassium/L. Topical cooling of the heart was performed in all patients. After installation of the last distal anastomosis, the patients were rewarmed to normothermia (1°C/3min). The mean hematocrit at the end of ECC was 28%. After termination of the ECC, heparin was antagonized by protamine (3 mg/kg intravenously). The residual priming solution was transferred to the patient through a transfusion system, guided by central venous and left arterial pressures.

Artificial ventilation was continued during transfer to the intensive care unit and as long as the patients remained asleep to maintain a PaCO_2 of 35-45 mmHg and a PaO_2 of 100-150 mmHg. During this time 1 ml/kg/h of 5% dextrose in Ringer's lactate solution was infused to maintain urine output at 0.8 ml/kg/h. All patients had adequate sedation and analgesia and were free of respiratory difficulties. Calculated blood losses were replaced as indicated by changes in arterial blood pressure, central venous pressure, and left atrial pressure.

ECG leads II and V_5 were applied upon arrival of patients in the operating theatre, at which time an intravenous infusion catheter (16 gauge) and a radial arterial cannula (18 gauge) for arterial blood pressure (AP) monitoring were also inserted. After induction of anesthesia, a catheter (16 gauge) was introduced through the jugular vein for monitoring central venous pressure (CVP). In one group of patients (N=10), a Swan Ganz thermodilution catheter was inserted through the right internal jugular vein to measure pulmonary artery pressure (PAP). Cardiac output (CO) was measured using the thermodilution technique (Edwards Laboratories) (Kohanna, Cunningham 1977). Systemic vascular resistance (SVR) was calculated as follows: $\text{SVR} = 80 \times (\text{mean arterial pressure (MAP)} - \text{CVP})$

/ CO dynes.cm⁻⁵. At the end of ECC, a catheter was placed in the left atrium at its junction with the superior pulmonary vein for monitoring left atrial pressure (LAP). All catheters were left in place for at least 48 h. The tri-ple index was calculated by multiplying heart rate (beats/min) by systolic blood pressure (mmHg) and LAP (mmHg).

Peripheral circulation was monitored using a plethysmograph applied to the ear lobe. Temperature sensors were placed on the forehead skin and in the nasopharynx. Upon arrival in the intensive care unit, the latter was replaced by a rectal probe. Capnographic recording of expired CO₂ was continued while patients remained in the intensive care unit.

A hypertensive episode was defined as a period of sustained increase in arterial systolic blood pressure (> 150 mmHg) when the increase in blood pressure was not reversed by simple sedation or analgesia; when there was no evidence of hypoxia, hypercarbia, shivering, or intolerance of the endotracheal tube; and when right and left filling pressures of the heart were adequate (CVP 5-10 mmHg; LAP 5-12 mmHg).

Intravenous administration of ketanserin was started when the intraarterial systolic blood pressure increased above 150 mmHg. Patients were sequentially allocated to one of three groups. Patients in group 1 (N=15) were treated with an intravenous bolus of 10 mg of ketanserin injected over a period of 3 min. Patients in group 2 (N=15) had continuous infusions of 4 mg of ketanserin per h for 2.5 h within 10 min after injection of 10 mg of ketanserin. Patients in group 3 (N=10) had an intravenous injection of 10 mg of ketanserin followed by continuous infusions of 4 mg of ketanserin for 1 h also within 10 min. In group 3 CO was measured and SVR calculated. If, however, the bolus injection of ketanserin did not result in a decrease of blood pressure within 10 min, nitroglycerin was administered to normalize blood pressure.

In all patients AP, heart rate, CVP, and LAP were measured before and 5, 15, 30, and 60 min after injection of ketanserin. In group 2 these variables were also recorded after 90, 120, and 150 min. In group 3, CO and SVR were determined before and 15 and 60 min after ketanserin administration.

Differences between values of the different variables before and at various intervals after the administration of ketanserin were evaluated for statistical significance by a paired t-test. A Mann-Whitney U test was used for statistical evaluation of the differences between the control values of the various variables (before ketanserin injection) in the three groups.

Results

The sex, age, and weight distributions of the patients in the three groups are shown in Table 1 with the number of bypass grafts and the duration of CPB, surgery, and anesthesia.

Table 5.1 Sex, Age, Weight Distribution, and Number of Bypasses, as well as the Duration of ECC, Surgery, and Anesthesia in the Patients Treated with Ketanserin. (Mean $\pm$ SEM.)

	Group 1	Group 2	Group 3
Sex (% males)	84.6	91.7	75.0
Age (years)	58.3 $\pm$ 1.97	56.5 $\pm$ 2.58	53.5 $\pm$ 2.33
Weight (kg)	74.5 $\pm$ 3.14	73.3 $\pm$ 2.91	78.9 $\pm$ 5.65
Number of bypasses	3.8 $\pm$ 0.41	2.9 $\pm$ 0.19	3.3 $\pm$ 0.37
Duration of ECC (min)	78.5 $\pm$ 6.72	66.75 $\pm$ 6.19	76.0 $\pm$ 7.29
Duration of surgery (min)	200.8 $\pm$ 9.64	175.8 $\pm$ 4.76	211.3 $\pm$ 15.55
Duration of anesthesia (min)	236.9 $\pm$ 11.17	204.2 $\pm$ 5.50	247.5 $\pm$ 16.09

No serious complications occurred during surgery in any of the patients. Mean blood loss during surgery was 400 ml. Urine production remained stable and normal during the surgical procedure as well as postoperatively. None of the patients developed hypo- or hyperthermia during the first 4 postoperative hours. Except for the lower systolic AP values in group 3 and the higher diastolic AP values in group 2 (Fig. 1), there were no significant differences between the values of the three groups before administration of ketanserin.

The bolus injection of 10 mg of ketanserin has a significant effect of too short duration on the hypertension in two patients in group 1, in three patients in group 2, and in two patients in group 3. In all of these patients (7/40; 17.5%) AP was normalized with an average infusion dose of 1.5 μ g/kg/min nitroglycerin. The results (AP and HR) obtained in these patients are illustrated in Figure 2. In the remaining patients, AP decreased significantly to normal values immediately following the administration of 10 mg of ketanserin (Fig. 1). When only the bolus injection was given (group 2), AP gradually increased, systolic pressure reached hypertensive levels again after 60 min. The hypotensive effect of a bolus injection could be maintained with a continuous infusion of 4 mg of ketanserin/h (groups 2 and 3). No rebound effect was observed after discontinuation of the infusions (Fig. 1). Heart rate decreased slightly but statistically significantly during continuous infusion of ketanserin (Fig. 3), while SVR decreased

Fig 5.1

Effect of ketanserin on systolic and diastolic arterial blood pressure.

□ = group 1: 10 mg of ketanserin IV (n = 13)

○ = group 2: 10 mg of ketanserin IV followed by 4 mg of ketanserin/h IV for 2.5 h (n = 12)

△ = group 3: 10 mg of ketanserin IV followed by 4 mg of ketanserin/h IV for 1 h (n = 8)

* = $p < 0.05$ (significant difference from pretreatment values)

** = $p < 0.001$ (significant difference from pretreatment values)

+ = $p < 0.05$ (significant difference from value at end of treatment)

Fig 5.2

Course of systolic (SBP) and diastolic (DBP) arterial blood pressure and heart rate (HR) in patients (n = 7) treated with a continuous infusion of nitroglycerin because response to ketanserin was too brief (10 min).

* = $p < 0.05$ (significant difference from pretreatment values)

significantly and cardiac output increased significantly (Fig. 4). Ketanserin had no substantial effect on PCWP or CVP. The administration of ketanserin was followed by a significant decrease in triple index (Fig. 5).

Discussion

The findings in the present study show that ketanserin, a specific S_2 -serotonergic receptor blocking agent, is effective in the treatment of hypertension following coronary artery bypass surgery. An intravenous bolus injection of the compound (10 mg) rapidly decreased arterial blood pressure to normal levels in 82.5% of patients. This level could be maintained with a continuous infusion of 4 mg of ketanserin/h following the bolus injection. No rebound phenomena were observed after discontinuation of the infusion. The decrease in arterial blood pressure most likely represents vasodilation of constricted vessels as indicated by the pronounced decrease of systemic vascular resistance to normal levels.

The antihypertensive activity of ketanserin was associated with either a slight decrease or no significant change in heart rate. The resulting decrease in triple index suggests that oxygen demands of the myocardium

Fig 5.3

Effect of ketanserin on heart rate. See Fig 5.1 for legend.

Fig 5.4

Effect of ketanserin on systemic vascular resistance, mean arterial blood pressure and cardiac output in patients treated with 10 mg of ketanserin IV followed by 4 mg of ketanserin/h IV for 1 h (n = 8).

* = $p < 0.05$ (significant difference from pretreatment values)

** = $p < 0.001$ (significant difference from pretreatment values)

Fig. 5.4.

were diminished by ketanserin, an advantage in the presence of potential myocardial ischaemia. Why the pronounced decrease in arterial blood pressure was associated with a decrease rather than an increase in heart rate is not completely understood. One explanation may be that ketanserin reaches the brain in sufficiently high concentrations to induce a partial centrally mediated hypotension, since ketanserin is known to bind to S_2 receptors in the brain (Laduron et al.1984). On the other hand, it is still a point of debate as to whether the serotonin released from platelets does exchange with serotonin in the brain.

The findings of this investigation could support the concept that serotonin is involved in the hypertension often seen following coronary artery bypass surgery (Estafanous et al.1973, Estafanous and Tarazi 1980, Roberts et al.1977, Salerno et al. 1981) The delayed onset of hypertension might support the hypothesis that the serotonin originates from the activated platelets (Wenzel et al.1979) and is then gradually released into the

Fig 5.5
Effect of ketanserin on triple index. See Fig 5.1 for legend.

circulation during the early part of the postoperative period. Whether the serotonin induced cardiogenic reflex (James et al.1975) plays a role in this postoperative hypertension cannot be concluded from the present study.

The lower initial systolic arterial blood pressure values in patients in group 3 than in patients in the other two groups may have been the result of the earlier administration of ketanserin.

Seven of the 40 (17.2%) patients treated for postoperative hypertension did not respond to ketanserin. One explanation may be that the dose of ketanserin administered in these patients was too low. Another possibility is that the elevated arterial blood pressure in these patients was not caused by serotonin.

In conclusion hypertension following coronary artery bypass surgery may be related to increased circulating levels of serotonin as evidenced by the responses to a S_2 -serotonergic receptor antagonist ketanserin. The usefulness of ketanserin in the treatment of hypertension following coronary artery bypass surgery may be particularly great because of the absence of reflex increases in heart rate.

Summary

In patients developing hypertension following coronary artery bypass surgery (CABG) the possible role of serotonin was investigated by injecting ketanserin, a specific S_2 -serotonergic receptor antagonist. Ketanserin was administered intravenously when intraarterial systolic blood pressure (SAP) exceeded 150 mmHg either as a 10-mg bolus (group 1, N = 15), or as a 10-mg bolus followed by infusion of 4 mg/h for either 2.5 h (group 2, N = 15) or for 1 h (group 3, N = 10). In 33 patients (82.5%), SAP and diastolic arterial pressure decreased significantly within 5 min after the 10-mg bolus. In group 1, SAP gradually increased after 30-50 min but in groups 2 and 3 SAP remained normal. The triple index (TI) decreased significantly in all groups. Heart rate decreased slightly but significantly in groups 2 and 3. Central venous and left atrial pressures did not change substantially in any of the three groups. Cardiac output increased significantly (0.51 ± 0.158 L/min); hence, systemic vascular resistance (SVR) decreased significantly (452.1 ± 50.57 dyn.s.cm⁻⁵-group 3). No rebound increase in SAP occurred after terminating the infusions (group 2 and 3). These findings indicate that serotonin plays a role in the majority of patients who develop hypertension following CABG. The decrease of SVR without reflex tachycardia is a favourable effect of ketanserin.

Chapter 6

Ketanserin in the treatment of postoperative hypertension following coronary artery bypass grafting: a double blind study

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Introduction

Hypertension following coronary artery bypass grafting (CABG) is considered to be a major problem in intensive care units (Estafanous and Tarazi 1980, Roberts et al. 1977). In addition to anesthetic factors like pain, arousal and intolerance to endotracheal intubation, postoperative hypertension may result from factors such as raised levels of catecholamines (Balasaraswathi et al. 1978), renin, angiotensin (Taylor et al 1977) and serotonin (Replogle et al. 1962, Frick 1980). The possible role of serotonin was substantiated by the earlier finding that ketanserin, a S_2 -serotonergic receptor blocking agent with α_1 -adrenergic antagonistic properties (Van Nueten et al. 1981), was effective in the treatment of hypertension following CABG, by decreasing systemic vascular resistance without causing reflex tachycardia (Van der Starre et al. 1983).

The aim of the present double blind study was to prove the effectiveness of ketanserin in the treatment of this type of hypertension.

Materials and methods

Twenty patients who developed hypertension (see below) during the early recovery phase after CABG were randomly allotted to two groups under double blind conditions. Treatment consisted of either 2 ml solvent or 10 mg ketanserin in 2 ml solvent IV. Both solvent and drug were administered intravenously as a bolus. All patients had given informed consent to participate in this study which was approved by the hospital ethics committee.

The pre-operative medication, in all patients consisting of beta-blocking agents, calcium channel blockers and long-acting nitrates, was continued until the day of surgery. Preoperatively all patients were normotensive and had a normal left ventricular function, as determined by the ejection fraction and the left ventricular end-diastolic pressure. All patients were NYHA classification II and III.

The anesthetic technique and postoperative management were standardized in both groups (chapter 5). Forty five minutes after intramuscular premedication consisting of 0.005 mg/kg scopolamine and 0.125 mg/kg morphine, anesthesia was induced with etomidate 0.2 mg/kg, fentanyl 15 μ g/kg and pancuronium bromide 0.15 mg/kg. Anesthesia was maintained with fentanyl (total dose 40-60 μ g/kg), diazepam 0.2 mg/kg and pancuronium bromide (total dose 0.3 mg/kg). The lungs were ventilated with 100% oxygen. Weaning from the extracorporeal circulation was uneventful in all patients, without the use of any vasopressor

agent. The patients were mechanically ventilated postoperatively, using 60% oxygen in air, to keep the blood gas values within acceptable limits (PCO_2 between 35 and 45 mmHg, PO_2 higher than 100 mmHg).

Arterial blood pressure was continuously monitored via a radial artery cannula, connected to an external pressure transducer (Bentley). Heart rate was determined from the E.C.G. Hypertension was defined as a period of sustained increase in arterial systolic blood pressure greater than 150 mmHg during at least 5 min, that could not be reduced by sedation or analgesics. The blood pressure and heart rate values were assessed before and 5, 10, 30, and 60 min after the administration of the study medication.

In the interest of the patients' safety and according to the protocol, patients who did not respond adequately to the study medication were treated with a continuous infusion of nitroglycerin. These failures were excluded from further analysis.

Intragroup differences were evaluated for statistical significance by us-

Table 6.1 General patient data in both treatment groups.

	Ketanserin	Solvent
Number of patients treated	10	10
Age (years)	54.0 + 2.21	59.1 + 3.04
Sex (F/M ratio)	1/9	5/5
Weight (kg)	76.0 + 2.42	72.8 + 3.38
Duration of anesthesia (min)	200.0 + 10.35	186.5 + 13.08
Duration of E.C.C. (min)	70.1 + 7.0	64.7 + 11.19
Number of bypass grafts	3.4 + 0.45	3.1 + 0.48
Onset of treatment postoperatively (min)	145.0 + 15.31	122.0 + 16.85
Night before surgery		
SBP (mmHg)	126.5 + 5.17	129.7 + 5.35
DBP (mmHg)	79.8 + 2.97	78.0 + 4.96
HR (b/min)	67.1 + 4.21	70.2 + 3.75
At time of		
SBP (mmHg)	158.0 + 4.22	155.2 + 5.43
DBP (mmHg)	80.3 + 9.97	76.8 + 12.31
HR (b/min)	87.0 + 14.72	90.9 + 11.26

F = female; M = male; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate (beats/min); E.C.C. = extracorporeal circulation.

All values are presented as mean $\pm$ SEM.

ing the Wilcoxon signed rank test, two tailed probability. Intergroup differences were evaluated according to the Mann-Whitney U-Test, two tailed probability. Differences were considered to be significant in case of a probability value $p < 0.05$.

Results

Both groups were comparable with regard to age, sex, body weight, duration of anesthesia, cardiopulmonary bypass time, number of bypass grafts and the onset time of postoperative antihypertensive treatment. At the time of treatment the systolic (SBP) and diastolic blood pressure (DBP) and heart rate (HR) values were not significantly different in the two groups, nor were they different on the day before surgery (table 1). The mean values ($\pm$ SEM) of SBP, DBP and HR in both groups at 0, 5, 15, 30 and 60 min are presented in table 2, and graphically depicted in the figures 1 and 2. In the ketanserin group SBP decreased significantly during 60 min, DBP during at least 30 min ($p < 0.05$) and HR did not change significantly. At 60 min 7 patients were still present in the study. In the sol-

Table 6.2

Values of systolic and diastolic blood pressure and heart rate in both groups.

Ketanserin					
Min	0	5	15	30	60
SBP	158 $\pm$ 1.3	127 $\pm$ 3.4*	135 $\pm$ 4.1*	138 $\pm$ 4.3*	127 $\pm$ 8.5*
DBP	80 $\pm$ 3.2	63 $\pm$ 2.8*	65 $\pm$ 3.8*	66 $\pm$ 4.1*	62 $\pm$ 5.9*
HR	87 $\pm$ 4.7	88 $\pm$ 4.8	92 $\pm$ 5.0	94 $\pm$ 5.5	91 $\pm$ 4.2
n	10	10	9	9	7
Solvent					
Min	0	5	15	30	60
SBP	155 $\pm$ 1.7	153 $\pm$ 2.3	163 $\pm$ 2.7	154 $\pm$ 12.2	139 $\pm$ 3.5
DBP	77 $\pm$ 3.9	77 $\pm$ 4.1	85 $\pm$ 5.5	91 $\pm$ 5.8	69 $\pm$ 6.5
HR	91 $\pm$ 3.6	90 $\pm$ 3.7	93 $\pm$ 4.1	103 $\pm$ 10.1	106 $\pm$ 9.5
n	10	10	9	3	2

SBP = systolic blood pressure (mmHg); DBP = diastolic blood pressure (mmHg); HR = heart rate (beats/min); n = number of patients without required additional treatment; Min = interval following study medication (minutes).

All values are presented as mean $\pm$ SEM.

* = $p < 0.05$ (significant difference vs control value min = 0)

vent group SBP, DBP and HR did not significantly change, and at 60 min only 2 patients were left in the study group because of the required additional treatment (nitroglycerin). Statistical analysis between the groups was only performed after 5 and 15 minutes because of the limited number of patients still included in the solvent group thereafter. At these intervals the difference between the effects of ketanserin and solvent was significant for systolic as well as diastolic blood pressure ($p < 0.01$). No significant differences in heart rate were observed between either group during the study period.

Fig 6.1

Graphic representation of systolic and diastolic blood pressure values ($\pm$ SEM) in the ketanserin ( ) and solvent ( ) group.

* = $p < 0.05$ (significant difference vs control value time = 0)

+ = $p < 0.01$ (significant difference between the groups)

Discussion

The findings in this double blind study show that ketanserin is effective in lowering arterial blood pressure in patients with postoperative hypertension following CABG, confirming previous findings in an open uncontrolled study (Van der Starre et al.1983).

The study design, in which strict limits were set for drop-outs because of the patients safety, confined the analysis period to 15 minutes because of the limited number of patients left in the solvent group thereafter. In concordance with the previous reports heart rate did not change significantly in the treatment group, as well as in the solvent group, suggesting in the first place that the patients were well sedated, relaxed and painfree, and in the second place that ketanserin might be able to block the barore-

Fig 6.2

Graphic representation of changes in heart rate ($\pm$ SEM) in the ketanserin (○) and solvent group (□).

ceptor response to a reduction in blood pressure, suggesting a centrally mediated mode of action, in addition to its S_2 -serotonergic and α_1 -adrenergic receptor blocking activity.

The role of serotonin in this type of hypertension is not well defined. It may be released from platelets, aggregating during uncontrolled suction and recirculation in the course of cardiopulmonary bypass (Wenzel et al.1979). It has also been suggested that heparin and protamin both can induce platelet aggregation (Eika 1972, Zucker 1974).

The treatment of this clinical syndrome consists mainly of the use of vasodilating agents like nitroprusside, nitroglycerin, trimetaphan or hydralazin (Stinson et al 1975). This study proved that ketanserin is equally effective in the treatment of this form of hypertension during at least 30 min when used as a bolus injection, with the advantage that it does not induce a reflex tachycardia, which is often seen with the other antihypertensive agents (Mehta et al 1978, Tinker and Michenfelder 1976).

Summary

In two groups of 10 patients developing postoperative hypertension following coronary artery bypass grafting, a double blind study was designed to verify the efficacy of 10 mg ketanserin, a S_2 -serotonergic receptor blocking compound with α_1 -adrenergic receptor blocking properties, in lowering arterial blood pressure.

The results of the study show that ketanserin was effective in significantly lowering arterial blood pressure, without causing reflex tachycardia.

Chapter 7

Nitroprusside and ketanserin in the treatment of postoperative hypertension following coronary artery bypass grafting: a haemodynamic and ventilatory comparison

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Introduction

Hypertension following coronary artery bypass grafting is a frequent complication in the intensive care unit, reported to occur in 30-60% of cases (Estafanous and Tarazi 1980, Roberts et al.1977). A rise in systemic vascular resistance is generally responsible for the rise in blood pressure in these patients, caused by changes in catecholamines, temperature and haemodilution (Wallard et al.1980, Taylor et al. 1977). Since the condition might lead to a rise in oxygen consumption, which is unwanted, treatment consists mainly of vasodilating agents, mostly nitroprusside (Tinker and Michenfelder 1976).

In earlier reports ketanserin, a specific S_2 -serotonergic receptor antagonist with possible α -receptor blocking properties, was effective in the treatment of this clinical syndrome (Van der Starre et al.1983). In this study nitroprusside and ketanserin were compared in this respect by measuring changes in haemodynamic and ventilatory patterns.

Materials and methods

Twenty patients who developed hypertension (systolic blood pressure higher than 150 mmHg) following coronary artery bypass grafting were randomly treated with either ketanserin (10 patients) or nitroprusside (10 patients). All patients were treated with long-acting nitrates, calcium channel blockers and beta-blockers until the morning of surgery. None of the patients had a concomitant disease or impaired left ventricular function. Premedication consisted of scopolamin 0.005 mg/kg and morphine 0.15 mg/kg 1 h before surgery and general anesthesia of intravenous anesthetics (fentanyl, benzodiazepines) and relaxants (pancuronium). Mechanical ventilation was applied with $F_{O_2} = 0.6$. The anaesthetical and surgical procedure were standardized, as was the extracorporeal circulation (chapter 3.3).

The aim of the study was to lower systolic blood pressure by 10-15% with either agent and to study other haemodynamic and ventilatory variables. To achieve this effect, the ketanserin dose administered was 10 mg bolus, followed by 0.13 ± 11 mg/kg per h. For nitroprusside the dose administered was 6.0 ± 0.3 μ g/kg per min.

All patients were mechanically ventilated, aiming at a pCO_2 of 45 mmHg and a pO_2 higher than 100 mmHg, sedated and relaxed if necessary. All patients had intra-arterial blood pressure monitoring in a radial artery, a Swan-Ganz catheter in the pulmonary artery to allow thermodilution cardiac output measurements and the electrocardiogram (lead II and V_5) and heart rate were continuously monitored (chapter 3.1).

The following variables were measured before and 30 min after the start of either therapy: systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), systemic vascular resistance (SVR), cardiac index (CI), central venous pressure (CVP), systolic pulmonary artery pressure (SPAP), diastolic pulmonary artery pressure (DPAP), pulmonary capillary wedge pressure (PCWP) and pulmonary vascular resistance (PVR).

In addition the shunt fraction (Q_s/Q_t) was calculated (Conroe et al.1968), for which reason the patients were ventilated for 5 min before measurement with 100% oxygen.

Statistical analysis was performed using the Wilcoxon matched-pairs signed-ranks test for intragroup differences and the Mann-Whitney U-test for intergroup differences. Differences were considered to be significant when $p < 0.05$.

Results

The results are summarized in Table 1, which shows that the two study

Table 7.1. Changes in absolute values (mean $\pm$ SEM)

	Ketanserin group	Nitroprusside group	Units
SBP	- 21.1 $\pm$ 6.6	- 19.1 $\pm$ 1.6	mmHg
DBP	- 5.7 $\pm$ 1.9	- 6.9 $\pm$ 1.7	mmHg
CVP	- 1.1 $\pm$ 0.02	- 0.8 $\pm$ 0.01	mmHg
PCWP	- 2.5 $\pm$ 0.25	- 1.8 $\pm$ 0.15	mmHg
CI	+ 0.3 $\pm$ 0.06	+ 0.4 $\pm$ 0.08	l/min/m ²
SPAP	- 2.2 $\pm$ 0.8	- 3.3 $\pm$ 1.6	mmHg
DPAP	- 3.3 $\pm$ 1.0	- 3.2 $\pm$ 0.7	mmHg
SVR	- 208 $\pm$ 83.0	- 424 $\pm$ 68.0	dyn.s/cm ⁵
PVR	- 54 $\pm$ 17.0	- 48 $\pm$ 12.1	dyn.s/cm ⁵
HR	- 0.1 $\pm$ 1.2	+15.2 $\pm$ 3.5*	beats/min
Q_s/Q_t	- 0.85 $\pm$ 0.72	+ 9.99 $\pm$ 1.44*	%

SBP = systolic blood pressure; DBP = diastolic blood pressure; CVP = central venous pressure; PCWP = pulmonary capillary wedge pressure; CI = cardiac index; SPAP = systolic pulmonary artery pressure; DPAP = diastolic pulmonary artery pressure; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; HR = heart rate; Q_s/Q_t = shunt fraction.

* = $p < 0.05$ (significant difference between the groups)

Fig. 7.1.

groups were comparable in age, weight, sex, systolic blood pressure and length of time elapsed after surgery before start of treatment. The effect of ketanserin and nitroprusside on the various measurements are shown in Figs 1 and 2. There appeared to be no significantly different changes between the two groups with respect to changes in SBP, DBP, CVP, PCWP, CI, SPAP, DPAP, SVR, and PVR.

Heart rate did not change in the ketanserin group (-0.1 ± 1.2 beats/min) but increased in the nitroprusside group ($+15.2 \pm 3.5$ beats/min), causing a significant difference between the two study groups.

The shunt fraction (Q_s/Q_t) did not change significantly in the ketanserin group ($-0.85 \pm 0.72\%$), but increased in the nitroprusside group ($+9.99 \pm 1.44\%$), causing a significant difference between the two groups as well. The individual patient data with respect to changes in the heart rate and shunt fraction are shown on Figs 3 and 4.

Discussion

Hypertension following coronary artery bypass grafting, consisting mainly of an increase in systolic blood pressure, is a main issue for treatment in the intensive care unit. Studies report a 30-60% incidence of hypertension for patients in the first postoperative hours (Estafanous and Tarazi 1980, Roberts et al. 1977). Because the operation uses hypothermic extracorporeal circulation, changes occur in catecholamines, renin, angiotensin and possibly serotonin levels (Wallard et al. 1980, Taylor et al. 1977, Stinson et al. 1975). This occurs in parallel with changes in the degree of haemodilution. Generally, temperature rises gradually during this period. All these phenomena together can lead to postoperative hypertension, mainly caused by an increase in systemic vascular resistance (Estafanous and Tarazi 1980, Roberts et al. 1977, Wallard et al. 1980).

Treatment consists of the use of vasodilating agents, such as nitroprusside, nitroglycerin, hydralazine and trimetaphan (Tinker and Michenfelder

Fig.7.1.

Changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), cardiac index (CI) and systemic vascular resistance (SVR, dynes.s/cm⁵) in both groups.

* = $p < 0.05$ (significantly different from control value)

** = $p < 0.01$ (significantly different from control value)

There was no significant difference between the groups with respect to these changes.

Fig. 7.2.

1976, Stinson et al. 1975). Earlier reports have shown that ketanserin is effective in the treatment of postoperative hypertension, with the advantage of an absence of reflex tachycardia (Van der Starre et al, 1983). This study, comparing nitroprusside and ketanserin, showed a statistically significant difference between the two groups with respect to changes in the heart rate and shunt fraction. Since all patients had coronary artery disease and one is never certain that revascularization has been successful in the early postoperative period, a reflex tachycardia can lead to an unwanted rise in myocardial oxygen consumption, with the possibility of ischaemia. In this respect ketanserin might be advantageous compared with nitroprusside, especially in patients who have already developed tachycardia postoperatively. Most patients develop an increase in lung water postoperatively following extracorporeal circulation, due to changes in water content and colloid osmotic pressure pre- and postoperatively (Shivah et al. 1982). This can lead to a rise in shunt fraction, followed by an impairment of oxygenation and ventilation. In agreement with earlier reports, in which nitroprusside caused hypoxia (Seltzer et al. 1976), this study showed the effect of both agents on the shunt fraction and proved that ketanserin was advantageous, especially in patients who already have increased lung water such as patients with pre-operative heart failure. Apparently, ketanserin did not abolish the hypoxic pulmonary vasoconstriction as nitroprusside did in other patients (D'Oliviera et al.1981).

This study indicates that ketanserin and nitroprusside are equally effective in the treatment of postoperative hypertension following coronary artery bypass grafting, but ketanserin might be advantageous in patients with already existing tachycardia, or with impaired oxygenation and ventilation, due to an increased shunt fraction.

Fig.7.2.

Changes in systolic pulmonary artery pressure (SPAP), diastolic pulmonary artery pressure (DPAP) and pulmonary vascular resistance (PVR, dynes.s/cm₅) in both groups.

* = $p < 0.05$ (significantly different from control value)

** = $p < 0.01$ (significantly different from control value)

There was no significant difference between the groups with respect to these changes.

Fig. 7.3.

Fig.7.3.

Upper panel: changes in heart rate in both groups (intragroup). There was a significant difference ($p<0.01$) in these changes between the groups.

Lower panel: individual patient data (—) with mean value (....) are depicted for both groups.

Summary

Postoperative hypertension following coronary artery bypass grafting is usually treated with vasodilating agents like nitroprusside. In recent studies ketanserin, a S_2 -serotonergic receptor antagonist, appeared to be effective in the treatment of this clinical syndrome. In 20 patients, divided into two comparable groups, nitroprusside and ketanserin were compared with respect to their haemodynamic and ventilatory profiles. The study showed that both agents were equally effective in decreasing the raised systolic blood pressure, but that ketanserin was more advantageous with respect to the absence of reflex tachycardia and the unchanged shunt fraction.

Fig. 7.4.

Legend to Fig.7.4.

Upper panel: changes in shunt fraction (Q_s/Q_t) in both groups. There was a significant difference ($p < 0.01$) in these changes between the groups.

Lower panel: individual patient data (—) with mean value (····) are depicted for both groups.

Chapter 8

Ketanserin in the treatment of pulmonary hypertension following valvular surgery: a comparison with sodium nitroprusside

Introduction

In patients with valvular heart disease the gradual impairment of left ventricular function causes pulmonary venous congestion and hypertrophic changes of the vessel walls leading to an increase in pulmonary vascular resistance and ultimately to pulmonary hypertension (Rounds and Hill 1984, Reid 1986). In these patients the pulmonary ventilation-perfusion ratio is significantly altered (Cortese 1978, Laver et al.1970, Anjou-Lindskog et al.1983) while the extravascular water content of the lungs is higher than in normal subjects (Laver et al.1970), causing a reduction in lung compliance and functional residual capacity (FRC) and an increase in residual volume (Hinds 1982). These patients are usually treated with diuretics, digoxin and vasodilating agents, like hydralazine, nitroglycerin, angiotensin converting enzyme inhibitors and calcium entry blockers, but these compounds are not able to normalize pulmonary arterial pressure (Bolen and Alderman 1976, Cohn and Franciosa 1977, Kopman 1979). Recurrent episodes of congestive heart failure, sometimes with severe pulmonary oedema, and serious impairment of the physical condition of the patient determine the indication for valvular surgery (Bonchek 1980, Hancock 1977, Pluth and Ellis 1969).

During surgery lung function further deteriorates because general anesthesia reduces FRC (Marshall and Wyche 1972, Rehder et al.1975, Ali et al.1974, Jonmarker et al.1986) while during cardiopulmonary bypass (CPB) extra-vascular lung water content increases (Boldt et al.1986, Sade et al.1985, Gallagher 1985) as a consequence of complement activation (Chenoweth et al.1981, Best et al.1984, Jones et al.1982, Cavarocchi et al.1986) causing increased permeability of the pulmonary capillary membranes (Kirklin et al.1986, Miranda et al.1982, Jones et al.1986). In these conditions substantial pulmonary hypertension in the early postoperative period leads to pulmonary oedema (Sniderman et al.1984) and right ventricular failure (Kaul et al.1976, Christakis et al.1986). Atelectasis, the most common pulmonary complication, is reported in 60 to 80% of these patients (Gale et al.1979, Turnbull et al.1974).

Vasodilating agents like hydralazine (Sladen and Rosenthal 1979, Packer et al.1982), prostacyclin (D'Ambra et al.1985), nitroglycerin (Gonen et al.1982, Rosenthal et al.1981) and sodium nitroprusside (Knapp and Gmeiner 1977) are frequently used to reduce pulmonary arterial pressure in the postoperative period, but an increase in pulmonary shunt fraction is one of the main side effects of these compounds (Parsons et al.1981, D'Oliviera et al.1981).

Ketanserin, a S_2 -serotonergic receptor antagonist with α_1 -adrenergic receptor blocking properties, has been reported to reduce pulmonary vas-

cular resistance in patients with acute respiratory failure (Huval et al.1984) and to improve pulmonary circulation in endotoxic shock (Meuleman et al.1983, Huval et al.1983, Vincent et al.1984, Koyama et al. 1985, Hechtman and Sherpo 1984).

It was the aim of the present prospective study to compare postoperatively the effects of ketanserin and sodium nitroprusside on pulmonary artery pressure, systemic haemodynamics and pulmonary shunt fraction in patients who underwent valvular surgery. The compounds were administered when pulmonary arterial pressure increased and cardiac output started to decrease.

Materials and methods

The study was performed on patients admitted to the ICU following surgery for single or double valvular replacement or annuloplasty. All patients were mechanically ventilated, aiming at a $p\text{CO}_2$ of 45 mmHg and a $p\text{O}_2$ between 100 and 150 mmHg. A positive end-expiratory pressure (PEEP) of 5 cm H_2O was applied. The patients received fluids at a rate of 1.5 ml/kg/hr, initially consisting of residual priming from the oxygenator and later of Ringer's lactate with dextrose 5%. If the colloid osmotic pressure, measured with the use of a membrane-transducer oncometer (Barclay and Bennett 1987), was lower than 16 mmHg, 100 ml of albumin 20% was slowly infused. Routinely temporary pacing wires were sutured on the epicardium before weaning of CPB. All patients were treated with a continuous infusion of dopamine, dobutamine or a combination of these agents, which was started in the operating room during weaning from CPB, to improve myocardial performance and consequently cardiac output. No other vasodilating or inotropic agents were administered during the study period.

All patients had a radial artery cannula. A Swan-Ganz thermodilution catheter was inserted before surgery into the pulmonary artery via an internal jugular or subclavian vein. ECG (lead II and V_5), heart rate (HR, assessed from the ECG), systolic (SBP), diastolic (DBP) and mean (MAP) arterial pressure, systolic (SPAP), diastolic (DPAP) and mean (MPAP) pulmonary arterial pressure, central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP) as well as rectal and peripheral temperature were monitored and recorded. Cardiac output (CO) was measured using the thermodilution technique (76). Systemic (SVR) and pulmonary (PVR) vascular resistance, left (LVSW) and right ventricular stroke work (RVSW) were calculated using the following equations:

$$SVR = \frac{MAP-CVP \times 80}{CO} \text{ dyn.s. cm}^{-5}$$

$$PVR = \frac{MAP-PCWP \times 80}{CO} \text{ dyn.s.cm}^{-5}$$

$$LVSW = \frac{1.36 (MAP-PCWP) \times \text{stroke volume (SV)}}{100} \text{ gm}$$

$$RVSW = \frac{1.36 (MPAP-CVP) \times SV}{100} \text{ gm}$$

Shunt fraction (Q_s/Q_t) was determined after ventilating the patients with 100% O_2 during 5 min, with the use of the following equation (Comroe et al.1968):

$$Q_s/Q_t = \frac{C_{cO_2} - C_{aO_2}}{C_{cO_2} - C_{vO_2}} \%$$

in which C_{cO_2} = end-capillary oxygen content; C_{aO_2} = arterial oxygen content; C_{vO_2} = mixed venous oxygen content.

Immediately following admission to the ICU the values of the above mentioned variables and parameters were determined. When MPAP had increased more than 5 mmHg and CO started to decrease, the patients were randomly treated with either sodium nitroprusside (SNP, $n = 14$), starting with a dose of 1 $\mu\text{g/kg/min}$ or ketanserin (KET, $n = 12$), starting with a dose of 1.7 $\mu\text{g/kg/min}$, with the intention to reduce MPAP to its early post-bypass value. The infusion rates of the study medication were adjusted according to the hemodynamic results. After 30 min of treatment the measurements and calculations were repeated. Ten patients in the SNP-group and 7 patients in the KET-group had a pacemaker-induced heart rate at the start of the study period.

All data are presented as mean $\pm$ SEM. Statistical analysis was performed with the use of the Wilcoxon signed-rank test for intragroup comparison, and the Mann-Whitney U-test for comparison between the groups. A probability level of $p < 0.05$ was considered to indicate statistical significance.

Results

The two study groups were comparable with regard to type of surgery and the postoperative use of inotropic agents (dopamine and dobutamine) (Tables 1 and 2). There was no significant difference in age (SNP-group 61 ± 6.6 yrs, KET-group 58 ± 1.8 yrs) and weight (SNP-group 67 ± 8.1 kg, KET-group 69 ± 2.6 kg) between the groups. The preoperative values of

Fig. 8.1.

Table 8.1. Demographic data of the patients in group 1 (ketanserin)

No.	Preoperative Diagnosis	Concomitant Disease	Preoperative PAP	Surgery	Postoperative Inotropics
1	MS	DM	60/32	MVR	dopa
2	AI	-	65/31	AVR	dobut
3	MS/MI	CAOD	68/31	MVR/ACB	dopa/dobut
4	AS	CAOD	58/28	AVR/ACB	dopa
5	AS/AI	COPD	60/30	AVR	dopa
6	MI	DM	71/35	MVR	dobut
7	MI	-	41/23	MPL	dopa
8	MI/TI	RA	68/35	MVR/TPL	dopa/dobut
9	MI	-	60/30	MVR	dopa
10	AS/AI	-	65/35	AVR	dopa
11	AI/MI	-	58/29	AVR/MVR	dopa/dobut
12	MS	COPD	56/25	MVR	dobut

PAP= pulmonary arterial pressure; AI= aortic insufficiency; AS= aortic stenosis;

MI= mitral insufficiency; MS= mitral stenosis; TI= tricuspid insufficiency;

CAOD= coronary artery occlusive disease; COPD= chronic obstructive

pulmonary disease; DM= diabetes mellitus; RA= rheumatic arthritis;

AVR= aortic valve replacement; MVR= mitral valve replacement; TPL= tricuspid valve

plasty; MPL= mitral valve plasty; ACB= aorto-coronary bypass; dopa= dopamine;

dobut= dobutamine.

SPAP, DPAP, MPAP and PVR were significantly higher ($p < 0.05$) in the KET-group.

During the study period in both groups MAP (fig 1), SVR (fig 1), MPAP (fig 2), PVR (fig 2), RVSW (fig 2), and SBP, DBP, SPAP, DPAP, CVP and PCWP (data not depicted) significantly decreased, whereas CO (fig 1) significantly increased. The decrease in MPAP ($p < 0.01$), PVR ($p < 0.01$) and RVSW ($p < 0.05$) was significantly more pronounced in the KET- than in the SNP-group (fig 2). LVSW did not change significantly in the SNP- and KET-groups. Qs/Qt significantly increased ($p < 0.001$) in the SNP-

Fig.8.1.

Changes in mean arterial pressure, cardiac output and systemic vascular resistance and control values (c) in the ketanserin (KET)- and sodium nitroprusside (SNP)-group (mean $\pm$ SEM).

* = $p < 0.001$ (significantly different from c)

Fig. 8.2.

Table 8.2. Demographic data of patients in group II (sodium nitroprusside)

No.	Preoperative Diagnosis	Concomitant Disease	Preoperative PAP	Surgery	Postoperative Inotropics
13	AI	CAOD	58/34	AVR/ACB	dopa
14	MS	DM	55/21	MVR	dobut
15	MI	-	60/22	MVR	dopa
16	AI/MI	COPD	56/24	AVR/MVR	dopa/dobut
17	MI/TI	-	65/28	MVR/TPL	dopa
18	AS/AI	DM	51/24	AVR	dobut
19	AI	-	38/20	AVR	dobut
20	MI	-	51/22	MVR	dopa
21	MI	DM	40/20	MVR	dopa/dobut
22	AS	DM	48/24	AVR	dobut
23	MS	COPD	58/24	MVR	dopa
24	MS/MI	-	65/30	MVR	dopa/dobut
25	AI/MI	-	71/32	AVR/MVR	dopa/dobut
26	AS	CAOD	48/20	AVR/ACB	dopa

For clarification of abbreviations see table 1.

group and significantly decreased ($p < 0.05$) in the KET-group (fig 3); a significantly different change in shunt fraction between the two groups ($p < 0.001$). In 6 patients in the SNP-group pacemaker-induced heart rate converted into a form of spontaneous rhythm (sinus rhythm or atrial fibrillation). This was observed in only 1 patient (sinus rhythm) in the KET-group.

The mean infusion rate in the SNP-group was $0.15 \pm 0.03 \mu\text{g/kg/min}$ sodium nitroprusside, and in the KET-group $2.33 \pm 0.91 \mu\text{g/kg/min}$ ketanserin. Apart from the routine protocol no additional fluids were administered during the study period.

Fig.8.2:

Changes in mean pulmonary arterial pressure, pulmonary vascular resistance and right ventricular stroke work and control values (c) in the ketanserin (KET)- and sodium nitroprusside (SNP)-group (mean $\pm$ SEM).

* = $p < 0.05$ (significantly different from c)

** = $p < 0.001$ (significantly different from c)

+ = $p < 0.05$ (significantly different from SNP-group)

++ = $p < 0.01$ (significantly different from SNP-group)

Discussion

The findings in this study demonstrate that both ketanserin, a specific S_2 -serotonergic receptor antagonist with α_1 -adrenergic receptor blocking properties, and sodium nitroprusside are able to reduce pulmonary hypertension, by decreasing pulmonary vascular resistance, in patients undergoing valvular surgery. In this respect, at the dose levels used ketanserin is more effective, resulting in a more pronounced reduction in right ventricular work following the administration of this compound. In contrast to ketanserin, sodium nitroprusside causes a significant increase in pulmonary

Fig.8.3:

Changes in pulmonary shunt fraction (Qs/Qt) and control values (c) in the ketanserin (KET)- and sodium nitroprusside (SNP)-group (mean $\pm$ SEM).

* = $p < 0.05$ (significantly different from c)

** = $p < 0.001$ (significantly different from c)

+ = $p < 0.001$ (significantly different from SNP-group)

shunt fraction. This finding is in accordance with the results of a previous study performed in patients with normal pulmonary arterial pressure following coronary artery bypass surgery (Van der Starre et al.1986)

From earlier studies it is known that sodium nitroprusside and nitroglycerin may cause hypoxemia by increasing pulmonary shunt fraction (Parsons et al.1981, D'Oliviera et al.1981). Although an increase in shunt fraction might be explained by an increase in cardiac output (Lynch et al.1979), the different influence of both compounds on shunt fraction at similar cardiac output levels suggests that ketanserin, as opposed to sodium nitroprusside, does not abolish the hypoxic pulmonary vasoconstriction. This is particularly advantageous in patients with pulmonary hypertension, who are prone to develop hypoxia. In the present study the shunt fraction is relatively high (16-33%). This is in accordance with the findings in previous studies (Clarke and Jackson 1971). An increase in shunt fraction necessitates an increase in inspired oxygen concentration during mechanical ventilation, to maintain acceptable arterial oxygenation. In addition oxygenation is also jeopardized by the reported impairment of the hypoxic pulmonary vasoconstriction (Heidenstierna et al.1986, Heneghan et al.1984). To optimize oxygenation PEEP was applied which might lead to an increase in PVR (Tyler 1983) and a decrease in cardiac output (Dorinsky and Whitcomb 1983, Jardin et al.1981).

In the immediate post-bypass period pulmonary artery pressure tends to be lower due to decreased viscosity of the blood, as a result of hemodilution, and possibly as a result of the implantation of a competent valve (Zener et al.1972). In the course of the early postoperative period pulmonary arterial pressure increases as a consequence of an increase in blood viscosity and sympathetic tone (McIllduff et al.1980, Heinonen et al.1985, Austen et al.1966, Salmenpera and Heinonen 1986). Because lowering of pulmonary arterial pressure might diminish complications, caused by a further increase in lung water content (Bernard and Brigham 1986) and right ventricular stroke work (Cohn and Franciosa 1977, Sibbald et al.1986), vasodilating agents which reduce pulmonary vascular resistance are primarily administered (Fyman et al.1986). Dobutamine, which was used in the study groups in equal amounts, is a vasodilating agent (Shoemaker et al.1986) able to reduce pulmonary vascular resistance (Molloy et al.1986). However, in the present study dobutamine was mainly used, alone or in combination with dopamine, to increase myocardial contractility (Lappas et al.1977, Sonneblich et al.1979, Lumley et al.1977, Loeb et al.1975, Kirk et al.1978, Salomon et al.1982).

A role for serotonin in pulmonary hypertension has been suggested, since the scavenging function of the lungs with respect to serotonin is impaired in these patients (Vanhoutte et al.1983). Noradrenaline levels are

also elevated, because the clearing capacity of the lungs for noradrenaline during pulmonary hypertension is insufficient. Since serotonin has an amplifying effect on the vasoconstrictive response to noradrenaline (Van Nuten et al.1982, Forster et al.1980), a contribution of these substances to the pathogenesis of pulmonary hypertension has been postulated (Breuer et al.1985).

The transformation from pacemaker dependent heart rate to spontaneous rhythm during the infusion of sodium nitroprusside might be explained by the reflex tachycardia generally observed following the administration of this compound. This was not observed in the patients receiving ketanserin, since ketanserin does not induce reflex tachycardia (Van der Starre et al.1983).

In conclusion both ketanserin and sodium nitroprusside are effective in the reduction of pulmonary hypertension following valvular surgery, but ketanserin has the advantage of lowering rather than increasing the pulmonary shunt fraction.

Summary

In a prospective randomized trial in patients with a history of preoperative pulmonary hypertension, undergoing surgery for valvular replacement or annuloplasty, the effects of ketanserin ($n = 12$) and sodium nitroprusside ($n = 14$) on the systemic and pulmonary circulation and pulmonary shunt fraction (Q_s/Q_t) were studied in the immediate postoperative period. The compounds were administered at the moment that pulmonary arterial pressure tended to rise and cardiac output started to decrease.

Following the administration of the study compounds systemic and pulmonary arterial pressure, systemic and pulmonary vascular resistance, and right ventricular stroke work decreased significantly in both groups. The decrease in mean pulmonary arterial pressure ($p < 0.01$), pulmonary vascular resistance ($p < 0.01$) and right ventricular stroke work ($p < 0.05$) was significantly more pronounced in the ketanserin than in the sodium nitroprusside group. Q_s/Q_t significantly increased ($p < 0.001$) in the nitroprusside group, but significantly decreased ($p < 0.05$) in the ketanserin group; a significantly different response between the two groups ($p < 0.001$). In 6 patients sodium nitroprusside converted pacemaker-dependent heart rate into a spontaneous rhythm, whereas this occurred in only one patient in the ketanserin group.

It is concluded that ketanserin, as opposed to sodium nitroprusside, reduces pulmonary vascular resistance without increasing shunt fraction in the lung, which is particularly advantageous in patients following valvular surgery.

Chapter 9

The α -adrenergic receptor blocking effect of ketanserin and the interaction between α -adrenergic and S_2 -serotonergic receptor blocking in lowering blood pressure in man

Introduction

Ketanserin is a selective S_2 -serotonergic receptor antagonist with α_1 -adrenergic receptor blocking properties (Van Nueten et al.1981, Leysen et al.1981). The compound has shown to be effective in the treatment of high blood pressure, in both essential hypertension (Hedner et al.1985, De Cree et al.1981, Wenting et al.1982) and hypertension following coronary artery bypass surgery (Van der Starre et al.1983, 1986). The mode of action of ketanserin in the treatment of hypertension, however, is incompletely understood. Recent studies in spontaneously hypertensive rats revealed that the antihypertensive effect of ketanserin cannot be explained on the basis of S_2 -serotonergic receptor blocking alone (Hosie et al.1987). In various studies it has been suggested that the antihypertensive activity of ketanserin may be partly attributed to the α_1 -adrenergic receptor blocking properties of the compound (Reiman and Frolich 1983, Pettersson et al.1984, Wenting et al.1984, Vanhoutte 1985, Zabudowski et al.1985, Gasic et al.1985) or to centrally mediated inhibition of sympathetic vascular tone (Phillips et al.1985, McCall and Schuette 1984, Copeland and Bentley 1985). Among the mechanisms postulated the simultaneous blockade of both α_1 -adrenergic and S_2 -serotonergic receptors (Van Nueten et al.1986) is an interesting concept, especially since serotonin and catecholamines have been shown to amplify each other as far as the effect on vascular tone (Van Nueten et al.1982) and arterial blood pressure (Scroop and Walsh 1968) is concerned.

In the present study we investigated the dose dependency of the α_1 -adrenergic receptor blocking properties of ketanserin, if any, the blocking properties of this compound for non-specific stimulation with angiotensin, and the α_1 -adrenergic receptor blocking properties and the blood pressure lowering activity of phentolamine, ritanserin and the combination of both compounds. Phentolamine is a mixed α_1/α_2 -adrenergic receptor antagonist (Champoux and Gauthier 1984, Gould and Reddy 1976) and ritanserin a selective S_2 -serotonergic receptor antagonist practically devoid of α -adrenergic receptor antagonistic effects (Janssen 1985). Phenylephrine was used as α_1 -adrenergic agonist. The study was performed on patients on cardiopulmonary bypass (CPB) undergoing coronary artery bypass grafting (CABG), a model shown to be suitable to investigate the vascular effects of vasoactive agents (Hsu et al.1979, Boldt et al.1985, 1986, Ellmauer and Brandt 1986, Pauca and Roy 1986).

Methods

The study was performed on 121 patients on stable CPB (nasopharyngeal temperature 30-32°C, flow rate 50 ml/kg bw and without the necessity of adding additional fluids) undergoing CABG. Patients with impaired myocardial function and/or peripheral vascular disease were excluded from the study. All patients gave informed consent and the study was approved by the Ethical Committee of the hospital.

The patients were ad random allotted to 11 different groups. The demographic data of the patients are depicted in table 1. The study design (table 2) in the various groups was as follows: 3 min after an initial dose (time 0) of 0.3 mg phenylephrine (a specific α_1 -adrenergic agonist), the study medication was injected, followed by a second and third dose of 0.3 mg phenylephrine at 5 and 10 min. In group 2 (NaCl, see below) only the second dose of phenylephrine was administered to prevent an unacceptable rise in blood pressure. In group 11 (see below) a fourth dose of phenylephrine was administered. Mean arterial blood pressure (MAP) was recorded and measured at one min intervals by means of a pressure transducer connected to a radial artery catheter. In the control group (group 1) except for phenylephrine no study medication was administered. In group 2 10 ml NaCl 0.9% was injected as study medication to assess whether the solvent itself did cause a significant change in MAP and whether the circulation was still sensitive to -stimulation at 5 min. In the groups 3 through 6 the study medication consisted of 2.5, 5, 10, and 20 mg of ketanserin, respectively. In group 7 droperidol (10 mg), a compound with α_1 -adrenergic receptor blocking properties, was used as study medication to assess whether the study design was reliable in this respect. In group 8 2.5 μ g angiotensin, a non-specific vasoconstricting agent, instead of the second dose of phenylephrine was administered following 20 mg ketanserin to assess whether the hypotensive effect of ketanserin was specifically related to α -adrenergic receptor blockade or to a non-specific mechanism. Phentolamine, 2.5 mg (group 9), ritanserin, 10 mg (group 10), and both compounds simultaneously (group 11) were administered as study medication to verify whether an interaction exists between α -adrenergic and S_2 -serotonergic receptor blocking as far as the lowering of arterial blood pressure is concerned. All compounds were administered into the venous reservoir of the oxygenator. The empirically chosen doses of phenylephrine and angiotensin cause an acceptable rise in MAP during CPB without interfering with the routine protocol of pressures and flow.

Table 9.2. Study design in all the groups.

Group	agonist at 0 min	study medication	agonist at 5 min	agonist at 10 min	agonist at 15 min
1	Phene				
2	Phene	NaCl			
3	Phene	Ket	2.5 mg	Phene	
4	Phene	Ket	5 mg	Phene	Phene
5	Phene	Ket	10 mg	Phene	Phene
6	Phene	Ket	20 mg	Phene	Phene
7	Phene	Drop	10 mg	Phene	Phene
8	Phene	Ket	20 mg	Ang	
9	Phene	Phent	2.5 mg	Phene	Phene
10	Phene	Rit	10 mg	Phene	
11	Phene	Phent	2.5 mg	Phene	Phene
		Rit	10 mg		

Phene = Phenylephrine 0.3 mg; NaCl = NaCl 0.9%; Ket = Ketanserin;

Drop = Droperidol; Ang = Angiotensin 2.5 µg; Phent = Phentolamine;

Rit = Ritanserin

Statistical analysis. The Wilcoxon signed rank test was applied to compare differences in MAP after the first administration of phenylephrine ($t=3$ min) and after the administration of the study medication ($t=4$ min). The same analysis was applied to compare changes in MAP following the second and third administration of phenylephrine with those after the first administration of phenylephrine.

The Mann-Whitney U-test was applied to compare the starting values of MAP, i.e. before the first administration of phenylephrine, between the various groups, the changes in MAP following the first administration of phenylephrine with those in the same period in the control group (group 1), the changes in MAP following the administration of the second dose of phenylephrine with those in the same period in group 2, the changes in MAP following the administration of the study medication in the different groups with those in the same period in group 2, and the changes in MAP following the administration of angiotensin (group 8) with those after the second dose of phenylephrine in group 6. To evaluate the effect of interventions on the response to the phenylephrine administrations in the various groups the changes in MAP after the second and third dose of phenylephrine were divided by the change in MAP following the first administration of this compound (A- and B-ratio, respectively). The A-ratios, as obtained in the various experimental groups, were compared with the

ratio obtained in the control (NaCl) group. The A- and B-ratios in the 5,10 and 20 mg ketanserin-groups and in the droperidol-group were also compared with each other, because only in these groups phenylephrine was administered for the third time. Differences, if any, were evaluated for statistical significance with the use of the Mann-Whitney U-test.

Apart from changes in MAP within the groups, in group 9 through 11, differences in the changes in MAP between the groups at comparable intervals were statistically evaluated by applying the Mann-Whitney U-test, group 9 serving as control.

The Mann-Whitney U-test was also used to evaluate differences in age and weight for statistical significance. Fisher's exact test was applied for the analysis of sex differences between the groups. The data are presented as mean $\pm$ SEM.

Results

There were no significant differences in age, weight and sex distribution between the patients in the various groups (Table 1). Except for the droperidol group (group 7), in the various groups the mean value of MAP before the first administration of phenylephrine was not significantly different from this value in the control group (group 1). Before the administration of phenylephrine the MAP value was significantly lower in the droperidol group ($p < 0.05$).

In all groups the first administration of phenylephrine significantly increased MAP (Fig 1 through 4). This increase was maintained during the

Table 9.1. Demographic data of all the groups (mean $\pm$ SEM)

Group	Number	Age (Yrs)	Weight (kg)	Male	Female
1	12	63.5 $\pm$ 1.55	68.4 $\pm$ 2.69	9	3
2	13	62.4 $\pm$ 1.71	74.8 $\pm$ 2.03	11	2
3	10	61.1 $\pm$ 1.95	74.7 $\pm$ 1.50	8	2
4	12	63.4 $\pm$ 2.13	70.8 $\pm$ 1.83	7	5
5	12	59.1 $\pm$ 1.13	70.1 $\pm$ 2.49	9	3
6	13	58.7 $\pm$ 2.71	73.0 $\pm$ 2.42	8	5
7	11	60.5 $\pm$ 2.07	74.7 $\pm$ 2.78	8	3
8	12	62.4 $\pm$ 1.95	75.4 $\pm$ 1.90	10	2
9	8	58.0 $\pm$ 3.00	72.3 $\pm$ 3.47	4	4
10	9	63.2 $\pm$ 1.68	74.1 $\pm$ 1.63	7	2
11	9	61.6 $\pm$ 2.86	74.6 $\pm$ 2.63	6	3

Fig. 9.1.

observation period of 13 min (Fig 1). Ketanserin (2.5, 5, 10 and 20 mg) caused a significant reduction of MAP ($p < 0.001$; Fig 2 and 3) as compared to the NaCl group (Fig 1), but the decrease in MAP after the administration of 2.5 mg ketanserin was significantly less than after the injection of 5 mg ($p < 0.05$), and 10 and 20 mg ($p < 0.01$). Droperidol (10 mg) significantly lowered MAP (Fig 2), as compared to the NaCl group. The reduction of MAP was more pronounced after the injection of droperidol than after the administration of 2.5 mg ketanserin ($p < 0.01$).

After the injection of 20 mg ketanserin, 2.5 μ g angiotensin caused a significantly higher increase in MAP ($p < 0.001$) than 0.3 mg phenylephrine (Fig 3). As compared to the NaCl group the A-ratio's were significantly smaller in the droperidol and all ketanserin groups than in the NaCl group (Table 3). The A-ratios in the 10 and 20 mg ketanserin groups were significantly smaller than those in the 2.5 mg and 5 mg ketanserin groups, and the droperidol group ($p < 0.05$ and $p < 0.01$, respectively). The A-ratio in the 5 mg ketanserin group was significantly smaller ($p < 0.05$) than that in the 2.5 mg ketanserin group. These ratios were not significantly different from the ratio in the droperidol group. The B-ratio in the 20 mg ketanserin group was significantly lower ($p < 0.001$) than that in the other groups, whereas the B-ratio in the 10 mg ketanserin group was significantly lower ($p < 0.01$) than that in the 5 mg ketanserin and droperidol groups. There was no significant difference in B-ratios between the 5 mg ketanserin and droperidol groups.

Phentolamine caused a significant decrease ($p < 0.05$) in MAP. The increases in MAP following the second and third dose of phenylephrine, administered after phentolamine, were significantly smaller ($p < 0.01$) than after the first dose (Fig 4). The administration of ritanserin did not significantly change MAP, while the increases in MAP were not significantly different following the first and the second administration of phenylephrine (Fig 4). The combination of phentolamine and ritanserin caused a significantly greater ($p < 0.01$) decrease in MAP as compared with the reduction of MAP after the injection of phentolamine alone (Fig 4). The increases in MAP following the second and third dose of phenylephrine

Fig 9.1.

Changes in mean arterial blood pressure (MAP, mean $\pm$ SEM) following the injection of 0.3 mg phenylephrine (t) alone (top), and before and after NaCl (bottom, control group).

* = $p < 0.01$ vs time = 0 min

** = $p < 0.01$ vs time = 5 min

Fig. 9.2.a.

Fig. 9.2.b.

Table 9.3. The degree of α_1 -adrenergic receptor blockade by ketanserin and droperidol, as assessed from A- and B-ratio's.

study medication	A-ratio	B-ratio
NaCl (control group)	0.99	--
Ketanserin 2.5 mg	0.49*	--
5 mg	0.30*	0.36*
10 mg	0.16*	0.25*
20 mg	0.10*	0.17*
Droperidol 10 mg	0.25*	0.48*

* = significant difference ($p < 0.01$) with respect to control group (NaCl)

A-ratio = the increase in mean arterial pressure (MAP) after the second dose of phenylephrine divided by the increase in MAP following the first dose of phenylephrine.

B-ratio = the increase in MAP after the third dose of phenylephrine divided by the increase in MAP following the first dose of phenylephrine.

were significantly smaller ($p < 0.01$) after the administration of the combination than after the injection of phentolamine alone (Fig 4). After the injection of the combination of both compounds the increase in MAP following a fourth dose of phenylephrine was still significantly less than after the first administration (Fig 4).

Discussion

The findings in this study show that ketanserin reduces the α_1 -agonistic effect of phenylephrine on blood pressure in a dose-dependent way up to a dose of 10 mg; a dose of 20 mg ketanserin does not further decrease blood pressure (fig 5). Even a moderate dose of 2.5 mg ketanserin causes a relatively substantial decrease in blood pressure. The degree and dura-

Fig 9.2.a. and Fig 9.2.b.

Changes in mean arterial blood pressure (MAP, mean $\pm$ SEM) in the ketanserin 2.5, 5 and 10 mg groups and the droperidol 10 mg group.

(t) = 0.3 mg phenylephrine

☆ = $p < 0.001$ vs NaCl (control) group

* = $p < 0.05$ (changes in MAP after the injection of phenylephrine at $t=5$ min and $t=10$ min vs change in MAP after phenylephrine at $t=0$ min).

tion of the α_1 -receptor blocking effect appeared to be dose-dependent as well, since the decreases in A- and B-ratio's were significantly more pronounced at increasing doses of ketanserin (table 3). The results obtained with the α_1 -adrenergic receptor blocking compound droperidol indicate that the model of cardiopulmonary bypass and moderate hypothermia is suitable to study this type of properties of drugs. The blood pressure lowering and α_1 -adrenergic receptor blocking effect of 5 mg ketanserin appeared to be comparable with those of 10 mg droperidol. The observation that ketanserin did not affect the increase in mean arterial blood pressure as induced by angiotensin, a non-specific vasoconstricting agent, indi-

Fig 9.5.

Decrease in mean arterial blood pressure (Δ MAP, mean $\pm$ SEM) following 2.5, 5, 10 and 20 mg ketanserin. Note the dose-dependent decrease up to a dose of 10 mg, when a maximum effect is reached.

* = $p < 0.05$ vs MAP in the 2.5 mg group

** = $p < 0.01$ vs MAP in the 2.5 mg group

Fig. 9.3.

cates that the α -blocking properties of Ketanserin are specific.

The findings in the present study also show that the blood pressure lowering effect of ketanserin cannot be explained by S_2 -serotonergic receptor blockade alone, since ritanserin, a specific S_2 -serotonergic antagonist which is rather devoid of α_1 -blocking properties, did not change mean arterial blood pressure. The moderate blood pressure lowering effect of phentolamine is substantially potentiated by ritanserin, demonstrating that combined S_2 -serotonergic and α -adrenergic receptor blocking is required to obtain a substantial reduction in blood pressure. Since ketanserin combines these two properties, it is likely that the blood pressure lowering effect of this compound results from blocking both S_2 -serotonergic and α_1 -adrenergic receptors.

A critique on the present study may be that we used phentolamine, a mixed α_1/α_2 -adrenergic receptor antagonist (Champoux and Gauthier 1984, Gould and Reddy 1976), rather than prazosin, a specific α_1 -adrenergic receptor antagonist, but in The Netherlands this compound is not available in the intravenous form for clinical use.

The model of cardiopulmonary bypass was used in this study because it is considered to be suitable to investigate the peripheral effects of vasodilating agents since feed back mechanisms through the heart are abolished (Hsu et al. 1979, Boldt et al. 1985, 1986, Ellmauer and Brandt 1986, Pauca and Roy 1986). At a constant flow rate the changes in MAP reflect the effect of the compounds on peripheral vascular resistance. The relatively long-lasting increase in arterial blood pressure following the injection of phenylephrine under these experimental circumstances (Fig 1) is a well-known, but incompletely understood phenomenon. It may be possible that the phenylephrine administered interacts with circulating catecholamines, the level of which is increased during cardiopulmonary bypass, or that the metabolism of the compound is delayed because of the

Fig 9.3.

Changes in mean arterial blood pressure (MAP, mean $\pm$ SEM) in the Ketanserin 20 mg-groups.

(▲) = 0.3 mg phenylephrine (top)

angiotensin (t) = 2.5 μ g angiotensin (bottom)

☆ = $p < 0.001$ vs NaCl (control) group

* = $p < 0.001$ (changes in MAP after the injection of phenylephrine at $t=5$ min and $t=10$ min vs change in MAP after phenylephrine at $t=0$ min)

+ = $p < 0.001$ (difference between the groups with respect to the change in MAP after the injection of phenylephrine (top) or angiotensin (bottom) at $t=5$ min).

Fig. 9.4.

moderate hypothermia.

In conclusion the results of the present study indicate that ketanserin has α -blocking properties, but that the blood pressure lowering activity of ketanserin likely results from a combined blockade of α_1 -adrenergic and S_2 -serotonergic receptors.

Summary

The α_1 -adrenergic receptor blocking effect of ketanserin, the blocking properties of this compound for non-specific stimulation with angiotensin, and the α -adrenergic receptor blocking properties and the blood pressure lowering effect of phentolamine, ritanserin and the combination of both compounds were studied in patients on cardiopulmonary bypass (constant flow rate, mild hypothermia) undergoing coronary artery bypass grafting. Phenylephrine was used as α_1 -adrenergic agonist. Ketanserin is a selective S_2 -serotonergic receptor antagonist with α_1 -adrenergic receptor blocking properties and ritanserin a selective S_2 -serotonergic receptor antagonist practically devoid of α -adrenergic receptor antagonistic effects. Phentolamine is a mixed α_1 -/ α_2 adrenergic receptor antagonist.

Ketanserin reduces the α_1 -agonistic effect of phenylephrine on blood pressure in a dose dependent way up to a dose of 10 mg. Ketanserin did not block the non-specific vasoconstriction, as induced by angiotensin. The moderate blood pressure lowering effect of phentolamine was substantially potentiated by ritanserin, which in itself did not affect blood pressure.

The findings in this study indicate that the blood pressure lowering activity of ketanserin results from a combined blockade of α_1 -adrenergic and S_2 -serotonergic receptors.

Fig 9.4.

Changes in mean arterial blood pressure (MAP, mean $\pm$ SEM) in the Ritanserin 10 mg, Phentolamine 2.5 mg and Ritanserin 10 mg $\pm$ Phentolamine 2.5 mg groups.

Δ = $p < 0.01$ vs time = 0 min

$\Delta\Delta$ = $p < 0.01$ vs time = 5 min

$\star$ = $p < 0.001$ vs NaCl (control) group $\pm$ = $p < 0.01$ (difference in change in MAP after the injection of phentolamine (middle) vs phentolamine + ritanserin (bottom) at $t=3$ min)

$*$ = $p < 0.001$ (difference in changes in MAP after the injection of phenylephrine at $t=5$, $t=10$ and $t=15$ min vs change in MAP after phenylephrine at $t=0$ min).

Chapter 10

Peripheral vascular effects of ketanserin and nifedipine during cardiopulmonary bypass

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J Hypertension (in press)

Introduction

Ketanserin, a specific S_2 -serotonergic receptor antagonist (Van Nueten et al.1981, Leysen et al.1981) with α_1 -adrenergic receptor blocking properties (Reimann and Frohlich 1983, Zabudowski et al.1985)), was reported to be an effective antihypertensive agent in patients with essential hypertension (Wenting et al.1984, De Cree et al.1981, McGourty et al.1984, Wing et al.1984), preeclamptic hypertension (Weiner et al.1984) and per- and postoperative hypertension (Van der Starre et al.1983, Griffiths and Whitwam 1986, Cashman et al.1986, Nalda et al.1985) following coronary artery bypass grafting (CABG). Haemodynamic investigations showed that ketanserin lowers arterial blood pressure by decreasing systemic vascular resistance without causing reflex tachycardia, as opposed to, for example, sodium nitroprusside (Griffiths and Whitwam 1986, Van der Starre et al.1984). Recently the mechanism responsible for the vasodilating properties of ketanserin has been ascribed to amplification of the S_2 -serotonergic and α_1 -adrenergic receptor blocking properties of the compound (Van der Starre et al.1987, Van Nueten et al.1986).

Nifedipine, a calcium channel blocking compound, has been extensively studied as cardioprotective (Clark et al.1979, Henry et al.1980) and anti-anginal agent (Emanuelson and Holmberg 1983, Moses et al.1981). More recently the compound was shown to have antihypertensive properties as well (Franklin et al.1986, Van Wezel et al.1986). It was the aim of the present prospective double blind study to investigate the peripheral vascular effects of ketanserin and nifedipine in patients on cardiopulmonary bypass (CPB). CPB was chosen as study model since it offers the possibility to measure independently changes in arterial and venous vascular resistance without the interference of reflex mechanisms of the heart (Hsu et al.1979, Boldt et al.1985,1986, Pauca and Roy 1986).

Materials and methods

In a double blind prospective study including two groups of 10 patients undergoing coronary artery bypass grafting (CABG) 10 mg ketanserin or 2 mg nifedipine were injected into the venous reservoir of the oxygenator during stable CPB when mean arterial blood pressure (MAP) was higher than 50 mmHg. All patients had a normal myocardial function and no peripheral vascular disease. They gave informed consent and the protocol was approved by the Ethical Committee of the hospital. The intravenous anesthetic technique consisted of fentanyl 75 μ g/kg, pancuronium bromide 0.1 mg/kg and midazolam 0.15 mg/kg. The patients were ventilated

with 100% O₂ and no inhalational agents were used. If hypertension (systolic blood pressure higher than 130 mm Hg) developed in the pre-bypass period, a nitroglycerin infusion was started. No anesthetics were administered during the study period in which the flow rate was kept constant at 50 ml/kg bw/min and the temperature (nasopharyngeal) at approximately 30°C. No fluids were added unless the fluid level in the reservoir of the oxygenator (Harvey) tended to become unacceptably low.

After the administration of the study medication MAP and the fluid level in the venous reservoir of the oxygenator were recorded after 30 sec, 1, 5 and 10 min. The Wilcoxon signed rank test was applied to evaluate intra-group differences and the Mann-Whitney U-test to evaluate intergroup differences for statistical significance. A probability value of $p < 0.05$ was considered to indicate a significant difference.

Results

The groups were comparable as far as age, weight and sex distribution are concerned (table 1). There was also no significant difference in the MAP

Table 10.1 Demographic data of the patients in both groups (mean $\pm$ SEM)		
	Ketanserin group	Nifedipine group
number (n)	10	10
age (years)	56 $\pm$ 11.3	60 $\pm$ 7.6
weight (kg)	75 $\pm$ 8.7	74 $\pm$ 6.9
sex (male/female)	9/1	8/2
The differences between the two groups were not statistically significant		

values and the fluid level in the venous reservoir of the oxygenator at the moment of the administration of the study medication (control values). After the injection of ketanserin MAP significantly decreased from 55 ± 2.5 to 38 ± 2.4 mmHg at 1 min ($p < 0.01$) and to 47 ± 2.3 mmHg at 5 min ($p < 0.05$). The control values were reached again 10 min after injection. (fig 1). The fluid level of the venous reservoir was significantly lower 5 and 10 min ($p < 0.05$) after the administration of the compound. At 10 min the level was significantly lower ($p < 0.05$) than at 5 min (fig 2). Immediately following the study period in 4 patients additional fluid (Ringer's lactate) had to be infused to prevent the fluid level in the venous

reservoir from falling to an unacceptably low level. After the injection of nifedipine MAP significantly decreased from 59 ± 3.2 to 44 ± 4.6 mmHg at 1 min ($p < 0.01$) and to 48 ± 4.9 mmHg at 5 min ($p < 0.05$). Ten min after injection the MAP values were not significantly different from the control values anymore (fig 1). The fluid level in the venous reservoir was slightly, but significantly increased at 1 min ($p < 0.05$). Five and 10 min after administration of the compound the levels were not significantly different from those in the control situation (fig 2). There were no significant differences between the changes in MAP in both groups, but at 10 min the

Fig.10.1

Changes in mean arterial blood pressure (MAP, mean $\pm$ SEM) during cardiopulmonary bypass following the administration of 10 mg ketanserin or 2 mg nifedipine.

...●... = nifedipine

—○— = ketanserin

* = $p < 0.05$ (intragroup)

fluid level in the venous reservoir was significantly lower ($p < 0.05$) in the ketanserin than in the nifedipine group.

Discussion

The findings in this study indicate that both ketanserin and nifedipine are potent arterial vasodilating agents, but that ketanserin, unlike nifedipine,

Fig.10.2

Changes in the fluid level of the venous reservoir of the oxygenator (VR, mean $\pm$ SEM) during cardiopulmonary bypass following the administration of 10 mg ketanserin or 2 mg nifedipine.

··●·· = nifedipine
—○— = ketanserin
* = $p < 0.05$ (intragroup)
+ = $p < 0.05$ (intergroup)

also dilates venous capacitance vessels. Venous vasodilatation might be important in antihypertensive treatment during and following cardiac surgery since venous tone gradually increases in the course of cardiopulmonary bypass (Gall et al.1982) due to increased catecholamine levels, mainly caused by hypothermia (Chernow et al.1983), hemodilution (Hine et al.1976) and non-pulsatile flow (Landymore et al.1979). The blood pressure lowering effect of ketanserin probably results from an interaction between the S_2 -serotonergic and α_1 -adrenergic receptor blocking properties of the compound, because S_2 -serotonergic receptor blockade alone did not change arterial blood pressure, but significantly potentiated the decrease in arterial blood pressure, as induced by α_1 -adrenergic receptor blockade (Van der Starre et al.1987).

Recently the antihypertensive activity of nifedipine has been studied (Hess and Meyer 1986, Majid and De Jong 1982) in patients with ischemic heart disease. Reflex tachycardia was reported as the main side effect. Such a reflex mechanism could also be responsible for the short-lasting venous vasoconstriction observed in this study. Apparently the arterial and venous side of the vasculature react differently when exposed to calcium channel blockers, which has been suggested before (Van Nueten and Wellens 1979, Mostbeck et al.1976). Calcium also plays a role in serotonergic-receptor stimulation (Erne and Pletscher 1985, Maggi et al.1983), but mainly as second messenger. The reflex tachycardia during antihypertensive treatment with nifedipine might be harmful to ischemic myocardium since it likely increases oxygen demand of the already deprived myocardium. Although ketanserin dilates both arterial and venous vessels, like nitroprusside and nitroglycerin (Gerson et al.1982), heart rate does not change during antihypertensive treatment with this compound (Van der Starre et al.1986). Ketanserin might block the baroreceptor reflex to arterial and venous vasodilatation as a consequence of a central mode of action (Phillips et al.1985, Copeland and Bentley 1985, McCall and Schuette 1984, Lakoski and Aghajanian 1985).

In conclusion ketanserin and nifedipine were found to be effective in lowering arterial blood pressure. Ketanserin appeared to have a dilating effect on both the arterial and the venous side of the vasculature, while nifedipine only dilates arterial vessels. Therefore, in the antihypertensive treatment during and following cardiac surgery ketanserin might have advantages over nifedipine, since venous tone is generally increased under these circumstances. Besides, the previously reported reflex tachycardia, as induced by nifedipine, is an unwanted side effect.

Summary

Ketanserin, a selective S_2 -serotonergic receptor antagonist with α_1 -adrenergic receptor blocking properties, as well as nifedipine, a classic calcium channel blocker, is used as antihypertensive agent during and following cardiac surgery. In a double blind prospective study, using hypothermic cardiopulmonary bypass as study model, ketanserin (10 mg iv) and nifedipine (2mg iv) were evaluated with respect to their effects on the peripheral circulation. The results showed that ketanserin and nifedipine dilate the arterial side of the vasculature, but that ketanserin, unlike nifedipine, also dilates the venous capacitance vessels; nifedipine even caused a short-lasting venous vasoconstriction. Since venous tone is increased during and following cardiopulmonary bypass, antihypertensive treatment with ketanserin might be advantageous under these circumstances.

Chapter 11

General discussion

General discussion

The findings in the studies presented in this thesis indicate that ketanserin is effective in the treatment of hypertension during and following coronary artery bypass surgery, but does not completely prevent per- and post-operative hypertension when administered as a continuous infusion from the start of anesthesia. The compound is also effective in the treatment of pulmonary hypertension. In contrast to sodium nitroprusside, ketanserin does not induce a reflex tachycardia and does not increase the pulmonary shunt fraction, either in the treatment of postoperative hypertension following coronary artery bypass surgery or in the treatment of pulmonary hypertension following valvular surgery. The compound improves diuresis peroperatively, and was found to be a potent arterial and venous vasodilating agent, in contrast to the calcium entry blocker nifedipine, which only dilates arterial vessels.

The antihypertensive effect of ketanserin in the postoperative period is caused by a decrease in systemic vascular resistance. A continuous infusion of ketanserin to prevent hypertension during surgery caused a lowering of arterial blood pressure, associated with a reduction of cardiac output and heart rate, and an increase in systemic vascular resistance, although this latter effect remained within acceptable limits. The higher systemic vascular resistance during ketanserin infusion than during infusion of its solvent can be explained by the significantly less frequent use of nitroglycerin in the ketanserin group. The decrease in arterial blood pressure in the presence of an increase in systemic vascular resistance probably results from predominant venous vasodilatation, especially since stroke volume decreases under these circumstances.

From the findings in the first clinical studies of this thesis it was concluded that serotonin plays a major role in the genesis of postoperative hypertension. At that time only the S_2 -serotonergic receptor blocking effects of ketanserin were known. Later the assumption was made that the blood pressure lowering effect of ketanserin is specifically due to α_1 -adrenergic receptor blockade (Reimann and Fröhlich 1983a, Gasic et al. 1985). However this is unlikely since ketanserin also lowers arterial blood pressure in patients with complete autonomic insufficiency (Wenting et al. 1984). Since ritanserin, a specific S_2 -serotonergic antagonist devoid of α_1 -adrenergic receptor blocking properties, does not affect arterial blood pressure, a pure S_2 -serotonergic receptor blockade as explanation for the blood pressure lowering effect is also unlikely. According to the findings in the study presented in chapter 9, ketanserin clearly demonstrates α_1 -adrenergic receptor blocking properties, since the α_1 -agonistic effect of phenylephrine was dose-dependently antagonized.

The maximal blood pressure lowering effect was obtained with a dose of 10 mg ketanserin IV. Increasing the dose up to 20 mg resulted only in an increase of the duration of the α_1 -adrenergic receptor blocking effect. In the same study S_2 -serotonergic receptor blockade appeared to amplify the α -adrenergic receptor blocking effect of phentolamine. This finding is in agreement with a previous study in animals (Van Nueten et al.1986), in which an interaction between S_2 -serotonergic and α -adrenergic receptor blockade was also reported. It is concluded that pre- and postoperative hypertension can be effectively treated by simultaneously blocking α_1 -adrenergic and S_2 -serotonergic receptors. Ketanserin combines both properties.

Heart rate does not change during the administration of ketanserin. This might be due to an interaction with the baroreceptor reflex (Smits et al.1987), but in a recent study in rabbits (Takata et al.1986) an alteration of baroreceptor function was found not to be involved in the antihypertensive effects of ketanserin. Several authors have suggested the possibility that ketanserin has a central mode of action (Pettersson et al.1984, Lakoski et al.1985, Mylechrane et al.1985), leading to an increased vagal and a decreased sympathetic activity (McCall and Schuette 1984). This could be an explanation for the absence of reflex tachycardia. In this context Fozard (1982) reported a reduction of heart rate in rats treated with ketanserin, which could be inhibited by vagotomy. An alternative explanation for the absence of reflex tachycardia could be that ketanserin directly slows the pacemaker-function of the sinus node (Saman et al.1985), but this could not be confirmed in a study in closed-chest dogs (Van de Water et al.1978). In a study on dogs (Furukawa et al.1986) the negative chronotropic effect of ketanserin was potentiated by propranolol. Since all the patients undergoing coronary artery bypass surgery studied were preoperatively treated with beta-adrenergic receptor blockers, an interaction between ketanserin and the residual level of beta-adrenergic receptor blockade might be postulated. Van de Water et al. (1985) observed an increase in heart rate after the acute administration of ketanserin in an intact dog model. This discrepancy with the reported clinical studies is incompletely understood, but might result from differences in baroreceptor sensitivity.

The finding that ketanserin is a potent dilator of the venous capacitance vessels is particularly important for patients undergoing cardiac surgery since cardiopulmonary bypass causes a substantial increase in venous tone (Gall et al.1982). In a study on human saphenous veins (Docherty and Hyland 1986) this effect was ascribed to specific S_2 -serotonergic receptor blockade, since α_1 - and α_2 -adrenergic receptor blocking compounds did not affect the serotonin induced contractions. In portal hypertensive rats ketanserin substantially reduced portal pressure

(Cummings et al.1986) due to venous dilatation and pooling of blood in the portal venous system. This effect was assumed to be secondary to blockade of S_2 -serotonergic receptors.

In the study on the venous dilatory properties of ketanserin (chapter 10) and in the study on the underlying mechanism of the blood pressure lowering effect of the ketanserin (chapter 9), cardiopulmonary bypass was used as study model, since it gives the opportunity to evaluate the peripheral effects of a compound without interference from reflex mechanisms of the heart. It was interesting to observe that peripheral (skin) temperature increased during the continuous infusion of ketanserin, despite a simultaneous increase in systemic vascular resistance. This effect might be related to specific S_2 -serotonergic receptor blockade in the skin.

The continuous infusion of ketanserin during surgery induces a significant increase in diuresis before and during cardiopulmonary bypass. The underlying mechanism of this effect is unclear. Previous reports mentioned that serotonin has an antidiuretic effect and causes vasoconstriction of the renal vessels (Garattini and Valzelli 1965). The presence of vasoconstricting agent identified as serotonin was related to the often observed oliguria during and following cardiopulmonary bypass (Frick 1960, Sarajas et al.1959). Recently glomerular filtration rate and renal blood flow were reported to remain unchanged during the administration of ketanserin despite a decrease in arterial blood pressure (Woittiez et al.1985, De Leeuw and Birkenhager 1985). In dogs ketanserin reversed the serotonin induced decrease in renal blood flow at a dose level not affecting the response to the administration of phenylephrine, indicating that this effect of ketanserin may be due to specific S_2 -serotonergic receptor blockade (Blackshear et al.1986). It is postulated that the improved diuresis during ketanserin infusion results from an enhanced renal blood flow, which is an important phenomenon since acute renal failure often complicates major surgery (Abel et al.1980, Hilberman et al.1979).

The finding that ketanserin does not increase pulmonary shunt fraction is particularly important for patients undergoing cardiac surgery, since shunt fraction substantially increases during these procedures due to such mechanisms as an increase in extravascular lung water (Boldt et al.1986, Gallagher 1985), complement activation (Chenoweth et al.1981, Jones et al.1982), mechanical ventilation and general anesthesia (Rehder et al.1975). The routine use of vasodilating agents like sodium nitroprusside, nitroglycerin and hydralazine cause an increase in pulmonary shunt fraction (D'Oliviera et al.1981, Berthelsen et al.1986, Sandoval et al.1986, this thesis) because they abolish the hypoxic pulmonary vasoconstriction. Apparently ketanserin does not cause a change in the distribution of pulmonary blood flow. In patients with pulmonary hypertension the scaven-

ging function of the lungs with respect to catecholamines and serotonin was reported to be reduced (Gillis et al. 1974), causing increased activity of these vasoactive compounds. Since ketanserin induces both S_2 -serotonergic and α_1 -adrenergic receptor blockade, the treatment of these patients with ketanserin, aiming at a reduction of pulmonary artery pressure may be preferred.

The findings in this thesis indicate that serum levels of serotonin do not change during and following cardiopulmonary bypass. This is in contradiction with the reports of other authors who previously suggested the involvement of serotonin in the development of perioperative hypertension (Sarajas et al.1959, Ilicin et al.1972, Replogle et al.1962, Swank et al.1964). The present findings are in agreement with those of Demos et al. (1970), Anger et al.(1986) and Feddersen (1985) who obtained similar results. This does not necessarily exclude a role for serotonin in the genesis of hypertension during and following coronary artery bypass surgery. The absence of an increase in serum serotonin levels might result from rapid elimination of serotonin from the plasma by endothelial cells and/or platelets. Serotonin amplifies the vasoconstrictive response induced by catecholamines (Van Nueten et al.1982), indicating that relatively small amounts of serotonin, locally released from activated platelets, might be enough to induce constriction of smaller arteries and arterioles, and hence cause hypertension.

In conclusion ketanserin, in patients undergoing coronary artery surgery, appeared to be an effective antihypertensive agent without causing an increase in heart rate and pulmonary shunt fraction. Ketanserin causes a stable hemodynamic condition if administered as a continuous infusion during surgery. Ketanserin induces an increase in diuresis before and during cardiopulmonary bypass. It reduces pulmonary artery pressure in patients with pulmonary hypertension following valvular surgery. The assumption that serotonin plays a role in the etiology of per and postoperative hypertension could not be confirmed. The blood pressure lowering effect of ketanserin may be explained by both α_1 -adrenergic and S_2 -serotonergic blockade.

Chapter 12

Summary

Summary

An important problem for the anesthesiologist is the prevention and treatment of hypertension during and following cardiac surgery.

In the introduction of this thesis the incidence and causes of this form of hypertension is reviewed. A distinction is made between the type of hypertension which develops before the start of cardiopulmonary bypass, during cardiopulmonary bypass, in the period immediately following the termination of cardiopulmonary bypass and postoperatively, in the first hours after arrival in the intensive care unit (ICU). The treatment of hypertension is particularly important in the period before cardiopulmonary bypass because it can cause myocardial damage, increased blood loss and possibly cerebral haemorrhage, especially in the elderly patient. Hypertension in this period is mainly caused by the stress of laryngoscopy, intubation, sternotomy and sternal spread. During these manipulations pressor effects occur leading to a significant increase in the plasma levels of catecholamines, vasopressin as well as renin and angiotensin. Increased plasma serotonin levels may also play a role.

Hypertension during cardiopulmonary bypass has other causes. The concentrations of catecholamines in the plasma increase, particularly under the influence of hemodilution, hypothermia, hypotension and the application of non-pulsatile flow. During cardiopulmonary bypass damage of blood platelets occurs, leading to the release of beta-thromboglobulin, platelet factor-4, thromboxane B₂ and possibly serotonin. In the period immediately following cardiopulmonary bypass hypertension rarely occurs because the heart has to recover from the ischemic insult resulting from aortic clamping during CPB. At this stage hypertension may develop only in the presence of severe peripheral vasoconstriction.

In the early postoperative phase in the ICU hypertension often develops (40-60% of the coronary bypass patients). Factors like the maintained elevated plasma levels of catecholamines, the diminishing efficacy of the pre-operative beta-blockade may be responsible for this hypertension. The patients arousal during this period may lead to intolerance of the endotracheal tube which may also cause hypertension. It is unclear whether serotonin plays a role in this process. In this phase hypertension may cause the same complications as in the period before cardiopulmonary bypass. In addition it is assumed that hypertension may lead to early closure of coronary bypass grafts.

Because perioperative hypertension is generally treated by means of vasodilators, a review is presented of the existing intravenous antihypertensive agents of which sodium nitroprusside and nitroglycerin are most commonly used. Recently developed antihypertensive compounds, like

urapidil, adenosine and ketanserin are discussed. The latter is a S_2 -serotonergic receptor antagonist with α_1 -adrenergic receptor blocking properties, which was found to be effective in the treatment of patients with essential hypertension.

Thereafter a short review is presented of the origin, metabolism and effects of serotonin. Serotonin is synthesized in the chromaffine cells of the gastro-intestinal tract. After release the compound is almost completely metabolized in the liver. The residual serotonin is taken up by endothelial cells, especially in the lung. Small amounts of serotonin, which pass the lung, are stored in blood platelets, resulting in very small amounts of free serotonin in plasma. Serotonin may cause vasodilatation as well as vasoconstriction, depending of the type of blood vessel and the basic vascular tone. Serotonin is liberated from aggregating platelets causing for example vasoconstriction in arteries, an effect mediated by S_2 -serotonergic receptors. Serotonin dilates arterioles probably via S_1 -serotonergic receptors, an effect in which the "endothelium-derived relaxing factors (EDRF)" may play a role. Serotonin also amplifies vasoconstriction, as induced by vasoconstricting agents, like catecholamines and angiotensin. Especially through this mechanism serotonin is believed to play a role in the origin of hypertension. In pathological conditions like atherosclerosis, pulmonary hypertension, endotoxic shock and eclampsia, an increased activity of serotonin has been demonstrated. Eventually in the last part of the first chapter the aim of this thesis is presented.

In the second chapter a short review is presented of the pharmacology of ketanserin. Ketanserin is a specific S_2 -serotonergic receptor blocker with α_1 -adrenergic receptor blocking properties. The compound is devoid of S_1 -serotonergic receptor blocking properties. It is a quinazoline derivative with a half life of 15 hours. Ketanserin is mainly metabolized in the liver to non-active metabolites. The most important application is its use as antihypertensive agent, especially in patients with essential hypertension, preeclampsia, pulmonary hypertension and neurogenic hypertension. It is also administered in patients with peripheral vascular disease like Raynaud's disease, Burger's disease and diabetes mellitus. Before the start of this thesis the antihypertensive effect of ketanserin was ascribed to different mechanisms: sole S_2 -serotonergic receptor blockade, sole α_1 -adrenergic receptor blockade, a combination of both or a blockade of the sympathetic outflow of catecholamines by an interaction on central α_1 -adrenergic receptors.

The clinical part of the thesis starts with a review of the techniques applied in anesthesia, surgery, cardiopulmonary bypass and general post-operative treatment (chapter 3).

The first clinical study (chapter 4) consists of a double blind prospec-

tive study, in which ketanserin or the solvent of ketanserin is administered pre and postoperatively as a continuous infusion in patients undergoing coronary artery bypass surgery. Changes in hemodynamics and the plasma levels of humoral factors are measured. In addition the amounts of fentanyl and nitroglycerin administered are determined, as well as perioperative diuresis. During ketanserin infusion blood pressure, heart rate and cardiac output are reduced, and peripheral vascular resistance is higher than during solvent administration. In both groups the plasma levels of catecholamines, renin and angiotensin increase significantly during and following surgery, but the concentrations of serotonin do not significantly change. In the ketanserin group the peripheral (skin) temperature and diuresis are higher, which might be caused by specific S_2 -serotonergic receptor antagonism in these tissues. During the infusion of ketanserin lower doses of fentanyl and less frequent administrations of nitroglycerin are necessary to treat hypertensive episodes.

In chapter 5 an open study is presented showing that ketanserin is effective in the treatment of postoperative hypertension following coronary surgery. The decrease in blood pressure is caused by a decrease in peripheral vascular resistance but heart rate does not increase, leading to a significant decrease of the triple index (the product of systolic blood pressure, heart rate and left atrial pressure), indicating that the oxygen demand of the heart diminishes.

In chapter 6 the results, as obtained in chapter 5 are evaluated in a prospective double blind study in a similar group of patients. Ketanserin decreases blood pressure in significantly more patients than does its solvent.

In chapter 7 ketanserin is compared with sodium nitroprusside, the intravenous antihypertensive agent routinely used, in a comparable group of patients as described in chapter 5 and 6. Both substances are effective in decreasing blood pressure. As opposed to ketanserin, sodium nitroprusside causes reflex tachycardia and an increase in pulmonary shunt fraction, probably caused by a decrease in hypoxic pulmonary vasoconstriction.

In chapter 8 ketanserin is compared with sodium nitroprusside in the treatment of pulmonary hypertension in patients undergoing valvular surgery. In these patients pulmonary dysfunction due to cardiac failure, has already existed for a long period of time. Both vasodilators are effective in lowering pulmonary vascular resistance. However, sodium nitroprusside causes an increase in pulmonary shunt fraction also in these patients, as opposed to ketanserin.

To obtain more insight into the underlying mechanism of the blood pressure lowering effect of ketanserin the model of cardiopulmonary bypass was used (chapter 9) because it allows the investigation of the ef-

fects of compounds on peripheral circulation without interference of cardiac reflexes. The blood pressure lowering effect of ketanserin is dose dependent, with a maximal effect at a dose of 10 mg. Ketanserin also appears to possess α_1 -adrenergic receptor blocking properties, the duration of which is dose-dependent. The specific S_2 -serotonergic receptor antagonist ritanserin does not affect blood pressure, but amplifies the blood pressure lowering effect of the α_1/α_2 -adrenergic receptor blocker phentolamine. It is concluded that per and postoperative hypertension may be effectively treated by means of simultaneous blockade of α_1 -adrenergic and S_2 -serotonergic receptors. Ketanserin combines these properties.

In the last clinical study (chapter 10), in which the same model as described in chapter 9 is used, ketanserin appears to be an arterial and venous vasodilator, as opposed to the calcium antagonist nifedipine, recently recommended as antihypertensive agent, which induces only arterial vasodilatation. Ketanserin may be preferred in the treatment of these patients, because venous vasoconstriction develops during and following cardiopulmonary bypass.

In chapter 11 the results, as obtained in the above mentioned studies, are discussed in general. Ketanserin is effective in the treatment of postoperative hypertension following coronary surgery, but it is not possible to completely prevent per and postoperative hypertension by the continuous infusion of the compound. Unlike sodium nitroprusside ketanserin does not induce reflex tachycardia and an increase in pulmonary shunt fraction. Ketanserin improves preoperative diuresis. The compound is a potent arterial and venous vasodilator. Ketanserin appears to possess both S_2 -serotonergic and α -adrenergic receptor blocking properties. The blood pressure lowering effect is maximal at a dose of 10 mg, and the duration of the α -adrenergic receptor blocking effect is dose-dependent. Also in man blocking of S_2 -serotonergic receptors amplifies the blood pressure lowering effect of α -adrenergic receptor blockade. Ketanserin combines these two properties. It could not be proven that serotonin plays an important role in the development of hypertension during and following heart surgery, but is assumed that it amplifies the vasoconstrictive effect of catecholamines at the level of the microcirculation.

Chapter 13

Samenvatting

Samenvatting

Een belangrijk probleem voor de anaesthesist is de preventie en behandeling van hypertensie tijdens en na hartchirurgie.

In het inleidende hoofdstuk van dit proefschrift wordt een overzicht gegeven van de incidentie en de oorzaken van deze vorm van hypertensie. Er kan een verdeling worden gemaakt tussen hypertensie die ontstaat voor het aansluiten van de hart-long machine (= cardiopulmonale bypass), tijdens cardiopulmonale bypass, in de periode onmiddellijk na het beëindigen van cardiopulmonale bypass en tijdens de postoperative periode in de eerste uren na aankomst in de intensive care unit (ICU). Met name in de periode voor cardiopulmonale bypass is de bestrijding van hypertensie erg belangrijk omdat het kan leiden tot hartspier beschadiging, verhoogd bloedverlies en eventueel een cerebrovasculair accident, met name bij oudere patiënten. De belangrijkste oorzaken van hypertensie in deze periode zijn laryngoscopie, intubatie, sternotomie en sternum spreiden. Bij deze handelingen ontstaan zogenaamde pressor effecten die leiden tot een significante stijging van de serumspiegels van catecholaminen als adrenaline en noradrenaline, als mede renine en angiotensine. Er wordt ook aangenemelijk gemaakt dat serotonine hierbij een rol speelt.

Hypertensie tijdens cardiopulmonale bypass kent andere oorzaken. Hierbij stijgen de catecholamine-concentraties in het bloed met name onder invloed van hemodilutie, hypothermie, hypotensie en het toepassen van niet-pulsatiele bloeddorstrooming. Tijdens cardiopulmonale bypass ontstaat beschadiging van bloedplaatjes, waarbij stoffen als beta-thromboglobuline, platelet factor-4, thromboxane B2 en mogelijk ook serotonine vrijkomen in het plasma. In de periode onmiddellijk na cardiopulmonale bypass komt hypertensie nauwelijks voor omdat het hart moet herstellen van de ischaemie die tijdens de operatie ontstaat wanneer de aorta afgeklemd wordt. Slechts ten gevolge van extreme perifere vasoconstrictie kan eventueel hypertensie ontstaan.

In de vroege postoperatieve fase in de ICU komt hypertensie veel voor (40-60% van de coronair chirurgische patiënten). Een combinatie van factoren ligt hieraan ten grondslag, zoals de nog steeds verhoogde catecholamine-concentraties, de verlaagde activiteit van de preoperatieve beta-blockade, en rigiditeit ten gevolge van het gebruik van narcotische analgetica (b.v. fentanyl of sufentanil). Tevens kan de patient ontwaken in deze periode, waarbij de endotracheale tube ernstige irritatie kan veroorzaken, hetgeen kan leiden tot hypertensie. Of serotonine hierbij een rol speelt is onbekend, maar wordt wel vermoed. In deze fase kan hypertensie dezelfde complicaties veroorzaken als in de periode voor cardiopulmonale bypass. Bovendien wordt verondersteld dat de hypertensie aanlei-

ding kan geven tot vroege afsluiting van de aangelegde coronaire omleidingen.

Omdat perioperatieve hypertensie in het algemeen wordt behandeld met behulp van vaatverwijdende stoffen (vasodilatoren), wordt vervolgens een overzicht gegeven van de bestaande intraveneuze antihypertensiva waarvan nitroprusside natrium en nitroglycerine de belangrijkste vertegenwoordigers zijn. Moderne antihypertensiva zoals urapidil en adenosine worden besproken, evenals ketanserin, een S_2 -serotonerge receptor antagonist, die effectief bleek bij de behandeling van patienten met bijvoorbeeld essentiële hypertensie.

Hierna volgt een korte beschrijving van het ontstaan, het metabolisme en de effecten van serotonine. Serotonine wordt gesynthetiseerd in de chromaffine cellen van de darm. Na vrijzetting wordt de stof vrijwel volledig opgenomen en gemetaboliseerd in de lever. De in het bloed overgebleven hoeveelheid serotonine wordt opgenomen door endotheelcellen, voornamelijk in de long. De kleine hoeveelheid serotonine die de long passeert wordt opgeslagen in de bloedplaatjes, zodat uiteindelijk slechts een zeer kleine concentratie vrij serotonine in het plasma kan worden aangetroffen. Serotonine kan zowel vasodilatatie als vasoconstrictie veroorzaken, afhankelijk van de soort bloedvaten en van de basale tonus. Serotonine vrijgezet uit aggregerende bloedplaatjes veroorzaakt bijvoorbeeld vasoconstrictie in de arterien, een effect dat via S_2 -serotonerge receptoren verloopt. De door serotonine veroorzaakte vasodilatatie, bijvoorbeeld op arteriolair niveau, verloopt waarschijnlijk via S_1 -serotonerge receptoren, waarbij zogenaamde "endothelium-derived relaxing factors" (EDRF) een rol spelen. Daarnaast kan serotonine de vasoconstrictieve werking van andere vasoconstrictoren als catecholaminen en angiotensine versterken. Met name door dit mechanisme wordt aan serotonine een rol toegedacht bij het ontstaan van hypertensie. In pathologische condities, zoals atherosclerose, pulmonale hypertensie, endotoxische shock en eclampsie, kan een verhoogde activiteit van serotonine worden aangetoond. Tenslotte worden in het laatste gedeelte van het eerste hoofdstuk de doelstellingen van het voorliggende onderzoek omschreven.

In het tweede hoofdstuk wordt een kort overzicht gegeven van de farmacologie van ketanserin. Ketanserin is een specifieke S_2 -serotonerge receptor blocker met α_1 -adrenerge receptor blockerende eigenschappen. De stof heeft geen S_1 -serotonerge receptor antagonerende werking. Het is een quinazolinederivaat, met een halfwaardetijd van 15 uur. Ketanserin wordt voornamelijk afgebroken in de lever tot niet-werkzame metabolieten. De belangrijkste toepassing betreft de antihypertensieve werking, met name bij patienten met essentiële hypertensie, preeclampsie, pulmonale hypertensie en neurogene hypertensie. Tevens vindt het een

toepassing bij perifeer vaatlijden zoals bij de ziekte van Raynaud, ziekte van Burger en diabetes mellitus. De antihypertensieve werking van ketanserin werd voor de aanvang van dit proefschrift aan verschillende mechanismen toegeschreven zoals een louter S_2 -serotonerge receptor blockade, een louter α_1 -adrenerge receptor blockade, een combinatie van beide of een centrale sympathico-inhibitie.

Het klinische gedeelte van de thesis begint met een overzicht van de toegepaste technieken op het gebied van anaesthesie, chirurgie, cardiopulmonale bypass en algemene postoperatieve behandeling (hoofdstuk 3).

De eerste klinische studie (hoofdstuk 4) betreft een dubbelblinde, prospectieve studie, waarbij ketanserin of het oplosmiddel van ketanserin per- en postoperatief als continu infuus worden toegediend bij patienten die een coronaire bypass operatie ondergaan en waarbij veranderingen in de haemodynamiek en de hormonale plasma spiegels worden gemeten. Tevens worden de gebruikte hoeveelheden fentanyl en nitroglycerine vastgesteld, evenals de peroperatieve diurese. De resultaten tonen aan dat ketanserin tijdens verschillende fasen van de studie een lagere bloeddruk, hartfrequentie en cardiac output, en een hogere perifere weerstand veroorzaakt dan het oplosmiddel van ketanserin. In beide groepen blijken de plasma spiegels van de catecholaminen, renine en angiotensine tijdens en na de operatie significant te stijgen, maar de serotonine-concentraties veranderen niet significant. In de ketanserin-group blijkt de perifere (huid) temperatuur hoger en de diurese groter te zijn, hetgeen wordt toegeschreven aan een mogelijk specifiek S_2 -serotonerge receptor antagonisme met betrekking tot deze orgaansystemen. Tenslotte wordt aangetoond dat tijdens de infusie van ketanserin lagere doseringen fentanyl en minder frequente toediening van nitroglycerine nodig zijn om hypertensieve fasen te bestrijden.

In hoofdstuk 5 wordt in een open studie aangetoond dat ketanserin effectief is in de behandeling van postoperatieve hypertensie na coronair chirurgie. De bloeddrukdaling komt tot stand via verlaging van de perifere weerstand waarbij opvalt dat tijdens de behandeling met ketanserin de hartfrequentie niet stijgt, hetgeen een significante daling veroorzaakt van de triple index (het produkt van systolische bloeddruk, hartfrequentie en linker atrium druk), een maat voor het zuurstofverbruik van het hart.

In hoofdstuk 6 worden de resultaten uit hoofdstuk 5 getoetst door middel van een prospectief dubbelblind onderzoek bij een vergelijkbare groep patienten. Ketanserin blijkt bij significant meer patienten de bloeddruk te verlagen dan het oplosmiddel van ketanserin.

In hoofdstuk 7 wordt ketanserin vergeleken met nitroprusside natrium, het meest gebruikte intraveneuze antihypertensivum, bij een vergelijkbare

groep patienten als in hoofdstuk 5 en 6. Beide substanties zijn effectief in het verlagen van de bloeddruk. In tegenstelling tot ketanserine blijkt nitroprusside natrium reflex tachycardie en een toename van de pulmonale shunt fractie te veroorzaken. Waarschijnlijk berust dit laatste verschil op het al dan niet intact laten van de hypoxische pulmonale vasoconstrictie.

Ketanserine wordt in hoofdstuk 8 vergeleken met nitroprusside natrium bij de behandeling van pulmonale hypertensie bij patienten die klepchirurgie hebben ondergaan en waarbij meestal sprake is van een reeds bestaande pulmonale dysfunctie ten gevolge van chronische decompensatio cordis. Beide vasodilatoren blijken effectief te zijn in het verlagen van de pulmonale weerstand. Ook in deze studie blijkt nitroprusside natrium de pulmonale shunt fractie significant te verhogen, dit in tegenstelling tot ketanserine.

Om het werkingsmechanisme van ketanserine verder te analyseren wordt gebruik gemaakt van het model van cardiopulmonale bypass (hoofdstuk 9), omdat dit de mogelijkheid biedt de effecten van geneesmiddelen op de perifere circulatie te bestuderen met uitsluiting van reflexmatige beïnvloeding door het hart. Hierbij blijkt dat het acute bloeddrukverlagend effect van ketanserine dosis-afhankelijk is, met een maximaal effect bij een dosis van 10 mg. Tevens blijkt dat ketanserine een α_1 -adrenerge receptor blockerende werking bezit, waarbij de duur van de α -blockade dosis afhankelijk is. Tenslotte blijkt dat de specifieke S_2 -serotonerge receptor antagonist ritanserine geen invloed uitoefent op de bloeddruk, maar wel een amplificerende werking heeft op het bloeddrukverlagende effect van de α_1/α_2 -adrenerge receptor blocker phenolamine. Er wordt geconcludeerd dat per- en postoperatieve hypertensie effectief behandeld kan worden met behulp van de gelijktijdige blockade van α_1 -adrenerge en S_2 -serotonerge receptoren.

In de laatste klinische studie (hoofdstuk 10), uitgevoerd in hetzelfde model als beschreven in hoofdstuk 9, wordt aangetoond dat ketanserine zowel een arteriele als veneuze vasodilatator is, maar dat de calcium antagonist nifedipine, recent als antihypertensivum aanbevolen, slechts een arteriele vasodilatator is. Omdat tijdens en na cardiopulmonale bypass veneuze vasoconstrictie optreedt, heeft ketanserine bij de behandeling van deze patienten de voorkeur.

In hoofdstuk 11 worden algemene conclusies getrokken uit de beschreven studies. Ketanserine is effectief in de behandeling van postoperatieve hypertensie na coronair chirurgie, maar het is niet mogelijk om met behulp van een continu infuus van ketanserine per- en postoperatieve hypertensie te voorkomen. Ketanserine veroorzaakt geen reflex tachycardie en geen stijging van de pulmonale shunt fractie. Ketanserine verbetert de peroperatieve diurese. De stof is een krachtige arteriele en veneuze vaat-

verwijder. Ketanserin blijkt, naast zijn bekende specifieke S_2 -serotonerge ook alpha-adrenerge receptor blockerende eigenschappen te bezitten, waarbij de bloeddrukverlagende werking een maximum kent bij 10 mg, en de duur van de alpha-adrenerge receptor blockade dosis afhankelijk blijkt te zijn. Tevens wordt aangetoond dat blockade van S_2 -serotonerge receptoren het effect van alpha-receptor blockade ook in de mens amplificeert. Tenslotte moet opgemerkt worden dat niet duidelijk kon worden aangetoond dat serotonine een belangrijke rol speelt bij het ontstaan van hypertensie tijdens en na hartchirurgie, maar mogelijk op het niveau van de microcirculatie de vasoconstrictieve werking van catecholaminen versterkt.

Chapter 14

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Anesthesiology Residency	Utrecht, Institute of Anesthesiology, september 1975- march 1979
Fellowship	Houston, Texas Heart Institute, april-november 1979
Anesthesiologist	Department of Anesthesiology, Medical Centre De Klokkenberg, Breda, december 1979-december 1987 Hospital "De Weezenlanden", Zwolle, januari 1988- present