Trick or treat?

Valorisation

Valorisation

Relevance

Worldwide, about 70 million people are estimated to have epilepsy.[1,2] Epilepsy is characterized by recurrent unprovoked seizures. Seizure control is imperative for medical reasons but also because the unpredictable paroxysmal nature of the symptoms (seizures), as well as feeling of loss of control may negatively impact the psychosocial situation affecting the emotional state, coping and consequently, quality of life. Moreover, some objective limitations go with the diagnosis with impact on the social position, such as losing driving license, or restrictions in some sports (such as swimming) as well as occupational limitations.

In most patients with epilepsy, antiepileptic drug (AED) treatment is the first choice of treatment. The best possible outcome of AED treatment is to achieve complete seizure freedom without adverse events. However, AED-induced cognitive side-effects are a major issue in the treatment of epilepsy. Deficiencies in attention, memory, language ability and reaction time are frequently reported side-effects of AEDs.[3] All AEDs have the potential for adverse effects on cognitive functioning. However, variability between types of drugs and individuals is considerable. Therapeutic dilemmas arise when reduction of seizure frequency can only be accomplished with medication that is associated with cognitive side-effects. As side-effects of AEDs have a major impact on health care costs[4] and given that most patients with epilepsy consider the adverse cognitive effects of antiepileptic medication to substantially influence their quality of life,[5] and to be an important reason for AED discontinuation,[6,7] the possibility of side-effects should be taken into the medical decision making as a top priority in the choice of AEDs or in the need to switch.

Target groups

The results of this thesis are relevant for patients with epilepsy and all physicians who treat patients with epilepsy (such as neurologists, child neurologists, general practitioners, pediatricians). Nowadays, as some AEDs are also used for other diseases such as migraine (valproate, topiramate) and neuropathic pain (carbamazepine, gabapentin, pregabalin), this makes this thesis also of interest for psychiatrics who should be aware of the cognitive effects of AED use.

Patients should be informed about the possible negative effects of an AED on their cognition. Furthermore, the outcomes of this thesis help to identify patients with epilepsy at risk for developing cognitive side-effects in an early stage. We paid special attention to subjective reports e.g. self-reported complaints and caregiver reports. Early recognition of patients with epilepsy at risk for cognitive impairments due to treatment through screening procedures can lead to early interventions in their

treatment strategies. Monitoring cognition and discussing their side-effects should be common in clinical practice when starting or changing AED treatment.
This results of this thesis are also interesting for pharmacologists and the pharmaceutical industry. In the industry-driven regulatory trials only a limited number of subjectively reported side-effects are recorded (using fixed systems such as the WHO-ART system). Objective assessment of side-effects is generally not included. We have highlighted the relevance of taking cognition as an outcome measurement in the randomized controlled trials. Until this is realized, identification of the cognitive profile of new drugs available for clinical practice in the naturalistic setting is a good, but slow, alternative.

Activities

The research described in this thesis have led to a more understanding of the cognitive adverse effects of AEDs in patients with refractory epilepsy. It has given an overview of the available literature about the cognitive functions that can be affected by antiepileptic treatment in adults and in children and has discussed some of the missing information. Furthermore, the focus has been not only at detecting side-effects, but a start has been made to explain why side-effects occur in specific patients in reaction to specific drugs. We used two (MR-)techniques to identify the neuronal substrates of cognitive side-effects.
The results of this thesis are published (or submitted) in international peer-reviewed journals and are discussed during (poster)presentations at (inter)national symposia. Furthermore, in the Dutch guidelines for epilepsy it is stated that a neuropsychological screening is indicated when cognitive deficits due to medication are reported and for patients using AEDs with a high risk for cognitive effects (such as phenobarbital, phenytoin or topiramate) or for behavioral effects (levetiracetam).

Innovation

Although the first studies about the cognitive side-effects of AED-treatment are from the late 1970's,[8] many newer AEDs became available of which the cognitive effects were unknown. Furthermore, evidence was and is clearly lacking for children compared to adult patients with epilepsy. In the last part of this thesis (chapter 12), five pertinent clinical questions could be answered based on the results discussed in this thesis. Some of these questions were also raised by the so-called 'anti-epileptic drug committee' ('Geneesmiddelen commissie') of our epilepsy center. This committee consisting of six neurologists, one pharmacist, three trial nurses, one clinical chemist, and one neuropsychologist is meeting every month to discuss the progress of all drug-related research that is performed in our center. This includes the implementation of the pharmacological studies initiated by the industry but also of investigator driven studies.

Implementation

The results of this thesis can be used in clinical practice and for further research implications which are also discussed in the discussion part of this thesis. We have highlighted that screening instruments can be used for early detection of side-effects that can be confirmed with a neuropsychological investigation. It is not known whether and when our recommendations for the pharmaceutical industry and for clinically driven studies will be implemented. At this moment, we are gathering data of patients with epilepsy using AEDs performing computerized cognitive tasks (assessing alertness and information processing speed) simultaneously with eye tracking, which measures eye positioning and eye movements. This might possibly be a new useful technique to investigate drug-induced impairments.

References

1. Ngugi AK, Bottomly C, Kleinschmidt I, Sander JW, Newton CR, Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. Epilepsia 2010;51:883-90.
2. Ngugi AK, Kariuki SM, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Incidence of epilepsy: a systematic review and meta-analysis. Neurology 2011;77:1005-12.
3. Aldenkamp AP, De Krom M, Reijs R. Newer antiepileptic drugs and cognitive issues. Epilepsia 2003;44: 21-9.
4. Kinderen RJA de, Evers SMAA, Rinkens R, Postulart D, Vader CI, Majoie MHJM, Aldenkamp AP. Side-effects of antiepileptic drugs: the economic burden. Seizure 2014;23:184-90.
5. Brunbech L, Sabers A. Effect of antiepileptic drugs on cognitive function in individuals with epilepsy: A comparative review of newer versus older agents. Drugs 2002;62:593-604.
6. Bootsma HPR, Coolen F, Aldenkamp AP, Arends J, Diepman L, Hulsman J, et al. Topiramate in clinical practice: long-term experience in patients with refractory epilepsy referred to a tertiary epilepsy center. Epilepsy Behav 2004;5:380-7.
7. White JR, Walczak TS, Leppik IE, Rarick J, Tran T, Beniak TE, et al. Discontinuation of levetiracetam because of behavioral side effects. Neurology 2003;61:1218-21.
8. Trimble M. The effect of anti-convulsant drugs on cognitive abilities. Pharmacol Ther B 1979;4:677-85.