Long Term Somatic Adverse Events of Antiepileptic Drugs

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Summary

Long term antiepileptic drugs (AEDs) side effects are a common concern in people with epilepsy. AEDs are suspected to be associated with several somatic and psychiatric adverse events. This review focuses on long term somatic adverse events and the difficulties of assessing their exact association with AEDs. Most AEDs have been suggested to induce, at varying degrees, bone metabolism changes, increased cardiovascular risk factors, or endocrine disturbances. These findings are however probably biased by the fact that epilepsy itself is associated with a greater burden of somatic co-morbidities, regardless to the exposure to AEDs.

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Key words: bone metabolism, cardiovascular risk factors, endocrine disturbances, co-morbidities

Langzeitnebenwirkungen von Antiepileptika

Langzeitnebenwirkungen von Antiepileptika (AE) stellen ein häufiges Problem dar, sowohl somatischer als auch psychischer Natur. Dieser Beitrag fokussiert auf somatische Aspekte und auf die Schwierigkeiten, deren Zusammenhang mit der pharmakologischen Behandlung zu erfassen. Veränderungen im Knochenmetabolismus, Erhöhung der kardiovaskulären Risiken und endokrinologische Entgleisungen wurden bei Patienten unter verschiedenen AE beschrieben. Diese Befunde sind jedoch im Hinblick auf die Möglichkeit zu betrachten, dass im Vergleich mit der Allgemeinbevölkerung Epilepsie-Patienten mehrere somatische Komorbiditäten ohne direkte Kausalität mit der medikamentösen Behandlung aufweisen können.

Schlüsselwörter: Knochenmetabolismus, kardiovaskuläre Risikofaktoren, endokrine Störungen, Komorbiditäten

Les effets secondaires à long terme des médicaments antiépileptiques

Les effets secondaires à long terme des médicaments antiépileptiques chez les gens souffrant d'épilepsie sont un problème fréquent. Plusieurs complications somatiques et psychiatriques sont suspectes d'être liés aux médicaments antiépileptiques. Cette revue se concentre sur les complications somatiques à long terme et les difficultés d'explorer leur association avec les traitements de l'épilepsie. Des changements du métabolisme osseux, une augmentation des facteurs de risques cardiovasculaires et des dérangements endocriniens ont été rapporté avec la plupart des antiépileptiques. Ces trouvailles sont au moins en partie biaisées par le fait que l'épilepsie elle-même peut être liée à une fréquence de comorbidités augmenté, sans lien avec l'exposition au traitement.

Mots clés : Métabolisme osseux, facteurs de risques cardiovasculaires, dérangements endocriniens, comorbidités

Gli effetti secondari a lungo termine dei medicamenti antiepilettici

Gli effetti secondari a lungo termine dei medicamenti antiepilettici (AE) rappresentano una problematica frequente nei pazienti con epilessia, siano essi di natura somatica o psichiatrica. In questo contributo ci si concentrerà sulle complicazioni somatiche e sulle difficoltà metodologiche nell' esplorare il legame di causalità con il trattamento farmacologico. La maggiorparte degli AE sono stati messi in relazione con perturbazioni della salute ossea, aumento dei fattori di rischio cardiovascolare, e con alterazioni endocrinologiche. Questi dati, però, sono almeno in parte distorti dalla presenza di comorbidità somatiche pre-esistenti, che sono più frequenti in pazienti con epilessia rispetto alla popolazione controllo.

Parole chiave: Perturbazioni della salute ossea, fattori di rischio cardiovascolare, alterazioni endocrinologiche, comorbidità

Long term side effects represent often a legitimate concern of people with epilepsy requiring an antiepileptic drug (AED) treatment on a long course. A wide range of adverse events (somatic and psychiatric) have been described in people on AEDs, though they may not only be the exclusive consequences of the treatment. This review will focus on somatic long term adverse events, and on confounding factors biasing the relationship between AEDs exposure and these effects. Well known short term adverse events of AEDs will not be discussed here.

Bone metabolism

Long term exposure to AEDs has been known for long to be associated with a decrease in bone density [1-3]. Older age, female gender, lower weight, longer exposure to AEDs, and AED polytherapy have been shown to be independent risk factors [4, 5]. Exposure to a wide range of AEDs was found to be associated with non-traumatic fractures, even after adjusting for demographic and socio-economic factors [6]. Enzyme-inducing AEDs were most implicated, though not exclusively, in the occurrence of osteoporosis [7], supposedly because of increasing the clearance of dihydroxylated vitamin D [8]. This may not be the (only) relevant mechanism, as decreased bone density was found to be independent of low vitamin D level [9-11], and calcium and vitamin D supplementation had little effect in the prevention of fractures in people taking AEDs [12]. An effect on sex hormones may be more important: decreased oestradiol in women taking enzyme-inducing AEDs was associated with decreased bone density, independently of vitamin D levels [13]. Pragmatically, a recent study suggested that switching from enzyme-inducing AEDs (phenytoin) to non-enzyme-inducing AEDs (levetiracetam) not only stops the progressive decrease but also increases bone density after two years of therapy [14]. Among newer AEDs, topiramate has also been suggested as potentially having long term effects on bones, as it decreases parathyroid hormone while increasing markers of bone turnover [15]. Lamotrigine and levetiracetam seem to not have (though not unequivocally [16]) significant effects on bone metabolism, while gabapentin was suggested to decrease bone density [17, 18], but it was not clear whether previous exposure to inducing AEDs was taken into account.

Cardiovascular risk factors

Enzyme-inducing AEDs have been shown to also play a role on cardiovascular risk factors. People on inducing AEDs show significantly higher total cholesterol, low-density lipoprotein cholesterol and triglyceride levels in the long term [19-21], which can be improved by switching to non-inducing AEDs [22]. Increased lipid synthesis is probably mediated by increased clearance of cholesterol metabolites, attenuating the negative feedback on cholesterol synthesis [23]. Levels of other cardiovascular risk factors markers such as lipoprotein (a), CRP [22] and homocysteine [24] were also found to be increased in people taking enzyme-inducing AEDs. A study in children [25] suggested that carotid artery intimal media thickness was significantly greater in children on phenytoin and carbamazepine than in healthy controls. Another study [26] prospectively found a significantly increased incidence of stroke in people taking phenytoin compared to valproate but also to carbamazepine. There is less experience with newer AEDs, and little is known about whether those agents can contribute to the occurrence of somatic conditions. Newer AEDs are either less potent liver enzyme-inducers (e.g. topiramate or oxcarbazepine) or devoid of inducing properties (e.g. levetiracetam, lamotrigine, pregabalin, gabapentin) [27]. Weakly inducing AEDs (topiramate and oxcarbazepine) and non-inducing AEDs (levetiracetam) also increase cardiovascular risk factors such as LDL cholesterol, homocysteinemia, and apolipoprotein B after six months of monotherapy [28]. This actually suggests that liver enzyme induction is not the exclusive mechanism implicated in cardiovascular risk factors, though non-inducing AEDs seem to have a more favourable profile [22]. Valproate was shown to be associated with increased insulin levels independent of weight, compared with healthy controls [29] or people on lamotrigine [30]; a young age at valproate initiation is a risk factor. It was suggested that valproate caused impaired liver insulin metabolism independently of weight [31]. Total cholesterol and triglyceride have also been described as significantly higher in people on valproate than on other AEDs, or healthy controls, even after adjustment for obesity [32]. Valproate, like the enzyme-inducing AEDs, has been suggested to induce persistently raised lipoprotein(a) [33], which is increasingly recognised as an independent cardiovascular risk factor [34, 35].

There is evidence, however, that treatment does not fully explain the increased burden of cardiovascular conditions in people with epilepsy. Increased intimal thickness was shown in patients on carbamazepine or valproate, but was also significantly increased in people with untreated epilepsy, though to lesser extent [36]; it was however not clear whether the latter had been previously exposed to AEDs. A large population study [37] showed that being on AEDs had only small effects on stroke and myocardial infarction incidence, or cardiovascular death. Excluding those with previous stroke, people with epilepsy, whether or not on AEDs, had significantly increased risk for vascular events compared with people without epilepsy. Despite many AEDs being associated with weight gain, the prevalence of being overweight and obesity were found to be only indirectly related to AED treatment. Among 554 people with epilepsy assessed in hospital settings in a

US study [38], no specific monotherapy was associated with weight gain and obesity, but the authors did not report whether they had considered all AEDs the person was exposed to. Previous exposure to AEDs favouring weight gain may have confounded the association with AEDs at the time of the assessment. Polytherapy and drug resistance were found to be associated with weight gain and obesity. This matter is further complicated by the fact that the choice of AEDs may depend on the socioeconomic level of the people being treated. A Swedish study recently showed in a paediatric population that newer AEDs (such as levetiracetam) are more often prescribed to children whose families have a higher socioeconomic level [39]. A higher rate of prescription of liver enzyme-inducers in people with lower socioeconomic levels may worsen further the already higher burden of somatic co-morbidities in people with lower socio-economic level.

Endocrine disturbances

Enzyme-inducing AEDs are also reported to decrease thyroid hormone levels (T3 and T4); this is not, however, associated with any change of TSH and therefore thought to be subclinical [40-42]. Enzyme-inducing AEDs have also been shown to decrease testosterone in men [43] and induce sexual dysfunction [44]. In women, these treatments also decrease levels of oestradiol and dehydroepiandrosterone (DHEA), which has been linked again with sexual dysfunction [45].

Valproate has also been recognised as a risk factor in the development of polycystic ovary syndrome for a long time. The mechanisms by which it can induce polycystic ovaries are probably multiple; hyperinsulinism/weight gain, combined with inhibition of testosterone conversion to oestradiol, alongside theca cell stimulation, result in increased testosterone levels and obesity [46]. Switching to lamotrigine improves the lipid profile, weight, fasting serum insulin, testosterone level and the number of cysts seen on ultrasonography [47]. These changes appear to be linked with the maturation of the reproductive system, as polycystic ovary syndrome has been shown to be more common (80% in one series [48]) if valproate was started before age 20.

Cancer

An association between AEDs and the occurrence of tumors in people with epilepsy has long been questioned [49, 50]. Older AEDs such as phenobarbital and phenytoin, have been incriminated as potential carcinogens [51]. Long-term prescription studies did not, however, find an association [52, 53]. Phenobarbital was particularly implicated in the occurrence of hepatocellular carcinoma [54]. This association is potentially biased by the early use of the carcinogenic contrast medium thorotrast [55]. Phenytoin exposure was suggested as being associated with the occurrence of lymphoma and multiple myeloma in small series [56, 57]. The lympho-proliferative processes can be mimicked by an acute drug reaction to phenytoin [58-61] and extensive investigations may be needed to distinguish between those two conditions [62, 63]. The occurrence of lymphoma was found to be increased in several epidemiological studies of epilepsy [50, 55], but no association with phenytoin exposure was found. Valproate was suggested experimentally as having a cancer protective effect [64-67]. Large epidemiological studies, however, failed to show a preventive effect of valproate exposure [68, 69]; the numbers of individual cancer types were, however, too small to assess a more specific effect. Newer AEDs have not shown carcinogenic properties in in vitro testing fulfilling regulatory requirement [51], but long term clinical experience is still limited.

Conclusion

Medical treatment of epilepsy is associated with the occurrence of several somatic long term complications. Newer AEDs inducing less metabolic consequences may have a more favourable profile. It is however difficult to disentangle the effects of the treatment from the somatic co-morbidities associated with epilepsy itself. Further, long-term and well designed studies are required to shed more light on these very important aspects.

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