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Adverse Metabolic Effects of Antiepileptic Drug Treatment

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1. Introduction

Active epilepsy with recurrent seizures is associated with a range of well-documented unfavourable consequences. Nevertheless, adverse metabolic effects of antiepileptic drug (AED) treatments have only recently received attention. Such effects may be subtle, insidious, take many years to become clinically apparent, and may have a negative impact on general health for many decades. Unfortunately, many neurologists are unaware of such AED-related side-effects.

The relationship between epilepsy and metabolic disorders is multi-factorial. Metabolic encephalopathies, including mitochondrial disorders and some of the progressive myoclonic epilepsies, are important causes of seizures in childhood. Acute metabolic disturbances associated with diseases affecting the kidneys, liver, or pancreas may give rise to seizures. Furthermore, alcohol- or drug-withdrawal may also be associated with seizures. From the other perspective, seizures themselves, in particular prolonged seizures such as in convulsive status epilepticus, may lead to a variety of metabolic abnormalities.

In this chapter I will summarize our current knowledge about the adverse metabolic effects of AED treatment and discuss whether these side-effects are so severe that a reconsideration of our prescribing habits would be beneficial.

2. Effects on bone metabolism

Accumulating evidence indicates an association between long-term use of AEDs and disturbed bone metabolism, resulting in decreased bone mineral density (BMD) and an increased risk of fractures (Lee, 2010). This is particularly problematic for people with epilepsy as their propensity to fractures is already elevated due to other drug side-effects (e.g. dizziness, ataxia), co-existing neurological deficits (e.g. cerebral palsy), and seizure-related falls (Mattson & Gidal, 2004). Furthermore, generalized tonic-clonic seizures are, themselves, associated with an increased risk of fractures, especially vertebral compression fractures (Pedersen et al., 1976).

It is common knowledge that steroids have a negative impact on bone metabolism. However, the bone-depleting effects of AEDs are less well-known. In a survey of 624 neurologists, only 28 % were familiar with AEDs being associated with reduced bone mass, and only 9 % of paediatric neurologists and 7 % of adult neurologists offered their patients prophylactic calcium and vitamin D supplements (Valmadrid et al., 2001). In another survey

carried out by Epilepsy Action, a British patient advocacy organization, 75 % of members surveyed reported that they had not been informed that osteoporosis was a possible side-effect of long-term AED use. Of those who had been informed, their epilepsy specialist was the primary source of this information (Epilepsy Action, 2003).

Although the results of studies on the impact of AEDs on BMD are diverse, as much as 75 % of epilepsy patients have been found to be osteopenic and up to 25 % osteoporotic (Coppola et al., 2009).

The drugs most consistently associated with skeletal abnormalities are those that affect the cytochrome P450 (CYP450) system (e. g. phenytoin, phenobarbital, carbamazepine, valproate) (Vestergaard et al., 2004; Pack et al., 2005; Souverein et al., 2006; Tsiropoulos et al., 2008). However, drugs that inhibit carbonic anhydrase (topiramate, zonisamide, acetazolamide) have also been suspected to affect bone health by causing metabolic acidosis. Nevertheless, a double-blind, randomized, preliminary study of topiramate as an anti-obesity drug did not indicate changes in bone turnover markers in comparison with placebo controls (Leung & Ramsay, 2006).

Data on the effects of the new generation AEDs on bone health are sparse. Animal studies have demonstrated that levetiracetam reduces bone strength and bone formation without altering bone mass (Nissen-Meyer et al., 2007), but there are no clinical data that either support or negate this observation. Neither lamotrigine nor oxcarbazepine have been found to interfere with bone mineral metabolism (Sheth & Hermann, 2007; Cetinkaya et al., 2009).

The mechanisms underlying the bone-depleting effects of AEDs are probably complex. For many years the main theory was that enzyme-inducing AEDs (e.g. phenobarbital, phenytoin, carbamazepine) accelerated vitamin D hydroxylation to polar inactive metabolites, thereby resulting in hypocalcaemia, secondary hyperparathyroidism, increased bone turnover, and higher rates of bone loss. Although this is still considered an important mechanism, later studies have shown that AEDs may cause bone loss even in the absence of vitamin D deficiency (Farhat et al., 2002; Andress et al., 2002). Furthermore, valproate, a CYP450 inhibitor, has also been shown to have an adverse effect on bone health, probably via completely different mechanisms (Sheth et al., 1995; Sato et al., 2001; Guo et al., 2001; Sheth, 2004). Decreased intestinal absorption of calcium, resistance to parathyroid hormone, calcitonin deficiency, interference with vitamin K metabolism, and a direct drug-effect on bone cell functions have also been suggested as possible mechanisms (Feldkamp et al., 2000; Petty et al., 2007). Other indirect effects of the drugs, such as hormonal changes, increases in homocysteine, reduction in insulin growth factor 1, and the effect of valproate as a histone deacetylase inhibitor, thereby reducing collagen I and osteonectin, may also contribute (Fuller et al., 2010).

3. Effects on lipid metabolism

The CYP450 enzyme system is involved in the synthesis and metabolism of cholesterol (Nebert & Russel, 2002). In particular, CYP51A1 plays a key role in cholesterol synthesis (Gibbons, 2002). Enzyme-inducing AEDs would therefore be expected to increase cholesterol production, and, in keeping with this hypothesis, several cross-sectional studies have demonstrated that patients treated with phenobarbital, phenytoin, or carbamazepine have elevated total cholesterol levels compared with normal controls (Isojärvi et al., 1993; Verotti et al., 1998; Eiris et al., 2000; Nikolaos et al., 2004). Specific studies have shown increases in most of the various lipid fractions, including low-density

and high-density lipoproteins and triglycerides. However, the increase in high-density lipoproteins tends to be modest relative to the other lipid fractions (Isojärvi et al., 1993; Nikolaos et al., 2004). A recent study of patients whose AED treatments were switched from the inducing agents, carbamazepine and phenytoin, to the non-inducing lamotrigine and levetiracetam, demonstrated a decline in total cholesterol, averaging 26 mg/dl after 6 weeks (Mintzer et al., 2009). The greatest change was in the atherogenic low-density lipoproteins.

Thus, most studies indicate that the effects of enzyme-inducing AEDs on specific lipid fractions favour an atherogenic profile, while the enzyme-inhibiting agent, valproate, exerts the opposite effect (Verotti et al., 1997; Verotti et al., 1998; Nikolaos et al., 2004).

4. Effects on homocysteine, lipoprotein A, and C-reactive protein levels

The amino acid homocysteine is prothrombotic, and is therefore considered a significant risk factor for cardiovascular mortality (Selhub, 2008), stroke (Spence, 2007), dementia (Ravaglia, 2005), and possibly also pharmacoresistant seizures (Sener, 2006). Whether the increased risk is associated with homocysteine itself, or whether homocysteine is merely a marker, is currently not determined. Homocysteine concentration is inversely related to plasma levels of folate, vitamin B6, and vitamin B12. Almost two-thirds of high homocysteine cases can be attributed to low vitamin status (Selhub, 2008).

Lipoprotein A has also been found to be an independent risk factor for cardiovascular disease (Danesh et al., 2000).

Some studies indicate that enzyme-inducing AEDs may increase the levels of both lipoprotein A and homocysteine (Schwaninger et al., 1999; Schwaninger et al., 2000; Apeland et al., 2001; Bramswig et al., 2003). Moreover, a recent study showed that homocysteine levels were significantly reduced when patients were tapered off phenytoin, but not carbamazepine (Minzer et al, 2009). Thus, it appears that the effects of inducing AEDs may not be entirely uniform.

C-reactive protein (CRP) concentration has been found to be correlated with risk of vascular disease, independent of serum lipids (Ridker et al., 1997). In the aforementioned study, in which patients were switched from the inducing drugs, carbamazepine or phenytoin, to the non-inducing agents, levetiracetam or lamotrigine, a reduction in CRP of almost one third was recorded after 6 weeks (Mintzer et al., 2009).

5. Valproate may cause metabolic syndrome and hyperammonaemia

Metabolic syndrome, as indicated by centripetal obesity, glucose intolerance, hypertension, elevated triglycerides, low high-density lipoprotein cholesterol, and hyperandrogenism/polycystic ovaries, occurs in 41 % of women treated with valproate, compared with 5.3 % of those treated with carbamazepine, and apparently none of those being treated with lamotrigine and topiramate (Kim & Lee, 2007). This syndrome appears to occur exclusively in those who develop obesity during valproate use (Verotti et al., 2010).

However, worth noticing is that it has been estimated that appproximately 25 % of the general population of adults in USA has metabolic syndrome.

Further, valproate and its metabolites interfere with several biochemical pathways in the mitochondria, leading to disruption of the urea cycle and thereby causing hyperammonaemia (Garcia 2009), and this may occur in 20-50 % of patients being treated

with valproate. In some patients this is well-tolerated, but in others elevated ammonia can be associated with encephalopathy with confusion, ataxia, reduced cognitive abilities, decline in conscious level, triphasic waves in EEG, and increased seizure frequency (Perucca, 2002).

6. Effects on body weight

Obesity has become epidemic in the western world (Aronne, 2002). People with epilepsy also have an increased rate of obesity, and this may be related to a high prevalence of depression (Gilliam et al., 2003), physical inactivity (Bjørholt et al., 1990), unhealthy diet, and AED treatment. Obesity may have many negative consequences, including insulin resistance, reproductive dysfunction, cardiovascular disorders, gall bladder disease, bone and joint disease, and cancer (Aronne, 2002).

AEDs may be associated with either increases or reductions in body weight (Biton, 2003).

Those AEDs that have most consistently been reported to increase body weight include valproate, carbamazepine, gabapentin, pregabalin, and vigabatrin (Sheth, 2008). Of these, the clinically most important is the valproate-associated increase in body weight. This appears to be cumulative over the course of many years of treatment (Biton et al., 2001), and seems to be an important risk factor for the development of non-alcoholic fatty liver disease, which occurs in 61 % of patients (Luef et al., 2004). Valproate is a fatty acid derivative and competes with free fatty acids for albumin binding, and, as a GABAergic agonist, is known to be involved in insulin secretion from pancreatic beta-cells. Thus, valproate-associated weight gain is probably due to hyperinsulinaemia with relative insulin resistance (Luef et al., 2004). Elevated levels of cortisol, leptin, and neuropeptide Y may also be contributory (Aydin et al., 2005).

Those AEDs most often associated with weight loss include felbamate, topiramate, and zonizamide. A prospective uncontrolled topiramate trial demonstrated that 86 % of patients had lost weight after 12 months of treatment (Ben-Menachem et al., 2003). Those with a body mass index (BMI) > 30 lost 12 % of their body weight, whereas those with BMI < 30 lost 5 %. Body fat loss represented 60-70 % of the weight loss. Serum glucose levels, glucose tolerance test, and blood lipid profiles improved, and serum leptin levels were reduced (Ben-Menachem et al., 2003).

Felbamate is associated with anorexia and loss of between 3 and 5 % of body weight in children, and mostly occurs during the first 3 months of therapy (Bourgeois, 1997).

A recent study on the effect of zonisamide on body weight revealed a mean decrease in body weight by 3.7 %. A weight loss > 5 % was documented in 35 % of patients in the study, and a weight gain > 5 % in 14 %. The weight loss was most prominent in those that were overweight prior to treatment. The weight changes did not appear to be dose-related, and were reversible after discontinuation of therapy (Wellmer et al., 2009).

Phenytoin, lamotrigine, and levetiracetam are assumed to be weight-neutral agents.

7. Some AEDs may induce metabolic acidosis

Metabolic acidosis results either when the kidney is unable to excrete dietary H+ load or when there is an excessive loss of HCO3- secondary to reduced renal tubular reabsorption. The three AEDs that inhibit carbonic anhydrase, acetazolamide, topiramate, and

zonisamide, are all associated with varying degrees of renal tubular acidosis. Topiramate causes a mild hyperchloraemic, non-anion gap metabolic acidosis with low levels of bicarbonate (Mirza et al., 2009), typically appearing soon after initiation of therapy. However, a marked reduction in bicarbonate occurs in less than 10 % of patients, and the reduction seems to be dose-related (Mirza et al., 2009).

8. Effects on gonadal steroids

The CYP450 enzymes are involved in both steroidogenesis and the metabolism of endogenous steroids (Nebert & Russel, 2002). As would be expected, studies of both men and women treated with enzyme-inducing AEDs have shown reduced testosterone levels compared with those taking non-inducing AEDs (Herzog et al., 2005; Løfgren et al., 2006; Talbot et al., 2008). However, whether the extent of reduction in testosterone levels is sufficient to compromise sexual functions has not yet been ascertained (Talbot et al., 2008). Nevertheless, decreased sexual function, with reduced sexual desire, orgasmic dysfunction, and low levels of oestradiol has been found in women with epilepsy (Bergen et al., 1992; Morrell et al., 2005).

9. Effects on serum concentrations of sodium

Asymptomatic hyponatraemia (serum sodium < 135 mmol/l) occurs in up to 50 % of patients using oxcarbazepine, and develops gradually during the first months of therapy. Severe hyponatraemia (serum sodium < 125 mmol/l) is found in approximately 3 % of patients with previously normal serum sodium (Schmidt et al., 2001; Holtmann et al., 2002) and may be associated with various symptoms, such as nausea, fatigue, or seizure worsening. Those most at risk of developing oxcarbazepine-associated hyponatraemia are the elderly and those using other sodium-depleting agents, including diuretics, oral contraceptives, or nonsteroidal anti-inflammatory drugs (Schmidt et al., 2001).

Valproate has also been reported to cause a syndrome of inappropriate antidiuretic hormone secretion (SIADH) or hyponatraemia (Beers et al., 2010).

The mechanism by which oxcarbazepine, and to lesser degree carbamazepine, lowers the sodium levels has not yet been fully elucidated.

10. Potential consequences of the metabolically adverse effects of AEDs

As the occurrence of osteoporosis rises with age, and life expectancy has increased, osteoporosis is a considerable health problem in the general population. Currently 50 million people worldwide are estimated to suffer from epilepsy, and this number, along with the rapid increase in use of AEDs for other indications (Landmark, 2008), suggests that millions of people will soon be adversely affected by the osteopenic effects of some AEDs.

The risk of fractures in patients with epilepsy has not been precisely defined, but is undoubtedly greater than in the general population. Both the epilepsy itself and the bone-depleting effects of AEDs are probably contributory factors to the increased risk (Mattson & Gidal, 2004). However, it should be acknowledged that most studies on AED-associated bone disorders have methodological limitations, and thus, their results should be interpreted with caution.

In comparison with the general population, people with epilepsy appear to have a 2-6 times greater risk of fractures (Andress et al., 2002; Mattson & Gidal, 2004; Sheth et al., 2006), and the fracture risk seems to increase with the cumulative duration of AED exposure, with the strongest association occurring in those with more than 12 years of use (Souverein et al., 2006). A meta-analysis of clinical studies investigating the effects of epilepsy and epilepsy treatment on fracture risk and BMD, found the relative risk to be increased by 2.2 for any fracture, by 5.3 for hip fracture, by 1.7 for forearm fracture, and by 6.2 for spinal fracture. The estimated risks of fractures were higher than would be expected from BMD TZ-scores (Vestergaard, 2005).

As enzyme-inducing AEDs change the lipid profile in an atherogenic direction and also elevate other surrogate vascular risk markers, it could be expected that those using such drugs are at increased risk of developing vascular disease. However, studies on epilepsy and comorbid vascular disease are conflicting. One Finnish study revealed a *lower* prevalence of ischemic heart disease in epilepsy patients than in a control group (Muuronen et al., 1985), while a Norwegian study showed no significant difference in coronary risk profile between epilepsy patients and controls (Nakken & Kornstad, 1998). Other studies have shown a mildly increased mortality from ischemic heart disease among epilepsy patients, with standardized mortality ratios between 1.2 and 2.5 (Annegers et al., 1984; Nilsson et al., 1997).

Those AEDs causing metabolic acidosis (acetazolamide, topiramate, zonisamide) may give rise to hyperventilation, acroparestesias, fatigue, anorexia, kidney stones, osteoporosis, and cardiac arrhythmias. In children, chronic metabolic acidosis may reduce growth rates. While the rate of kidney stones is estimated to be approximately 0.5 % in the general population, with some geographical variations, users of zonisamide and topiramate are found to have 1-4 % risk of developing nephrolithiasis, with men at greater risk than women (Vega et al., 2007).

As with the effects of enzyme-inducing AEDs on the lipid profile, more studies are needed to elucidate more fully the clinical consequences of the drugs' effects on gonadal steroids.

11. How to manage adverse metabolic effects associated with AED use

Low bone mass associated with AED use is largely unrecognized, undetected, and untreated (Sheth, 2004). Further, there are no formal guidelines for monitoring, prevention, and management of bone disease among those patients using AEDs (Lee, 2010).

However, those AEDs that involve the CYP450 enzyme system should be avoided, if possible, in high risk patients (Table 1). Osteoprotective behaviour should be promoted; sunlight exposure and weight-bearing exercise should be encouraged, and known risk factors, like smoking and alcohol consumption, should be avoided.

Table 1. Patients with an increased risk of fractures

- Old age (> 70 years)
- Postmenopausal women
- Using enzyme-inducing AED(s)
- Previously experienced low-energy fractures
- DEXA-values below 2.5 SD of normal
- A combination of risk factors, such as low BMI, smoking, sedentary lifestyle, poor diet, and modest sun exposure
- More than 3 cm reduction of body height in persons < 70 years, more than 5 cm in persons > 70 years

I recommend that patients with epilepsy that are taking AEDs on long-term basis should ensure that their dietary intake of calcium and vitamin D is adequate; vitamin D 800 IU/day and calcium 1000 mg/day. High risk patients should take higher doses; vitamin D 1000-4000 IU/day and calcium 1500 mg/day (Nakken & Taubøll, 2010).

BMD screening is warranted for persons with long-term AED exposure, particularly for those using enzyme-inducing AEDs or valproate, or patients with other risk factors for bone loss. A Dual-Energy X-ray Absorptiometry (DEXA) measurement should be conducted five years after the initiation of AED treatment in all patients, and should be conducted every 2-3 years in high risk patients.

Hormonal replacement therapy may be useful in menopausal women with other significant climacteric symptoms, including hot flashes. However, oestrogen may in some women reduce the seizure threshold.

The role of antiresorptive agents, like bisphosphonates, in the treatment of AED-associated bone loss is currently unresolved. However, based on general treatment principles for osteoporosis, I suggest that the use of bisphosphonates should be discussed for patients with DEXA T-scores that are below –2.5, and for those with T-scores between –1 and –2.5 who have experienced low energy fractures.

Serum sodium should be measured regularly in patients treated with oxcarbazepine, and combination with other sodium-depleting drugs should be avoided. If severe hyponatraemia (serum sodium < 125 mmol/l) should occur, then dose reduction or switching to another AED is recommended.

Patients being treated with valproate should be followed up closely with respect to weight changes, and valproate should be avoided, if possible, in patients with an obesity problem. If valproate-associated metabolic syndrome occurs, another AED should be used. If patients treated with valproate develop signs that are consistent with encephalopathy, particularly in the presence of asterixis and/or delta slowing on EEG, checking for hyperammonaemia is a reasonable precaution (Perucca, 2002). Hyperammonaemia develops in the context of normal liver functions and is associated with carnitine deficiency. Thus, carnitine supplementation has been recommended (Hamed & Abdella, 2009).

Topiramate or zonizamide should not be offered to patients with a previous history of anorexia or kidney stones, or those on a ketogen diet (Paul et al., 2010). Increasing fluid intake and urine output can help in reducing the risk of kidney stone formation.

12. Conclusion

The adverse metabolic effects of AEDs are probably currently underestimated, and thus represent an area of legitimate concern. As most of these effects develop insidiously over many years, they might either be overlooked or not associated with the drug therapy. Most adverse metabolic effects are associated with the older generation of AEDs, especially those with enzyme-inducing or enzyme-inhibiting properties. Although the side-effect profiles of the new generation of AEDs are not completely elucidated, many of these drugs do not affect liver enzymes. Assuming that the seizure reducing effects of the new AEDs are comparable to those of the old ones, as indeed has been indicated in some studies (Brodie et al., 1999; Brodie et al., 2007; Marson et al., 2007), and have a preferable adverse effect profile, the new drugs should be selected as first-line treatment in patients with newly diagnosed epilepsy.

13. References

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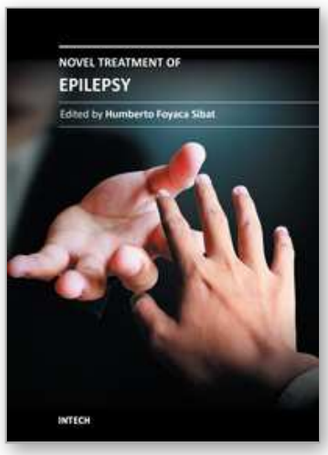

Novel Treatment of Epilepsy

Edited by Prof. Humberto Foyaca-Sibat

ISBN 978-953-307-667-6
Hard cover, 326 pages
Publisher InTech
Published online 22, September, 2011
Published in print edition September, 2011

Epilepsy continues to be a major health problem throughout the planet, affecting millions of people, mainly in developing countries where parasitic zoonoses are more common and cysticercosis, as a leading cause, is endemic. There is epidemiological evidence for an increasing prevalence of epilepsy throughout the world, and evidence of increasing morbidity and mortality in many countries as a consequence of higher incidence of infectious diseases, head injury and stroke. We decided to edit this book because we identified another way to approach this problem, covering aspects of the treatment of epilepsy based on the most recent technological results â€œin vitroâ€ from developed countries, and the basic treatment of epilepsy at the primary care level in rural areas of South Africa. Therefore, apart from the classic issues that cannot be missing in any book about epilepsy, we introduced novel aspects related with epilepsy and neurocysticercosis, as a leading cause of epilepsy in developing countries. Many experts from the field of epilepsy worked hard on this publication to provide valuable updated information about the treatment of epilepsy and other related problems.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Karl O. Nakken (2011). Adverse Metabolic Effects of Antiepileptic Drug Treatment, Novel Treatment of Epilepsy, Prof. Humberto Foyaca-Sibat (Ed.), ISBN: 978-953-307-667-6, InTech, Available from: http://www.intechopen.com/books/novel-treatment-of-epilepsy/adverse-metabolic-effects-of-antiepileptic-drug-treatment

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