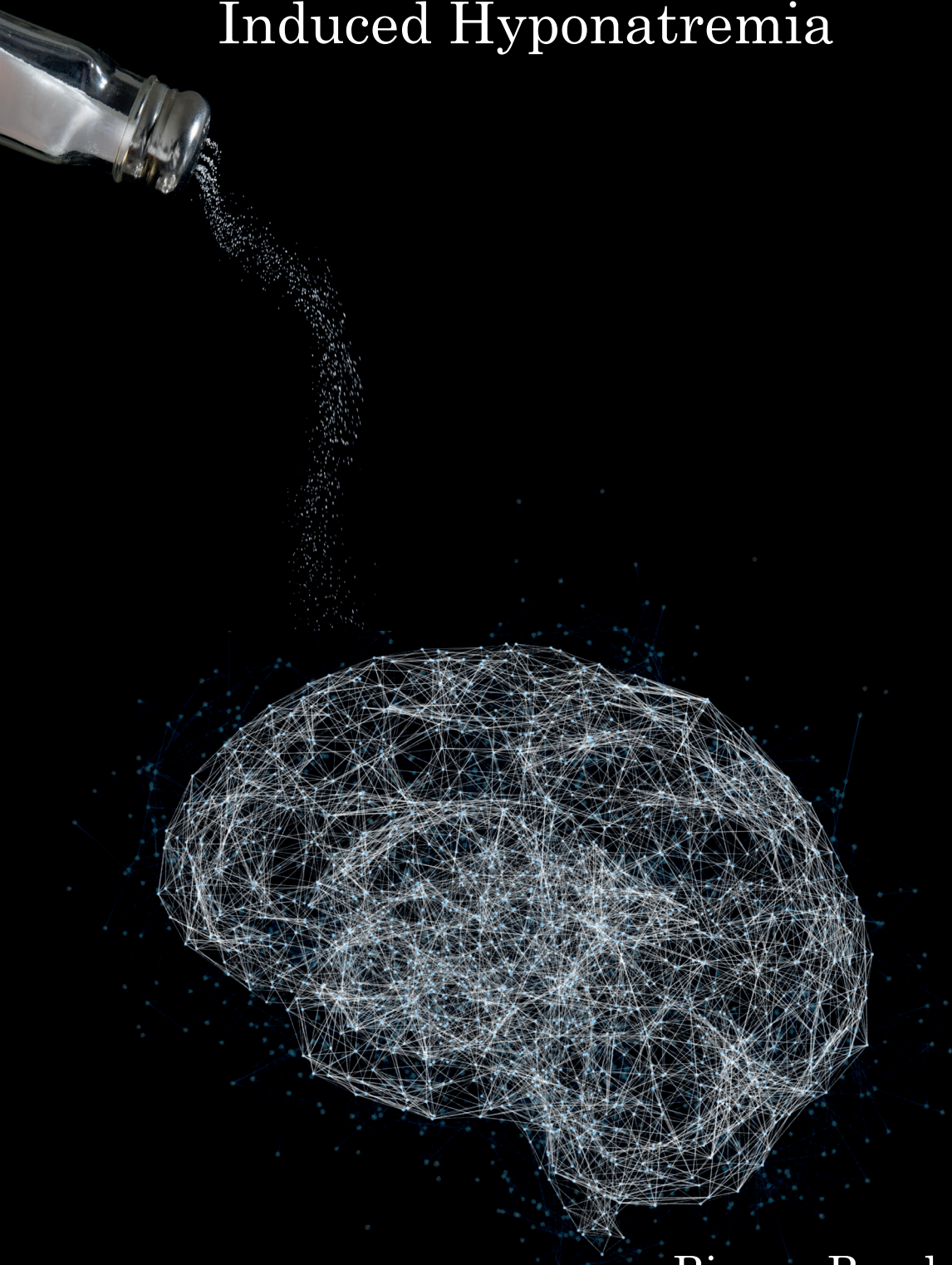
Carbamazepine and Oxcarbazepine Induced Hyponatremia



Bianca Berghuis

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Carbamazepine en oxcarbazepine geïnduceerde hyponatriëmie

(met een samenvatting in het Nederlands)

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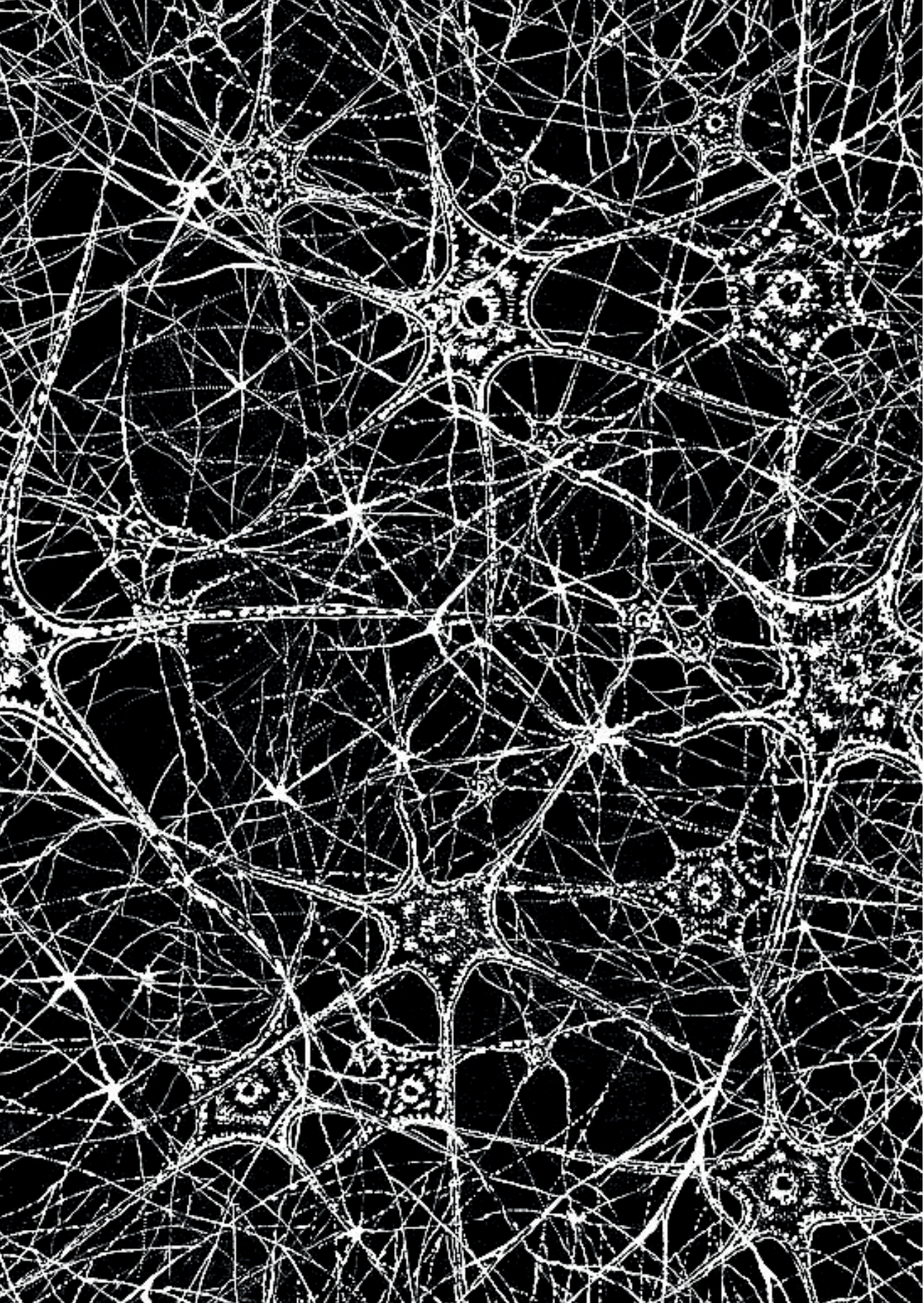

CHAPTER 1

General introduction

General Introduction

History of epilepsy treatment and its consequential adverse effects

Epilepsy affects about 1 % of people and can be subdivided into two main forms; focal and generalised epilepsy.[1,2] Both are mainly treated with anti-seizure medication (ASM). ASMs influence the quality of life of individuals with epilepsy by their therapeutic and their adverse effects (AEs). Epilepsy, although already described in ancient times, was first effectively treated in 1857 with bromide.[3] The anticonvulsive properties of phenobarbital were discovered in 1912. This drug was and still is very efficacious in treating epilepsy, but also very sedative. It took over 20 years to develop an efficacious but less sedating drug, namely phenytoin. Another 30 years passed before valproate and carbamazepine got on the market, and each came with its spectrum of AEs. This first development illustrated already the inevitable balancing act of epilepsy treatment consisting of managing efficacy versus AEs, which fuelled the continuous development of novel ASMs. Still, with the development of second and third generation ASMs and over 20 ASMs currently available today, epilepsy treatment has not become more efficacious. Less than 70% of people with epilepsy achieve reasonable seizure control with medication alone.[4-6]

ASMs have been developed with different modes of action and pharmacokinetic properties, which we will further discuss below. Double-blind randomised trials have found no difference in efficacy between these different ASMs types. ASMs introduced since 1980 generally have a more gentle AEs profile and fewer interactions than their predecessors, while their efficacy is comparable. They are for instance less teratogenic, which has been confirmed by extensive post-marketing surveillance.[7]

Seizures in about a third of people with epilepsy cannot be controlled by ASMs.[5] Part of this problem relates to the magnitude of ASM dosage and the probability of seizure control on the one hand and AEs on the other. Higher ASM dosing usually leads to an increased risk of AEs preventing effective dosing. In a group of

individuals with drug-resistant epilepsy (DRE), discontinuation of a newly introduced ASM was due to side effects in 35% and lack of efficacy in 61%.[8] Also, in the group where ASM controls seizures, individuals experience a lower quality of life caused by AEs of the drugs.[9] Not always are these AEs recognised or addressed appropriately. Patient surveys provide valuable insight into what matters to individuals and uncover discrepancies between patients' perceptions and that of physicians. Survey data show that physicians underestimate the number of people experiencing AEs from ASMs and the impact on the quality of life.[10] Screening questionnaires can help physicians quickly identify problems due to AEs and recognise comorbidities. Ultimately, successful management of epilepsy requires a holistic approach to care, with treatment tailored to the individual patient's needs. In this introduction, I will first discuss the neurophysiological basis of epilepsy and how drugs can affect this. Then, I will focus on the specific ASMs carbamazepine (CBZ) and oxcarbazepine (OXC) and continue with the commonly associated but often unrecognised AE hyponatremia. Lastly, I will discuss the influence of genetics in epilepsy, especially in AEs in epilepsy treatment.

Interplay between neurophysiology of epilepsy and pharmacology

ASMs prevent the occurrence of seizures; there is no evidence that they have disease-modifying properties.[3] To understand the working mechanism of ASMs, one needs to have some knowledge of the neurophysiological basis of epilepsy.

Epilepsy is a central nervous system disorder characterised by recurrent seizures unprovoked by an acute systemic or neurologic disorder. A seizure is the clinical manifestation of an abnormal, excessive, hypersynchronous discharge of a population of cortical neurons. Two concurrent events characterise seizure initiation: 1) high-frequency bursts of action potentials and 2) hypersynchronisation of a neuronal population.[11]

The primary mechanism of neuronal excitability is the action potential. Action potentials occur due to depolarisation of the neuronal membrane by influx of Na^+ (sodium) ions. When depolarisation reaches axon terminals, it triggers the release of neurotransmitters into the synaptic cleft, which in turn opens ion channels in the

postsynaptic neuron. The inputs of excitatory and inhibitory postsynaptic potentials can begin a new action potential in the postsynaptic neuron. A hyper-excitable state of neurons can result from increased excitatory synaptic neurotransmission, decreased inhibitory neurotransmission, an alteration in voltage-gated ion channels, or an alteration of intra- or extra-cellular ion concentrations in favour of membrane depolarization.[11]

ASMs are designed to counter the hyper-excitable state of neurons and suppress action potentials by different modes of action: ASMs facilitate gamma-aminobutyric acid(GABA)-ergic transmission to enhance inhibition, block neuronal ion channels (either sodium, calcium or potassium channels) to decrease activation, attenuate glutamate-mediated excitatory neurotransmission, or modulate neurotransmitter release via presynaptic action.[3] (see figure 1)

The largest group of ASMs consists of sodium channel blockers, including the key players of this thesis, CBZ and OXC. The function of the sodium channels these ASMs block and how they interact is briefly reviewed below.

Voltage-gated sodium channels, allowing the influx of Na^+ ions, are responsible for the depolarisation of the nerve cell membrane and the conduction of action potentials across the surface of neuronal cells. Voltage-gated sodium channels exist in three primary conformational states: resting, open, and inactivated. At hyperpolarised potentials, the channel is in a resting state, closed. At depolarisation the channel makes a transition to an open state permeable to sodium ions; following depolarisation, the channel enters a closed inactivated state. The transition rate from inactivated to resting state determines when the channel can participate in the subsequent membrane depolarisation. ASMs with sodium channel blocking properties have the highest affinity for the channel protein in the inactivated state and binding slows the conformational recycling process. This results in a limitation of repetitive neuronal firing and therefore inhibition of seizure initiation.[12]

A small portion of sodium channels undergo late openings in response to depolarisation and give rise to a sodium current that fails to inactivate; the so called persistent current. CBZ may also block the persistent sodium current, which contributes to suppressing sustained depolarisations without interfering with single action potentials and low frequency firing.[13]

Knowledge about the working mechanism of different ASMs combined with knowledge about genetics, aetiology and pathophysiological mechanisms of epilepsy may help the physician to choose the best option for a given individual. For example, in people with epilepsy due to specific pathogenic *SCN1A* mutations, a sodium channel blocker should not be prescribed because it could make the epilepsy worse.[14]

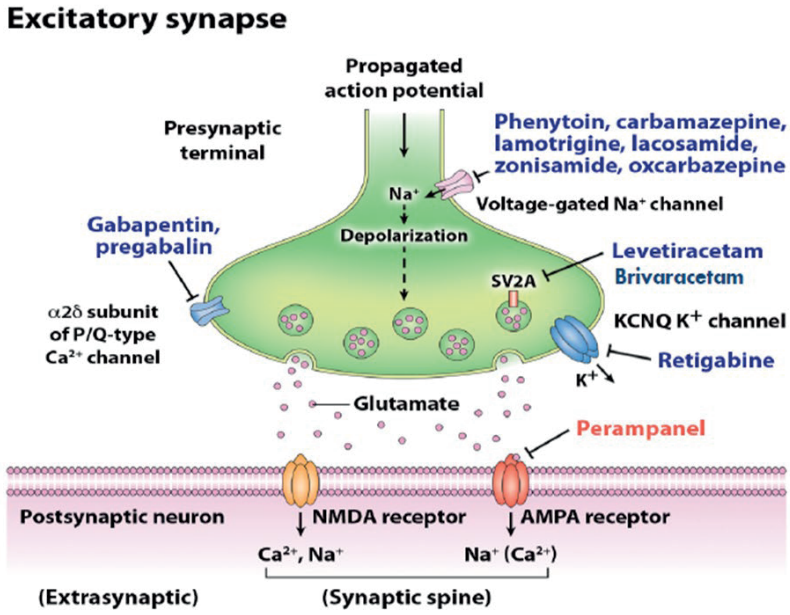

Figure 1, modified figure from Rogawski.[15]

Carbamazepine

Chemist Walter Schindler discovered CBZ in Switzerland (1953).[16] It was first marketed as a drug to treat trigeminal neuralgia in 1962. CBZ has been used as an anticonvulsant and antiepileptic since 1965.[17] It is most effective against focal seizures and primarily generalised tonic-clonic seizures. It is generally inactive against or can aggravate most other generalised epilepsies. In 1966, CBZ was also

found to be beneficial in people with diabetes insipidus, a disorder characterised by polydipsia and polyuria caused by a lack of pituitary vasopressin production.[18] CBZ was assessed for its beneficial effect in bipolar disorder throughout the 1970s.[19] CBZ is slowly and inconsistently absorbed from the gastrointestinal (GI) tract; peak serum concentrations are achieved approximately 4 to 8 hours after oral administration. It is moderately (60% to 85%) protein-bound. CBZ is metabolised by CYP3A4 and is a potent inducer of CYP3A4, CYP2C9, CYP1A2, and UGT enzymes. The induction of CYP3A4 is of particular interest as it can accelerate the metabolism of several drugs. It can also induce its own metabolism, such that elimination half-life can fall from 18 to 55 hours to 5 to 20 hours over a matter of several weeks, generally reaching a plateau after 3 to 5 weeks.[17]

Almost sixty years after the introduction of CBZ, it is still on the World Health Organization's List of Essential Medicines. This list defines the safest and most effective medicines needed in a health system. Despite newer ASMs, CBZ is still among the drugs of choice in treating focal epilepsy. In 2017, CBZ was the 176th most prescribed drug in the United States, with more than three million prescriptions.[20] In 2021, it dropped to the 204th position. Lamotrigine was the only sodium channel blocker higher in this list (63rd in 2017, 68th in 2021). In the Netherlands, there were 50,000 users of CBZ in 2016 (Stichting farmaceutische kerngetallen)[21], the GIPdatabank showed 33,000 users in 2020 (38,600 in 2016).[22]

With effective drug treatment, up to 70% of people with active epilepsy have the potential to become seizure-free, regardless of the type of ASM they use. In comparison with phenobarbital, valproate and vigabatrin, there was no difference in efficacy with CBZ.[23-25] Compared to other ASMs, including the newer ones, CBZ also had no superiority or inferiority in efficacy.[26] CBZ had the highest risk of discontinuation due to intolerable AEs. The most common AEs of CBZ were dizziness, diplopia, drowsiness, headache, ataxia, slurred speech, skin rash, leukopenia, osteoporosis, hepatotoxicity and hyponatremia.[27,28]

CBZ causes severe hypersensitivity reactions in a few people, and this AE has been extensively evaluated. In 2004, it was found that *HLA-B*1502* was strongly associated with CBZ-induced Stevens-Johnson syndrome (SJS) in Chinese people of Han ethnicity, increasing the risk about 100-fold, later confirmed by studies in other populations. The current recommendation is that people of Asian descent (regions prevalent in *HLA-B*1502*) should be screened for this genotype before CBZ is

prescribed.[29] In ethnic Caucasians, in whom the allele frequency of *HLA-B*1502* is very low (<0.1%), an association was found between CBZ hypersensitivity and *HLA-A*3101* (allele frequency 2-5%). This allele increased the risk of SJS with a factor of 12 in European populations, much lower than the risk of the HLA-B*1502.[30] The same year, similar results for *HLA-A 3101* were found in the Japanese people with a risk factor of 11.[31] These findings did not result in preventive screening.
Other AEs like hyponatremia are less well assessed, perhaps because physicians felt they were of minor importance and didn't recognise the influence they can have on the well-being and treatment of the patient.

Oxcarbazepine

OXC has been on the market since 1990 and is used in monotherapy and add-on treatment for focal seizures and generalised tonic clonic seizures, similarly to CBZ. In 2020 (list 2020, data from 2017), OXC was the 207th most prescribed, with over two million prescriptions. In 2021 it had risen to the 158th position.[20]
OXC, a structural derivative of CBZ, is metabolised mainly to its pharmacologically active 10-monohydroxy derivative licarbazepine (10,11-dihydro-10-hydroxy-carbazepine, MHD). OXC is rapidly absorbed after oral administration and reaches a peak concentration within 1-3 hours after a single dose. The MHD peak occurs within 4-12 hours. At a steady state, the peak occurs within 2-4 hours after drug intake. The plasma protein binding of MHD is about 40%. Elimination half-lives in healthy volunteers are 1–5 hours for OXC and 7–20 hours for MHD. Elimination half-lives can be longer in the elderly and shorter in children. There is no auto-induction.[32] About 27% of the dose is recovered in the urine as unchanged MHD and a further 49% as a glucuronide conjugate of MHD.[33] OXC appears to be a less-potent metabolic inducer than its parent compound. However, it still can deliver pharmacokinetic interactions with CYP3A4 substrates. Further, it is a weak inducer of CYP3A5 and uridine 5'-diphospho-glucuronyltransferase (UGT) and inhibits CYP2C19.[33]
OXC was introduced as being as effective as CBZ but with better tolerability. In the first randomised controlled trial (RCT), discontinuation because of severe side effects was almost half in the OXC group compared to the CBZ group (13/92 14% vs

25/98 26%).[27] No significant difference was found in the number of people with AEs, and the nature of the AEs was the same. Later in a Cochrane review, CBZ and OXC were equally well tolerated,[34] though it became more apparent that OXC had a higher prevalence of hyponatremia.[35]

In a post-marketing surveillance study, treatment with monotherapy OXC decreased seizure frequency by an average of 76% and AEs were reported in 10,8 %, causing 2,5 % of participants to discontinue OXC.[36]

The efficacy of OXC monotherapy is like that of phenytoin. The most-reported AEs associated with OXC monotherapy and/or adjunctive therapy are somnolence, dizziness, headache, nausea, and vomiting. OXC monotherapy is better tolerated than phenytoin, and although 75 to 90% of adults in five recent monotherapy studies reported AEs while receiving OXC, <8% withdrew from treatment due to them.[37]

Also, for OXC, skin hypersensitivity reactions were associated with HLA genotypes, in the same way as with CBZ, and similar screening recommendations are used for Asians.[38]

Carbamazepine- and oxcarbazepine-induced hyponatremia

Prevalence

Since epilepsy is a common disease requiring long-term treatment with ASMs, AEs such as hyponatremia can be a significant problem. Hyponatremia is defined as a serum sodium level <135 mmol/L. The reported prevalence of CBZ and OXC induced hyponatremia (COIH) varies greatly; for CBZ, the reported estimates are between 4 and 40%, whilst for OXC between 23 and 73%.[35,39-44] The prevalence is typically higher in OXC than in CBZ. In a large study looking at hospitalisation due to hyponatremia a strong association was found with newly initiated treatment with CBZ (OR 9.3 CI 5.69; 15.86) and OXC (no in the control group), but also with levetiracetam (OR 2.86 CI1.01; 8.48), although less strongly. The risk of hyponatremia was lower during ongoing treatment.[45,46] It was suggested that individuals with a susceptibility to develop severe hyponatremia were forced to stop with the ASM quickly, leaving a group of less vulnerable individuals in the ongoing treatment group.

Data on risk factors for COIH hyponatremia are limited. A few studies have looked at sex, age, dose, and use of other ASMs.[35,41,42] Age seems to be the most critical risk factor. Several studies found a significant relationship between COIH and age.[41] In a group of 414 individuals with epilepsy treated with monotherapy OXC age above 60 was associated with a higher risk of hyponatremia.[47] Others found a higher risk in individuals over 40 using CBZ and OXC.[35]

In a population-based study in the elderly, CBZ users (monotherapy) were 8.2 times more likely to be hospitalised with hyponatremia within 30 days of drug initiation than non-users.[48] The users were matched for age to the non-users, so the effect of age cannot directly be extracted from this study.

Hyponatremia induced by drug use has a preference for the female gender. There were gender-related differences in the mechanisms of Na^+ transport studied in rats. Female rats expressed significantly more vasopressin receptor 2 (V2R) in kidneys than males. This implicated that females may be more susceptible to the development of dilutional hyponatremia because of a greater sensitivity to endogenously secreted arginine vasopressin (AVP) and V2R agonist administration.[49] Reasons for preference for the female gender in humans to develop hyponatremia are yet unknown.[50] In an extensive study on the use of ASMs in psychiatric practice, cases of OXC induced severe hyponatremia were observed more frequently in women.[51] For COIH studies in people with epilepsy, conflicting results were reported about the gender influence on the risk of hyponatremia; most did not find an association with a specific gender and COIH.[35,39,42]

Potential risk factors for COIH like the dose of CBZ/ OXC and concomitant use of other ASMs were inconclusive. In a small study of 73 people on OXC, higher dosages and number of concomitant ASMs increased the risk of hyponatremia.[52] In a larger study of 414 individuals using OXC, these factors were both not associated with an increased risk, but in this group, the frequency of COIH was relatively low (9%).[47]

Pathogenesis

Several mechanisms can lead to hyponatremia. Water balance, osmotic balance and sodium homeostasis are mainly regulated by the renin-angiotensin-aldosterone (RAAS) system and the antidiuretic hormone (ADH) pathway. To understand how CBZ or OXC can induce hyponatremia, one needs to know how the average water balance works.

ADH, vasopressin, or arginine vasopressin (AVP) is synthesised in the hypothalamus and released from the posterior pituitary gland. It primarily affects the ability of the kidney to reabsorb water. In hyperosmolar states and states of hypovolemia ADH is released and binds to the V2R on the kidney principal cells within the late distal tubule and collecting ducts. Binding to the receptor triggers an intracellular cyclic adenosine monophosphate (cAMP) pathway which causes phosphorylation of the aquaporin-2 (AQP2) and subsequently it's insertion into the apical membrane. AQP2 is a water channel allowing reabsorption of water in the kidney.[53]

The ADH/V2R pathway responds quickly, in minutes-hours, to changes in volume or tonicity. The RAAS system is responsible for more chronic alterations. The juxtaglomerular cells of the kidney produce renin in response to decreased blood pressure or reduced sodium levels in the distal convoluted tubule. Renin cleaves angiotensinogen into angiotensin I, which can be converted by angiotensin-converting enzyme (ACE) to the active angiotensin II (A-II). A-II stimulates the release of aldosterone, a steroid hormone that causes an increase in sodium reabsorption in the distal tubule and collecting duct of the nephron. A-II also directly increases sodium reabsorption in the proximal convolute tubule of the kidney, stimulates thirst and the release of ADH, and it gives vasoconstriction in systemic arterioles.[54]

Hyponatremia is caused by too much water (polydipsia or inappropriate antidiuresis) or too little salt (low intake or salt wasting). Hyponatremia related to drugs is mainly caused by inappropriate antidiuresis, reabsorbing too much water and diluting sodium.[55] Drugs can influence the pathway at different parts to increase water reabsorption. It can stimulate ADH release from the pituitary gland, increase sensitivity of the V2R to vasopressin (ADH), or directly stimulate the receptors in the distal renal tubules itself. In individuals with COIH, both elevated and lowered vasopressin levels were found, not differentiating how CBZ/ OXC induced hyponatremia.[18,56-58] During a water loading test with volunteers using CBZ, vasopressin levels were less responsive to water deprivation and water loading. Further diuresis was impaired during the use of CBZ, while vasopressin levels were not changed.[59] Water loading tests with OXC use seem to affect the water balance system in the same way by creating a hypotonic hyponatremia without changing the vasopressin levels, suggesting a direct effect of CBZ and OXC in the renal tubules.[60] Finally, both in vitro experiments as rodent studies confirmed the ability

of CBZ to increase water reabsorption and AQP2 expression, even in the absence of vasopressin.[61]

Symptomatology

The clinical spectrum in hyponatremia ranges from mild, non-specific symptoms such as fatigue, headache, and gait instability to life-threatening symptoms such as seizures, coma and ultimately death, secondary to brain oedema.[62-64]

Cerebral oedema only occurs in acute severe hyponatremia and myelinolysis when sodium levels are reversed too quickly to normal. Rarely acute hyponatremia can already occur with an incidental double dosage of CBZ. A sharp drop of sodium to 122 mmol/L after ingesting a single dose of 1,200 mg of CBZ with subsequent tonic-clonic seizures was described [65] Another case report described a seven year old boy who suffered from a hyponatremic coma (with sodium level 113 mmol/L) after treatment with OXC was recently initiated and after two weeks increased in dosage from 300 mg to 450 mg/day.[66] Fortunately, these were sporadic events, but when CBZ or OXC treatment is combined with polydipsia or concurrent use of co-medication with antidiuretic properties the risk of acute hyponatremia increases.[67]

Gradually developed hyponatremia usually 'only' gives mild symptoms, but they can still impact quality of life daily. There is only limited evidence on how often mild symptoms due to COIH are experienced. One small study reported that five out of 18 (27.8%) people with OXC-induced hyponatremia had hyponatremia symptoms, including headache (n = 1), general malaise (n = 3), gait disturbance (n = 1), and somnolence (n = 1).[52] Sodium levels were prospectively collected, interviews and clinical records reviews retrieved data on symptoms. How hyponatremic symptoms were defined was not clearly described. [52]

Studies on mild chronic hyponatremia not associated with ASM use taught us that people with presumed asymptomatic hyponatremia have a significantly higher risk of admission for falls, marked gait and attention impairments, and a higher risk of bone fracture after accidental fall in the ambulatory elderly. [62,68]

Lessons learned from case histories

- AEs like COIH can interfere with adequate dosing and impede seizure control.

After the onset of focal and bilateral focal seizures at the age of 37, a woman was prescribed OXC. At the initiation of the drug, dosed 2x900 mg/day, she experienced headaches and blurry vision, tremor, fatigue, and dizziness. Her sodium level was 127 mmol/L. OXC was lowered to 2d 600 mg/day, her sodium level increased to 138 mmol/L, and the symptoms disappeared. No complaints were reported for a year, but the seizures continued. After this episode, she again felt fatigued, slow, less alert, suffered from headaches, and her sodium turned out to be 124 mmol/L. The OXC was replaced by lacosamide, which resulted in an increase of her sodium level to 141 mmol/L and both seizures and symptoms stopped. (SEIN case)

- CBZ (/OXC) combined with antipsychotics and polydipsia increases the risk of hyponatremia (episodic).

A 45-year-old female with refractory focal epilepsy was treated with CBZ 1,200 mg/day for over a decade, concomitant to phenytoin, valproate and diazepam. Some of her seizures led to postictal psychoses and, when necessary, were treated with haloperidol and lorazepam. Her sodium levels were usually normal, around 137 mmol/L. Psychotic episodes became more frequent, and haloperidol was given regularly, which decreased her sodium level to 131-133 mmol/L and made her dizzy and unstable. In one of her following psychoses, she drank a lot of water, and her sodium dropped to 122 mmol/L. Because of tiredness and after another seizure, she was admitted to the hospital. Fluid restriction restored her sodium level, and we decided to switch CBZ to lacosamide to prevent a similar event. (SEIN case)
SIADH has been described in almost all psychotropic drugs. For haloperidol, rat experiments recently showed, just as for CBZ, that it induces upregulation of V2R and AQP2 in the absence of vasopressin.[69] In a cross-sectional study, the prevalence of hyponatremia with first-generation antipsychotics was 26%, and the use of haloperidol was associated with an increased risk of polydipsia.[70] Combinations of

several drugs with antidiuretic properties and polydipsia can be hazardous and even end with a fatal outcome.[71]

- Symptoms due to hyponatremia can mimic other problems; it can be challenging to diagnose the correct cause of symptoms. Correction of sodium levels can help to differentiate between causes.

A 78 years old man had pain and weakness in the lower extremities, combined with an unsteady gate and had a history of lumbar spinal stenosis. His serum sodium level was 127 mmol/L with the use of OXC. OXC was switched to topiramate, the sodium level normalised to 143 mmol/L, and his gait improved without treatment of the lumbar stenosis.[72]
A 68-year-old man known with focal epilepsy, localised to the left frontal lobe, was treated with CBZ. After an increase in dosage from 600 to 800 mg/day, his seizure frequency reduced, but his family complained about his memory. His sodium level was 125 mmol/L at that time. Fluid restriction was prescribed, but sodium levels did not change. His walking also deteriorated, and a CT scan showed normal pressure hydrocephalus. Because of the memory deficit, the individual often forgot to restrict fluids. CBZ was replaced by lacosamide. According to family members, as the sodium level corrected to normal levels, he became more alert, and his memory function improved. His gait was still unstable and only improved after the hydrocephalus was treated by drainage. (SEIN case)

- Individuals with COIH may be unaware of the AEs caused by the hyponatremia until the ASM is switched and the sodium levels are normalised.

A 51-year-old man was treated with OXC to control his (bilateral) focal seizures successfully. Twenty years ago, his sodium levels fluctuated between 130 and 136 mmol/L. His compliance was not always perfect until he experienced the recurrence of a seizure. With good adherence, his sodium dropped to 120 mmol/L. Although he reported no complaints, the physician advised fluid reduction and a salty diet. With this regime his sodium got no higher than 127 mmol/L and subsequently, OXC

was replaced by levetiracetam. After this replacement and normalisation of his sodium levels, he felt more alert, bright and could focus his eyes better. (SEIN case)

- COIH is not always considered as a potential cause of complaints.

A young male in his twenties had a difficult to treat focal epilepsy with mesio-temporal sclerosis (MTS). With low dosage CBZ his sodium levels fluctuated between 130-133 mmol/L. Because of refractory seizures, CBZ slowly increased in dose (1,100 mg concomitant to valproate 4,000 mg and phenytoin 300 mg/day), and he complained of diplopia. He was operated on for MTS and became seizure-free. He continued to complain of dizziness and gait problems. He was referred to an ear-nose & throat specialist, who didn't find a cause. Subsequently, CBZ dose was gradually decreased to 700 mg/day, but sodium levels were not checked. After this, he experienced a recurrent seizure, was admitted, and CBZ increased again. While in the hospital, he experienced dizziness and nausea, and his sodium level was found to be 128 mmol/L. CBZ was gradually decreased to 600 mg/day and PHT stopped, and with sodium levels fluctuating between 130-134 mmol/L there were no reports of complaints.

These cases illustrate the difficulties in linking sodium levels to symptoms, both for the physician and the individual. The person will not always mention the aspecific symptoms. When mentioned, the physician will have difficulty differentiating causes, attributing the symptoms to a comorbidity or direct effects of the medication on the nervous system, or thinking of COIH.
Knowledge about the prevalence and type of symptoms due to COIH is lacking and necessary for optimal treatment of epilepsy patients.

Genetics of epilepsy and adverse effects

The genetic architecture of epilepsy is starting to be unravelled. Currently, in 40-70% of familial and sporadic epilepsy with a presumed genetic origin, a genetic cause is detected.[73,74] In some rare (familial) epilepsies, the detection of pathogenic variants shortens the time to correct diagnosis, provides improved prognosis, and can even direct treatment for some genetic epilepsies. Earlier I mentioned the example of epilepsy associated with an *SCN1A* mutation, which can cause Dravet syndrome and in which sodium blockers should be avoided. For some cases of tuberous sclerosis, with mutations in the mTOR pathway genes, complex mTOR-inhibitors can be helpful in the treatment of resistant focal seizures.[75,76]

Genetic studies do not only study genes to explain aetiology, but also look at responsiveness to treatment and AEs of treatment.

In a genome-wide association study (GWAS) in 893 European subjects with generalised epilepsy, no genomic loci were significantly associated with lamotrigine, levetiracetam, and valproate responsiveness.[77] Also, in a cohort of 1,128 subjects with non-lesional focal epilepsy, no gene in the GWAS reached genome-wide significance for drug-resistance.[78] Small pieces of the puzzle are getting together though, by research focusing on drug transport proteins and metabolising enzymes. The allelic variant *Cyp3A4*1B*, which increased gene expression, was a risk factor for developing drug resistance in paediatric patients with focal epilepsy without structural lesions.[79] Excessive activation of glycoprotein-P (P-gp) , associated with certain polymorphisms of the *MDR1* gene (encoding P-gp), is also related to resistance to ASMs. Confirmation of this relationship would allow the development of new treatment directions, for example, combining ASM with a P-gp inhibitor.[80]

The study with the most impact on treatment was of an AE, namely skin rash, during CBZ treatment. *HLA-B*1502* was found to be strongly associated with CBZ-induced Stevens-Johnson syndrome (SJS) in Chinese people of Han ethnicity, increasing the risk about 100 fold.[81] In the South-East Asian population, screening for *HLA-B*1502* before CBZ prescription is now routinely performed.[82] In individuals of European descent, *HLA-A 3101* was identified as a clinically relevant predictor for the full spectrum of CBZ-induced hypersensitivity reactions.[30]

Another AE in epilepsy treatment has been studied genetically. In some people treated with VPA, severe hyperammonemia has been observed in the absence of liver failure and may result in encephalopathy. In a cohort of 142 Caucasians, an association with a polymorphism in the carbamoyl phosphate synthetase 1 (*CPS1*) gene was found.[83]

To date, no genetic risk factors have been associated with COIH. For thiazide induced hyponatremia polymorphisms were found in the *KCNJ1* gene encoding for the renal outer medullary potassium channel (ROMK), which plays a role in renal reabsorption of sodium.[84] Considering the impact of the finding of the genetic markers in CBZ-induced SJS and the finding of a genetic marker for hyponatremia induced by another drug, provide a strong motivation to search for genetic markers in COIH.

Aim and outline of this thesis

This thesis aims to show the clinical importance of COIH and define biomarkers to improve clinical management. In the first chapter, we review what is known about this AE in literature and zoom in on the mechanism of the antidiuretic effect of CBZ and OXC. In the second chapter, we evaluate the clinical characteristics of hyponatremia and aim to determine the prevalence and possible determinants of COIH. In the third chapter, we aim to uncover the type of symptoms experienced by people with COIH and determine if they can be attributed to COIH. To do so, we compare the symptoms and AEs between people taking the same ASMs with and without the development of hyponatremia. In the last chapter, we attempt to uncover genetic factors contributing to COIH and the clinical and genetic factors contributing to CBZ metabolism.

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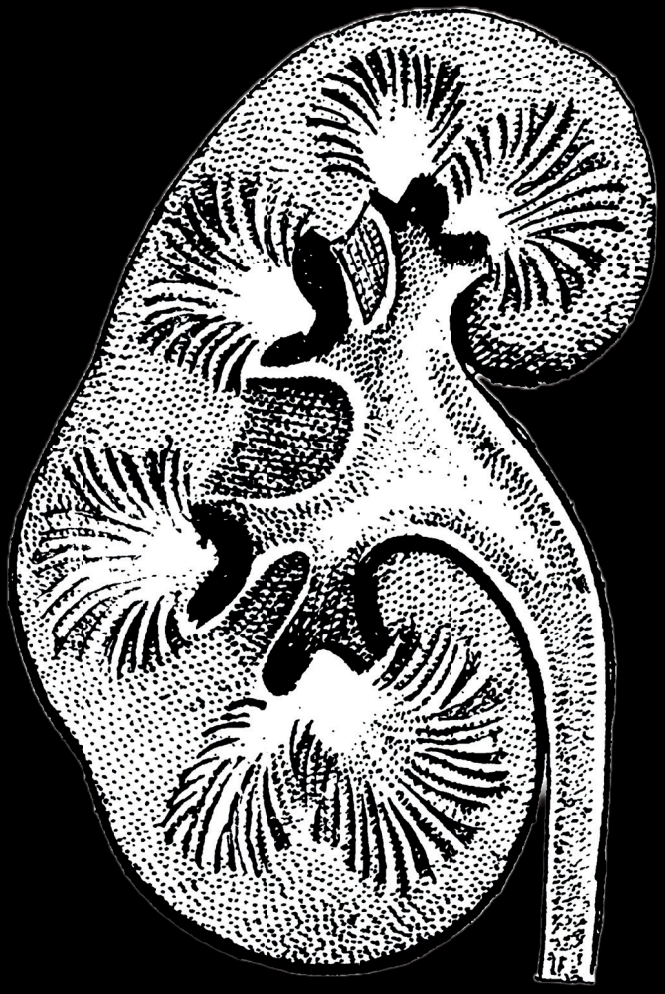

CHAPTER 2

Epidemiology, pathophysiology and putative genetic basis of carbamazepine- and oxcarbazepine-induced hyponatremia

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Epidemiology, pathophysiology and putative genetic basis of carbamazepine- and oxcarbazepine-induced hyponatremia

Abstract

The use of carbamazepine (CBZ) and oxcarbazepine (OXC) as first line antiepileptic drugs in the treatment of focal epilepsy is limited by hyponatremia, a known adverse effect. Hyponatremia occurs in up to half of people taking CBZ or OXC and, although often assumed to be asymptomatic, it can lead to symptoms ranging from unsteadiness and mild confusion to seizures and coma. Hyponatremia is probably due to the antidiuretic properties of CBZ and OXC that are, at least partly, explained by stimulation of the vasopressin 2 receptor (V2R)/Aquaporin 2 (AQP2) pathway. No known genetic risk variants for CBZ and OXC induced hyponatremia exist, but likely candidate genes are part of the vasopressin water reabsorption pathway.

Introduction

Carbamazepine (CBZ) and its keto-analogue oxcarbazepine (OXC) are antiepileptic drugs (AEDs) widely used in the treatment of focal epilepsy. The use of CBZ and OXC is, however, limited by hyponatremia, a major adverse effect (AE) associated with these AEDs. CBZ and OXC induced hyponatremia (COIH) seems due to water retention. The way in which the antidiuretic effect of these AEDs is exerted, is not fully understood. To date no genetic risk factors has been associated with COIH as pharmacogenomic studies are lacking.

The clinical use of pharmacogenomics in epilepsy was well demonstrated by CBZ-induced severe cutaneous reactions. In 2004 it was found that *HLA-B*1502* was strongly associated with CBZ-induced Stevens-Johnson syndrome SJS in people of Han-Chinese ethnicity, increasing the risk about 100 fold.[1] In the South-East Asian population screening for *HLA-B*1502* prior to CBZ prescription is now routinely performed.[2]

Here, we review the clinical importance of COIH, the mechanism of the antidiuretic effect and the potential role for pharmacogenomics in uncovering the genetic predisposing factors.

Antiepileptic drugs

Carbamazepine was first introduced in 1962.[3] In the central nervous system, CBZ reduces neuronal hyperexcitability and exerts its action mainly by inhibition of voltage-gated sodium channels.[4] Fifty years later it is still recommended as a drug of first choice for treating focal epilepsy despite recent concerns about its potential to induce liver enzymatic systems.[5,6] CBZ is also prescribed in the treatment of trigeminal neuralgia and bipolar disorders. Frequent adverse effects (AEs) of CBZ include drowsiness, loss of coordination, vertigo, rash, leucopenia, osteoporosis, hepatotoxicity and hyponatremia.

OXC, introduced in 1990, was developed to bypass the formation of the epoxide metabolite of CBZ.[7] OXC and CBZ appear to be similarly effective. In a double-blind study comparing OXC and CBZ in people with newly diagnosed epilepsy, complete seizure control was achieved in 52% with OXC treatment and in 60% with CBZ treatment, a non-significant difference.[7] Similarly, a 50% reduction in seizure

frequency was seen in 80% of people taking OXC and 81% taking CBZ.[7,8] Subsequent studies showed better tolerability of OXC, apart from hyponatremia. Several studies have demonstrated that CBZ induces hyponatremia in 5-40 % of individuals.[9,10] For OXC the incidence appears to be even higher at 30-51%.[10,11] This serious AE sometimes results in dose decrease or even in complete withdrawal, limiting the use of CBZ and OXC.[12]

The adverse drug response

Hyponatremia is defined as a serum sodium level < 136 mEq/l resulting in excess total body water relative to total solute. It is considered mild when sodium levels are between 131 and 135 mEq/l, moderate when 125-130 mEq/l and severe when < 125mEq/l.[13,14] Acute severe hyponatremia is associated with neurological symptoms such as seizures and coma and should be treated urgently to prevent life-threatening complications such as cerebral oedema and encephalopathy.[13,15] Chronic hyponatremia causes more subtle neurological symptoms such as unsteadiness, difficulty concentrating, reduced attention span, mild confusion and personality changes.[16,17] These symptoms are often mistakenly attributed to the underlying disorder, personality or direct drug toxicity without considering hyponatremia as a potential cause.

Several risk factors exist for hyponatremia associated with CBZ use, including age > 40 years, concomitant use of drugs associated with hyponatremia[18] (table 1), menstruation, psychiatric conditions, surgery, (psychogenic) polydipsia and female gender.[19,20] Similar risk factors exist for OXC, but age> 40 years has an even stronger correlation, as shown by the higher rate of hyponatremia in people over 40 years of age taking either OXC (60%) or CBZ (20%).[10] A study of OXC-induced severe hyponatremia in a large cohort (n=1009) provided further support for age, concomitant use of diuretics and AED polytherapy as independent risk factors.[21] To date no clear dose-effect relationship between OXC and occurrence of hyponatremia was found.[10] Conversely, for CBZ a negative relationship between plasma sodium concentration and CBZ serum concentration, as well as the cumulative daily dose, has been described;[22,23] though not confirmed in other studies.[24]

Table 1 Other drugs associated with hyponatremia.[18]

Drugs associated with hyponatremia	affecting sodium homeostasis	affecting water homeostasis	
		SIADH	*Renal effect*
Diuretics	✓		✓
Antidepressants		✓	
Antipsychotic drugs		✓	
Opiates		✓	
Anticancer agents		✓	✓
Antiepileptic drugs		✓	✓
Antidiabetic drugs			✓
Nonsteroidal anti-inflammatory drugs			✓

The effects of hyponatremia: a case

An individual with epilepsy attending our Centre was successfully treated with OXC for over 10 years. Serum sodium levels were chronically low (121-129 mEq/l) and mild dizziness was accepted as the cost for complete seizure control. Due to hypertension, a combination of the ACE-inhibitor perindopril and the thiazide-like diuretic indapamide was added and the sodium level dropped to 114 mEq/l within a few days of the start, causing falls, cognitive slowness and hospitalization. Indapamide was stopped, the sodium level increased to 123 mEq/l and the symptoms disappeared. This case is an illustration of the care needed when adding medication associated with hyponatremia in people using CBZ/OXC.

The mechanism

There are several different biological mechanisms that can lead to hyponatremia. Simplified, there is either too much water (polydipsia, inappropriate antidiuresis) or too little salt (low intake or salt wasting) present.[14] Hyponatremia related to drugs is mainly caused by the syndrome of inappropriate antidiuresis (SIAD).[14] An antidiuretic effect of CBZ was first reported in 1966 when it was found to be

beneficial in people with diabetes insipidus, a disorder characterized by polydipsia and polyuria caused by a lack of pituitary vasopressin production.[25,26] In early case reports of CBZ-induced hyponatremia both elevated[27,28] and lowered[29]levels of vasopressin (also called antidiuretic hormone, ADH) were found. These findings suggested that CBZ either stimulates vasopressin secretion from the posterior pituitary gland or has a direct renal effect itself. According to the renal effect theory, CBZ is thought to increase the sensitivity of osmoreceptors to vasopressin in the renal distal convoluted tubules and collecting ducts or to exert a direct effect on these receptors leading to water retention (Fig 1).[9]

A combined central and renal effect has been suggested.[30] In a cross-over study, water loading tests were performed in 12 healthy volunteers before and after receiving 600 mg/day CBZ for seven days. With CBZ, vasopressin levels increased less during water deprivation and decreased less during water loading, without affecting plasma sodium concentration and plasma osmolality. It was concluded that osmoreceptors were less responsive as a result of CBZ.[30] Impaired diuresis during CBZ use was also observed, despite similar vasopressin concentration at peak diuresis when on and off CBZ.[30] It could be argued that this is a direct effect of CBZ on receptors in the renal tubules.

For OXC a similar cross-over design study was performed in a group of people with epilepsy and a group of healthy controls. Exposure to OXC for 3 weeks resulted in significant reduction in serum osmolality (i.e. hypotonicity) and serum sodium concentration after a water loading test in both groups. Hypotonic hyponatremia was not associated with a significant change in serum vasopressin levels, but was the result of both a relative inability to dilute the urine and a reduction of over 50% in water excreted after the water loading test.[31]

Vasopressin exerts its antidiuretic action by binding and activating the arginine vasopressin receptor 2 (V2R), resulting in an increase in intracellular cyclic adenosine monophosphate (cAMP). cAMP promotes shuttling of intracellular vesicles, containing Aquaporin 2 (AQP2) water channels, to the apical membrane of the collecting-duct cells. Water permeability is thereby increased, inducing anti-diuresis.[32,33] A rodent study suggested that CBZ could activate the vasopressin receptor in the renal medulla and that CBZ can induce renal water absorption by acting directly on the V2R -protein G complex and increasing the AQP2 expression.

In vitro microperfusion experiments showed that CBZ was able to increase water (re)–absorption in the absence of vasopressin. Tests with selective cAMP and V2R inhibitors showed that the CBZ effect on water absorption is cAMP-dependent and acts in the V2R-protein G-complex. In vivo tests were done in three groups: controls; rats on a CBZ diet; and rats initially taking lithium, subsequently taking lithium and CBZ. The CBZ diet alone did not increase AQP2 expression compared with controls. CBZ was, however, able to correct nephrogenic diabetes insipidus (NDI) in rats receiving lithium. Lithium decreases AQP2 expression since it blocks vasopressin action. Addition of CBZ reversed 20% of the decrease in AQP2 expression.[32]

Paradoxical effects were observed in another rodent study in which CBZ therapy increased diuresis and electrolyte loss. After rats received the V2R antagonist savaptan, urinary flow and natriuresis were further increased by CBZ.[34] Thus even though CBZ has a comparable pharmacological effect to a V2R agonist, some findings in rat studies suggest that other pathways also play a role.

One pathway of interest is the influence of prostaglandins on water transport. Prostaglandin E2 (PGE2), a product of arachidonic acid (AA) metabolism by cyclooxygenase (COX), inhibits vasopressin-induced water permeability by reducing cAMP levels(fig 1).[35,36] Inhibition of PGE2 synthesis potentiates antidiuresis. Nonsteroidal anti-inflammatory drug-induced hyponatremia has been associated with the inhibition of synthesis of renal prostaglandins due to COX inhibition.[37] As well as COX, other enzymes are involved in AA metabolism; lipoxygenase and cytochrome P450 (CYP450) also metabolize AA. Induction of the CYP450 pathway results in less AA being available for metabolism by COX, resulting in less renal prostaglandin synthesis.[38] It is conceivable that CBZ, a major P450-enzyme inducer, potentiates antidiuresis through this mechanism. It is unlikely that this is the only mechanism as OXC is a weaker CYP450 inducer than CBZ, whereas the incidence of hyponatremia associated with OXC use seems higher.

Lithium (Li)-induced polyuria due to resistance to vasopressin is mediated by increased PGE2 signalling acting via P2Y receptors. For COIH this pathway has not yet been assessed.[39,40]

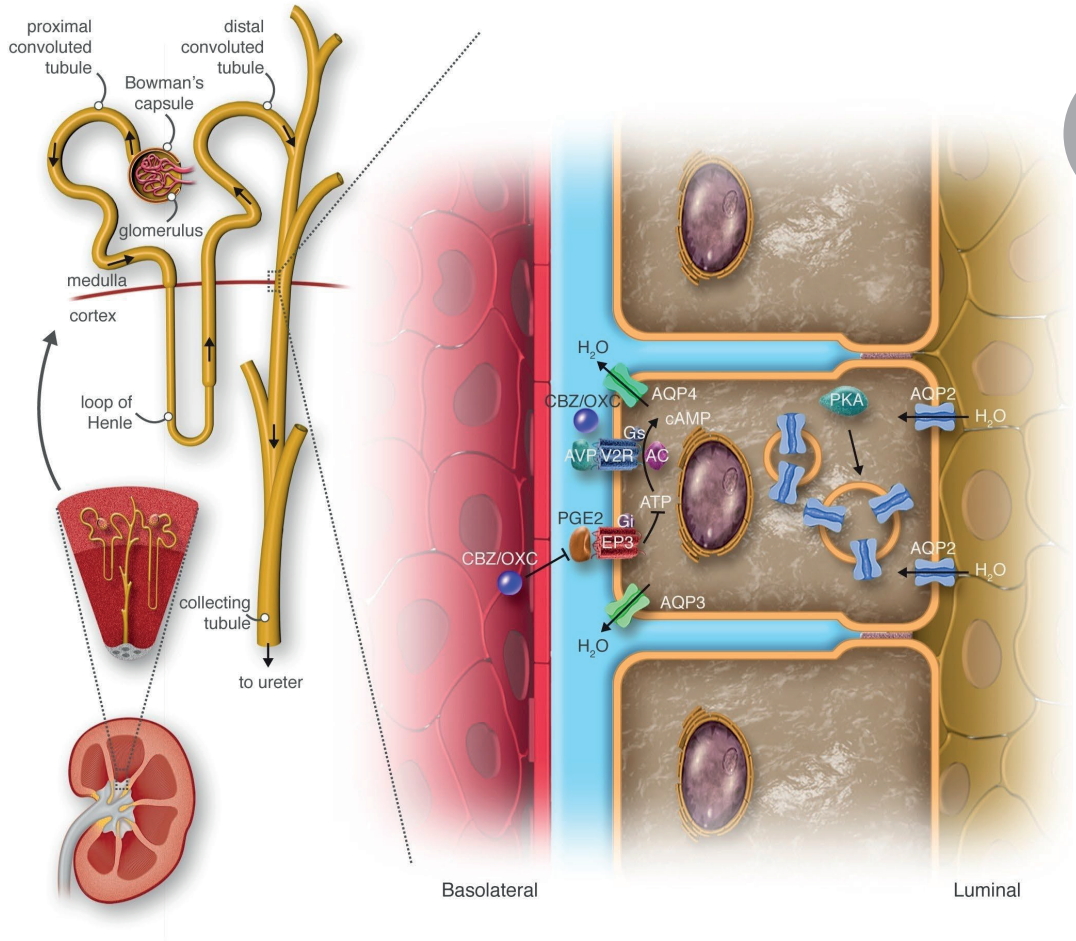

Figure 1. Vasopressin dependent water regulation. Vasopressin (AVP) acts on V2 receptors (V2R) in the basolateral plasma membrane. Through the GTP-binding protein Gs, adenylyl cyclase (A.C.) is activated, stimulating the production of cAMP from ATP. cAMP binds and activates protein kinase A (PKA), which than phosphorylates AQP2 in intracellular vesicles. AQP2 moves to the apical plasma membrane to increase water permeability. PGE2 inhibits this process by binding to the Prostaglandin receptor E3 (EP3)and reducing the production of cAMP. CBZ/OXC influences the water regulation by activating the V2R/AC complex and/or by inhibiting PGE2 formation.

Genetics and pharmacogenomics

In a large cohort study for both CBZ and OXC the future risk of persistent hyponatremia was highly correlated to the initial sodium level measured soon after starting the drug. Age, gender and other AEDs had minimal influence on the follow-up outcome. This implies that there exists a subgroup of persons who are inherently susceptible to COIH.[10]

Recently a genetic risk factor was found for two other drugs which are known to induce hyponatremia. Antidepressant users homozygous for the *CYP2D6*4* allele had a significantly lower serum sodium concentration than antidepressant users with the wild-type genotype. CYP2D6 poor metabolizers had higher plasma concentrations of antidepressants and were therefore more likely to suffer from adverse drug events.[41] Ecstasy induced hyponatremia was also associated with low active CYP2D6 and COMT (catechol-*O*-methyltransferase) genotypes.[42] CBZ is mainly metabolised by CYP3A4. OXC is rapidly reduced to the active metabolite (10-monohydroxy derivative, MHD) by cytosolic enzymes in the liver. MHD is further metabolised by glucuronosylation. A role for these pathways in the risk of hyponatremia has not yet been assessed.

Thiazide induced hyponatremia was associated with 2 polymorphisms in the KCNJ1 gene, encoding for the renal outer medullary potassium channel (ROMK) which plays an important role in the sodium reabsorption in the thick ascending limb of the Loop of Henle (TAL).[43] Mutations in ROMK lead to Bartter syndrome, a renal salt wasting condition further characterized by hypokalemic metabolic alkalosis and hyperreninaemic hyperaldosteronism.

CBZ and OXC do not seem to influence salt reabsorption, but water reabsorption. Mutations in the V2R/AQP2 pathway regulating water reabsorption can cause disorders clinically similar to SIAD associated with CBZ/OXC use.

Nephrogenic syndrome of inappropriate antidiuresis (NSIAD) was first described in two unrelated infant boys and was characterized by excess hypotonic fluid and undetectable vasopressin levels.[44] Both were hemizygous for an X-linked *AVPR2* mutation and presented with seizures, hyponatremia (123 and 118 mEq/l respectively), and serum hypo-osmolality with inappropriately elevated urinary osmolality and sodium levels. Functional studies showed that basal levels of cAMP production in cells expressing the mutated V2R were four times the levels in cells

expressing wild-type V2R (P=0.01). These *AVPR2* mutations created a constitutively active V2R explaining the hyponatremia with increased urinary osmolality.[44] Families described with NSAID show great variability in phenotype, and the disorder may go unrecognized for years.[45,46] All asymptomatic family members (hemizygous and heterozygous), however, had an abnormal response (including hyponatremia) when challenged by a mild water load.[46]

X-linked, inactivating mutations in the arginine vasopressin receptor 2 gene (*AVPR2)* and autosomal mutations in *AQP2* cause nephrogenic diabetes insipidus, characterized by the inability of the kidney to concentrate urine leading to polyuria, dehydration and hypernatremia.[47]

Despite recent advances in understanding renal sodium and water regulation, much is still unknown. Thus even a long list of candidate genes containing all known regulators in the water reabsorption pathway may not contain the causative variant to explain genetic susceptibility to COIH. It may be that techniques such as whole exome sequencing or Genome Wide Association Study (GWAS) may be more successful.

Conclusion

Hyponatremia should no longer be considered an asymptomatic condition.[16] Symptoms such as unsteadiness, dizziness, difficulty concentrating, reduced attention span, mild confusion, and lethargy in people taking CBZ or OXC should alert the physician to check the sodium levels. In people with multiple risk factors, hyponatremia might occur much faster with more severe, even life threatening, symptoms. Preventive fluid restriction can be of great value in these situations.

The mechanism of COIH is still not fully elucidated but there is evidence that the antidiuretic effect is, at least partly, caused by stimulation, direct or via PGE2, of the V2R/AQP2 pathway. In people with NSIAD serum sodium levels and serum and urine osmolality are changed in the same direction as seen with the use of CBZ and OXC. It is possible that other variants in *AVPR2* with influence on the activation state of V2R make people more susceptible to the antidiuretic effect of CBZ and OXC. Future research should attempt to clarify the underlying mechanism of COIH and to find genetic variants which may identify people at risk of developing clinically relevant COIH. In these people CBZ and OXC should be gradually withdrawn and

alternative antiepileptic drugs should be prescribed. When the person at risk is dependent on CBZ or OXC for seizure control, electrolytes should be intensively monitored.

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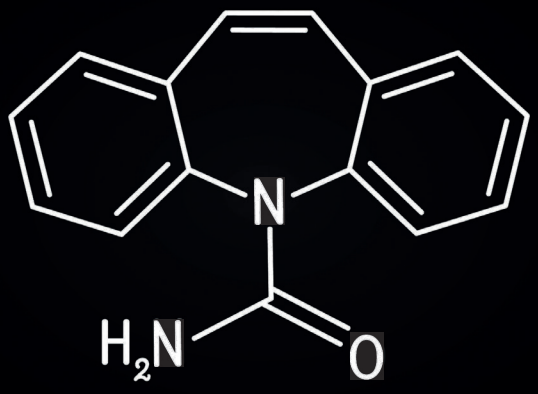
Carbamazepine



$C_{15}H_{12}N_2O$

Oxcarbazepine

$C_{15}H_{12}N_2O_2$

CHAPTER 3

Carbamazepine- and oxcarbazepine-induced hyponatremia in people with epilepsy

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Carbamazepine- and oxcarbazepine-induced hyponatremia in people with epilepsy

Abstract

Objective To ascertain possible determinants of carbamazepine (CBZ) and oxcarbazepine (OXC) induced hyponatremia in a large cohort of people with epilepsy.

Methods We collected data on serum sodium levels in people with epilepsy attending a tertiary epilepsy centre while on treatment with CBZ or OXC. We defined hyponatremia as $Na^+ \leq 134$ mEq/L and severe hyponatremia as $Na^+ \leq 128$ mEq/L.

Results We identified 1,782 people who had used CBZ (n=1,424) or OXC (n=358) of whom 50 were treated with both drugs. Data on sodium level measurements were available in 1,132 on CBZ and in 289 on OXC. Hyponatremia occurred in 26% of those taking CBZ and 46% taking OXC. This was severe in 7% in the CBZ group and 22% in the OXC group. Hyponatremia was symptomatic in 48% and lead to admissions in 3%. Age over 40 years, high serum levels of CBZ and OXC and concomitant use of other antiepileptic drugs were the main risk factors for hyponatremia in both treatment groups. Females on OXC were at a higher risk of hyponatremia than males. The risk of hyponatremia on CBZ was significantly associated with the risk of hyponatremia on OXC within a subgroup that used both drugs consecutively.

Significance Hyponatremia is a common problem in people taking CBZ or OXC. Regular ascertainment of sodium levels in those taking either drug is recommended and results should be acted upon.

Introduction

The antiepileptic drugs (AEDs) carbamazepine (CBZ) and its keto-analogue oxcarbazepine (OXC) are among the drugs of choice for the treatment of focal epilepsy. The use of CBZ and OXC is limited by hyponatremia. It can lead to symptoms ranging from unsteadiness and mild confusion to seizures and coma although it is often assumed to be asymptomatic.[1,2] Its severity depends on the absolute sodium levels and the rate of decline of sodium.[3] The reported prevalence of CBZ and OXC induced hyponatremia (COIH) varies greatly; for CBZ the reported estimates are between 4 and 40% whilst for OXC they are between 23 and 73%.[4,5] Data on risk factors for hyponatremia are limited. A few studies have looked at sex, age, dose and use of other AEDs, but results were inconclusive, often due to low sample size.
We aimed to confirm previous observations, evaluate the clinical characteristics of hyponatremic and identify possible determinants of COIH in a large cohort of people treated for epilepsy.

Methods

An electronic database designed for pharmacogenomics studies (www.epipgx.eu), capturing all relevant clinical data with an emphasis on AED history, has been in use since 2010 at a tertiary referral centre for epilepsy (http://www.sein.nl/en/). It was used to identify all individuals who were prescribed CBZ or OXC and who had a recorded serum sodium level during therapy. Levels were measured during the course of routine monitoring. For each sodium level measurement, we recorded the date, serum level of CBZ or OXC and concomitant use of other AEDs. Most individuals had several measurements and we used the lowest sodium level recorded for each for the analysis. We defined hyponatremia as a sodium level ≤134 mEq/L, and severe hyponatremia as ≤128 mEq/L, in line with previous studies. [5,6] Potentially predictive variables for hyponatremia tested were: CBZ and OXC serum levels, age, sex and concomitant AEDs. Clinical characteristics of those hyponatremic were retrieved from case notes. Symptoms present at the time of

hyponatremia, which could not be explained by another clear cause such as overt AED intoxication or comorbidity were scored.

Statistics: Sodium levels were modelled either as a continuous variable or as a dichotomized variable (≤or >134 mEq/L). Independent samples T-Tests for continuous variables and 2*2 tables with chi-squared tests for categorical variables were used to examine the association of the individual risk factors with hyponatremia. Linear regression was used to assess the relationship of these variables with sodium levels as a continuous variable in a multivariate analysis. The appropriateness of the multivariate linear regression was assessed by plotting standardised residuals, which were visually inspected for normality. Multivariate logistic regression was used to assess the relationship of these variables with hyponatremia as a dichotomous variable.
In people with a sodium level ≤128 mEq/L information on co-medication other than AEDs was retrieved from case notes and differences in mean sodium levels between those using and not using these various medications were analysed with independent samples T-Tests.
In the subgroup analyses for users of both CBZ and OXC, means of sodium levels were compared with the paired samples T-Test and the McNemar test was used to analyze the differences for binary data, such as the occurrence of hyponatremia.
The statistical analysis was carried out on SPSS version 22.0 for Windows (SPSS Inc., Chicago, IL).

Ethics: The Ethical Committee of UMC Utrecht approved this investigation. All participants had previously provided written informed consent for data retrieval.

Results

We identified 1,732 people (94% Caucasians) who had used CBZ (n=1,424) or OXC (n=358); sodium levels were not measured or not recorded in 361 (21%). Fifty people in the cohort had sodium levels measured during both CBZ and OXC treatment; no one used both drugs at the same time. Sodium levels were measured and recorded in 1,132 (79%) treated with CBZ (616 males) with a mean age of 41.8

±15.6 (years ±SD) and a mean Na^+ level of 138.4 ±4.2 mEq/L. In the OXC group sodium levels were measured and recorded in 289 people (81%; 150 males), with a mean age of 37.2 ±16.2 and a mean Na^+ level of 135.7 ±5.5 mEq/L. The average number of Na^+ measurements was 1.71±1.0 (min 1, max 11). Hyponatremia was seen in 26% (294/1,132) in the CBZ group and 46% (134/289) in the OXC group. Severe hyponatremia was found in 7% (81/1,132) in the CBZ group and in 22% (65/289) in the OXC group.

Hyponatremia was symptomatic in 48% (194/402, 26 missing data) of those found to have low sodium levels (35% in people with mild hyponatremia and 72% in severe hyponatremia). Among those symptomatic 6% had CBZ or OXC levels above the therapeutic range (10 with CBZ levels ≥11, one with OXC level ≥35). Symptoms were mostly mild: dizziness (94/194; 48%), diplopia (48/194; 25%), unsteady gait (63/194; 32%), lethargy (37/194; 19%), cognitive slowness (26/194; 13%), tiredness (71/194; 37%) headache (30/194; 15%), nausea and vomiting (34/194; 18%). Falls were reported by 11% (21/194; 11%) and two who had severe hyponatremia sustained a fracture due to falling. In the group with severe hyponatremia seizure aggravation was seen in 22% (22/102). Six (3%, 5 with severe hyponatremia) were admitted to hospital for treatment.

CBZ/OXC and sodium levels

Sodium levels were significantly associated with serum levels of CBZ (p<0.001) and OXC (p=0.001)(table 1), but explained only a small part of the variance in the continuous sodium levels (R^2=0.03 and 0.04, respectively, figure 1). Adjustment for age, sex and number of concomitantly used AEDs did not influence this association. All these cofactors were independently associated with continuous sodium levels. (suppl fig 1 for age and sodium levels) Mean sodium levels were lower in females (136.9 mEq/L with CBZ, 133.3 mEq/L with OXC) than in males (137.6 mEq/L with CBZ, 135.4 mEq/L with OXC) (p=0.012 in CBZ and p=0.005 in OXC).

Table 1. Univariate and multivariate analysis of demographic and clinical data with sodium level (mEql/l) as dependent variable.

	Univariate Analysis								Multivariate Analysis			
	Carbamazepine				Oxcarbazepine				Carbamazepine		Oxcarbazepine	
	N	R^2	Regr. coeff	*P-value*	N	R^2	Regr. coeff	*P- value*	Regr. coeff	*P-* value	Regr. coeff	*P-* value
Drug level (mg/L)	1,008	0.025	-0.34	<0.001	257	0.039	-0.17	0.001	-0.31	<0.001	-0.19	<0.001
Age (years)	1,132	0.078	-0.09	<0.001	289	0.040	-0.08	0.001	-0.08	<0.001	-0.06	0.007
Sex*	1,132	0.006	0.76	0.010	289	0.027	2.11	0.005	0.91	0.002	2.30	0.003
NcoAEDs	1,087	0.018	-0.77	<0.001	277	0.054	-1.81	<0.001	-0.64	<0.001	-1.32	0.005
									n=968	R^2=0.116	n=245	R^2=0.135

NcoAEDs = number of concomitant AEDs used. Regr. coeff= regression coefficient.

* reference group= female

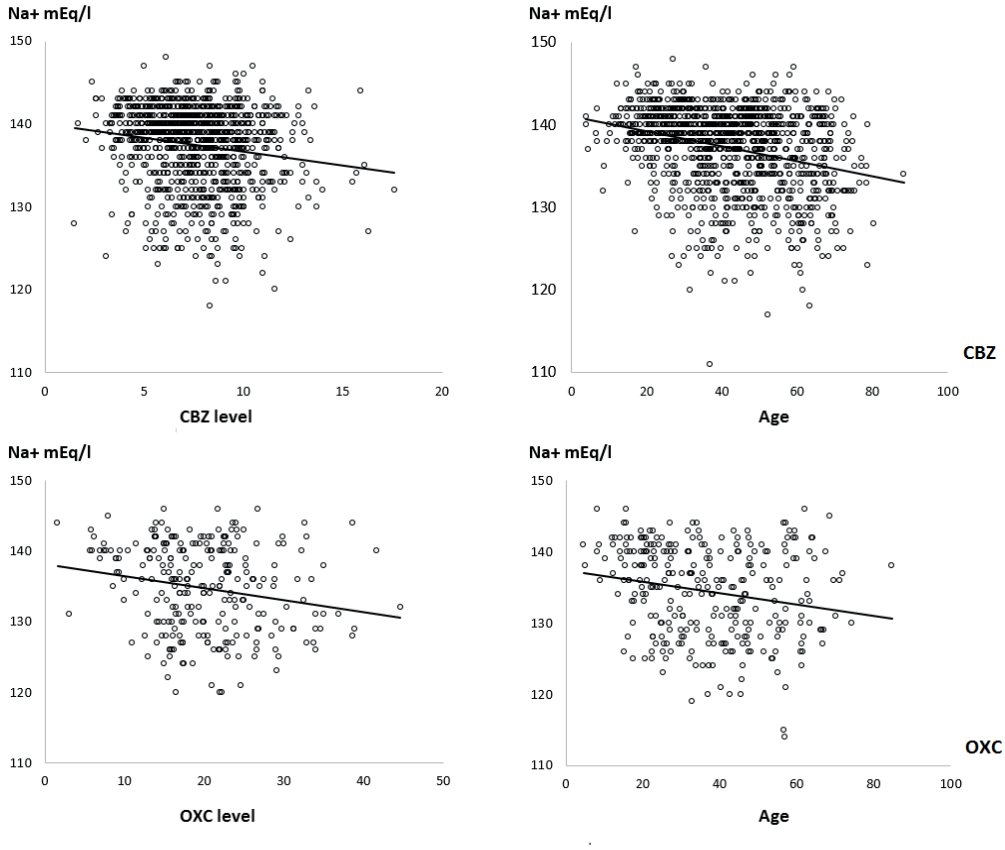
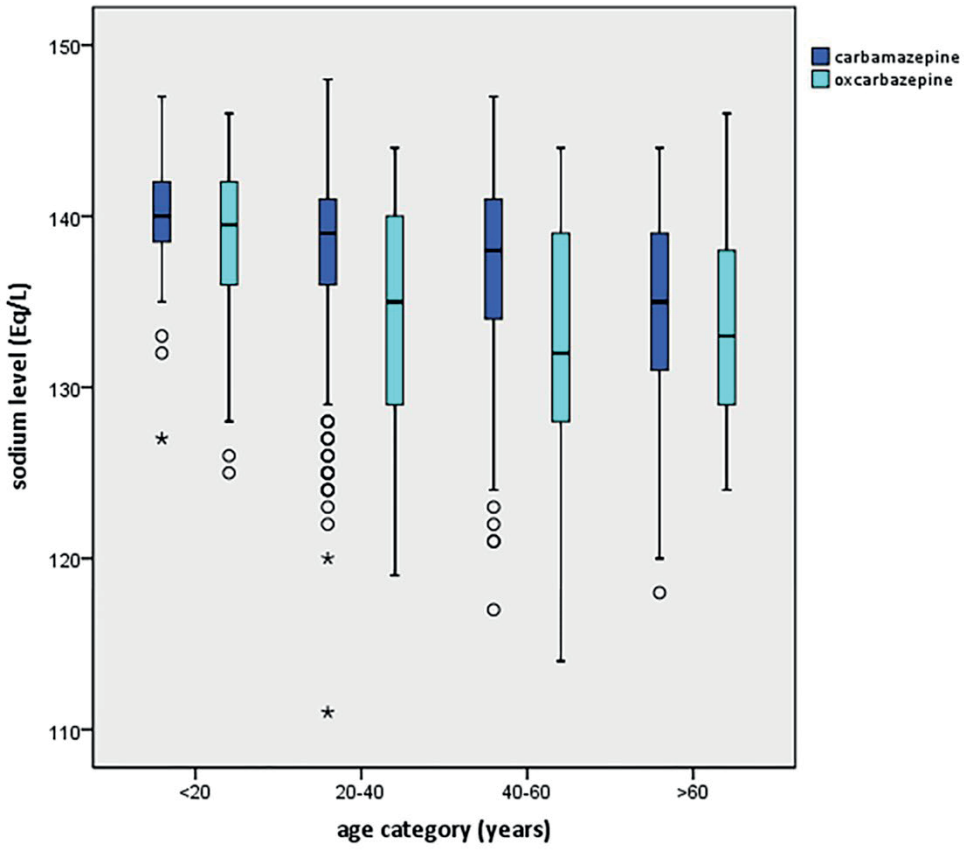


Fig 1. Sodium levels in relation to drug levels and age
Relationship between sodium level (Na^+ mEq/L) and drug level (mg/L) and relationship between sodium level and age (years) within both the carbamazepine (CBZ) and oxcarbazepine (OXC) treatment group.



Suppl. fig 1.
Mean sodium levels in different age categories for carbamazepine and oxcarbazepine users.

CBZ/OXC and hyponatremia

Serum levels of CBZ and OXC were significantly associated with hyponatremia, increasing the risk by a factor 1.20 (95% CI 1.12-1.28, $p<0.001$) and 1.06 (95% CI 1.02-1.10, $p=0.001$) per unit (mg/L) increase, respectively. (table 2) This association remained significant in the multivariate logistic analysis. (table 3)

When sodium levels were used as a dichotomized variable, sex remained a risk factor for hyponatremia in the OXC group, but not in the CBZ group. Women in the OXC group were more likely to develop hyponatremia (55%) than men (39%).

In those over 40 years hyponatremia was seen in 34% (compared with 17% <40 years) in the CBZ group and in 56% (compared with 39% <40 years) in the OXC group. In a multivariate logistic regression analysis, age over 40 increased the odds of hyponatremia by a factor 2.5 in the CBZ group and 2.2 in the OXC group. The hyponatremia frequency in different age categories for CBZ and OXC users is shown in supplementary figure 2.

Monotherapy was associated with a lower risk of hyponatremia than polytherapy. After correction for drug levels, age and sex this association did not reach significance in the OXC group. The risk of hyponatremia was significantly increased with increasing number of concomitant AEDs in both groups. Independent risk factors in both treatment groups were the concomitant use of clobazam (CLB) and phenytoin (PHT). Valproate (VPA) and phenobarbital (PB) were additional risk factors for hyponatremia in the CBZ group.

These observations were similar across sodium levels in three categories (≤ 128, 129-134, ≥ 135) but numbers in the severe hyponatremia group were small (results not shown).

Table 2. Univariate analyses of demographic and clinical data with hyponatremia (Na ≤ 134 mEq/L) as dependent variable.

		Carbamazepine			Oxcarbazepine		
		na< =134	**na>134**	***p*-value**	**na< =134**	**na>134**	***p*-value**
Mean drug level (mg/L)		8.3	7.4	<0.001	21.7	18.7	0.001
Mean age (yrs)		49.1	39.3	<0.001	40.6	34.3	0.001
AgeCat40	≤ 40	88 (17%)	440 (83%)	<0.001	64 (39%)	101 (61%)	0.003
	>40	206 (34%)	398 (66%)		70 (56%)	54 (44%)	
Sex	m	152 (25%)	464 (75%)	0.28	58 (39%)	92 (61%)	0.006
	f	142 (28%)	374 (72%)		76 (55%)	63 (45%)	
Monotherapy	yes	53 (17%)	260 (83%)	<0.001	29 (36%)	52 (64%)	0.03
	no	230 (30%)	544 (70%)		99 (51%)	97 (49%)	
CLB	yes	56 (42%)	80 (59%)	<0.001	31 (70%)	13 (30%)	<0.001
	no	227 (24%)	724 (76%)		97 (42%)	136 (58%)	
PHT	yes	34 (38%)	56 (62%)	0.008	17 (77%)	5 (23%)	0.002
	no	249 (25%)	748 (75%)		111 (44%)	144 (56%)	
VPA	yes	90 (31%)	197 (69%)	0.02	28 (44%)	35 (56%)	0.73
	no	193 (24%)	607 (76%)		106 (47%)	120 (53%)	
PB	yes	22(38%)	36(62%)	0.03	5 (71%)	2 (29%)	0.18
	no	261(25%)	768(75%)		129 (46%)	153 (54%)	

AgeCat40 = age category split at 40 years; CLB=clobazam, PB= phenobarbital, PHT= phenytoin, VPA= valproic acid

Table 3. Multivariate logistic regression analysis of demographic and clinical data with hyponatremia as dependent variable

	Carbamazepine (n=968)				Oxcarbazepine (n=245)			
	Odds Ratio	95% C.I. Lower	Upper	*P*-value	Odds Ratio	95% C.I. Lower	Upper	*P*-value
Drug level (mg/L)	1.23	1.14	1.315	<0.001	1.08	1.04	1.12	<0.001
Age (years)	1.04	1.03	1.05	<0.001	1.03	1.01	1.04	0.004
Sex*	1.29	0.95	1.76	0.11	2.25	1.29	3.93	0.004
NcoAEDs	1.45	1.22	1.73	<0.001	1.98	1.13	2.26	0.008
AgeCat>40[a]	2.51	1.83	3.45	<0.001	2.24	1.28	3.90	0.004
Monotherapy[b]	0.43	0.30	0.62	<0.001	0.64	0.35	1.16	0.14
VPA[b]	1.82	1.29	2.58	0.001	1.20	0.64	2.27	0.57
PB[b]	1.98	1.075	3.66	0.03	3.27	0.53	20.18	0.20
CLB[b]	2.41	1.57	3.68	<0.001	3.84	1.75	8.41	0.001
PHT[b]	2.40	1.43	4.01	0.001	6.30	2.04	19.43	0.001

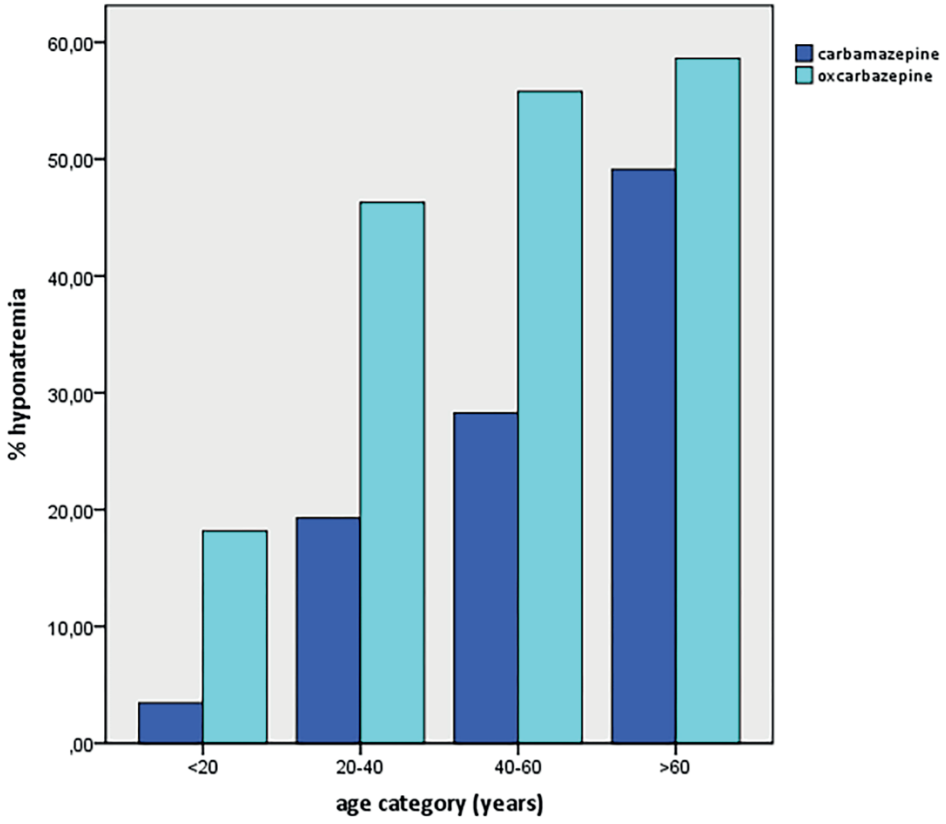
AgeCat>40 =age category above 40 years, NcoAEDs = number of concomitant antiepileptic drugs,

* reference group= male

a Model with covariates: drug level, sex and NCoMed

b Each therapy is separately tested in a model with covariates: drug level, age and sex

Clonazepam, ethosuximide, lacosamide, lamotrigine, levetiracetam, gabapentin, topiramate, vigabatrin were not significantly associated with hyponatremia in a multivariate analysis.



Suppl. fig 2. Hyponatremia frequency in different age categories for carbamazepine and oxcarbazepine users.

Severe hyponatremia and co-medication

In those with a sodium level of ≤128 mEq/L (n=146) concomitant use of antidiabetics (n=5), NSAIDS (n=20), antipsychotics (n=15), antidepressants (n=10), antihypertensive drugs (n=25) (especially diuretics (n=4) and ACE inhibitors (n=8)) and proton pomp inhibitors (n=16) was checked. In those treated with OXC, additional use of antihypertensive drugs and use of co-medication that, as a group, can influence sodium levels were significantly associated with a lower sodium level. (table 4)

Table 4. The effect of non-AED co-medication in severe CBZ and OXC induced hyponatremia (Na≤128 mEq/L).

		Carbamazepine			Oxcarbazepine		
Comedication		**mean Na^+**	**N[a]**	***P*-value**	**mean Na^+**	**N[a]**	***P*-value**
Antihypertensive drugs	no	125.1	56	0.29	125.7	52	0.001
	yes	126.0	17		121.9	8	
Diuretics	no	125.4	71	0.69	125.3	58	0.03
	yes	124.5	2		120.5	2	
ACE inhibitors	no	125.2	67	0.32	125.3	58	0.03
	yes	126.5	6		120.5	2	
Comedication	no	125.3	40	0.81	125.8	36	0.04
	yes	125.4	33		124.2	24	

a No data on co-medication was available for 13 people.

Users of CBZ and OXC

Sodium levels were measured during CBZ and OXC treatment in 50 individuals who used the drugs sequentially (64% had CBZ first, then had OXC). Mean sodium levels were significantly lower on OXC (131 mEq/L) when compared to CBZ treatment (135 mEq/L, $p<0.001$). Hyponatremia was seen more frequently than in the total cohort; during CBZ use in 40% (20/50) and during OXC use in 68% (34/50). The risk of hyponatremia on CBZ was significantly associated with the risk of hyponatremia on OXC within this group ($p=0.001$). (table 5) Eighteen of the 20 who had hyponatremia on CBZ also developed hyponatremia on OXC. The remaining two were mildly hyponatremic (≥132 mEq/l).

Table 5. Hyponatremia in subgroup using both carbamazepine and oxcarbazepine sequentially.

			Oxcarbazepine		Total
			Na≤134	Na>134	
Carbamazepine	Na≤134	N	18	2	20
		% within Na≤134	90,0%	10,0%	
	Na>134	N	16	14	30
		% within Na>134	53,3%	46,7%	
Total			34	16	50

McNemar test: p= 0.001

Discussion

CBZ and OXC are widely used but physicians should be aware of the high prevalence of COIH. We have seen a relatively high frequency of severe hyponatremia, especially in those treated with OXC. We checked potential co-medication that might also trigger hyponatremia. People who were on antihypertensives had a significantly lower mean sodium level in the OXC group. Only 3% (2/58) of this group used diuretics and 14% antihypertensives (including diuretics) compared with 24% use of diuretics in another study with a larger cohort of OXC treated people and a lower prevalence (11%) of severe hyponatremia.[6] Co-medication does not seem to explain the higher prevalence of severe hyponatremia in the OXC group.

The rate of COIH was higher in the elderly and this was in line with previous reports.[5-7] The odds of hyponatremia were doubled in people over the age of 40 years. Thirst sensation, renal function, urine concentrating abilities and hormonal modulators of salt and water balance are often impaired in the elderly, which makes older people more susceptible to COIH.[8] In a previous study a much stronger age effect was reported in the OXC treated group than in those treated with CBZ but the sample was smaller.[5] We found that the age effect was comparable in both groups.

The subgroup analysis of those who used CBZ and subsequently OXC suggests that an individual with hyponatremia associated with CBZ is also likely to develop

hyponatremia while taking OXC. In an individual who does not develop hyponatremia with CBZ, there is a 53% chance of hyponatremia if subsequently OXC is used. The underlying mechanisms are likely to be similar but seem apparently more efficient when OXC is used. This analysis also implies that a subset of people may be genetically predisposed to COIH.

Our findings suggest that women seem to be at higher risk of developing hyponatremia if taking OXC. In the CBZ group being female was a risk factor in the linear regression analysis, but with a very small effect size. COIH is probably caused by antidiuresis where CBZ and OXC are thought to stimulate the vasopressin water reabsorption pathway.[9] The *AVPR2* gene, coding for the vasopressin 2 receptor (V2R) which plays a key role in water reabsorption, is located on the X chromosome in a region (Xq28) with high probability of escape from inactivation.[10] Escape from inactivation results in higher expression of levels of transcript in females.[11,12] This provides a possible explanation for why women are at a higher risk of hyponatremia, especially with the use of drugs that stimulate V2R. The underlying mechanisms seem to be more susceptible to OXC possibly through a stronger effect of OXC, compared with CBZ, on V2R. The use of OXC could therefore have a larger influence in women.

In a larger cohort study on OXC induced hyponatremia a sex difference was not found but within this cohort the mean age was 15 years higher than the mean age in our OXC cohort.[6] The effect of impaired renal function at older age on the COIH risk was stronger in this study than the effect of sex difference. So in an older cohort this sex effect could be missed. Perhaps also the difference in ethnic background plays a role. Previous studies reported conflicting results regarding the association between CBZ and OXC dose and hyponatremia. Some smaller studies did find a dose response relationship,[13-16] but larger studies could not confirm this.[5,6] We found a significant relationship between CBZ and OXC drug levels and hyponatremia, but the effect size was small. This might explain why this was not seen in some other studies. Staying below the 'mean relatively safe drug level' (7.4 mg/L for CBZ and 18.7 mg/L for OXC) might lower the need to withdraw these drugs due to hyponatremia.

We found that concomitant use of CLB and PHT in both groups and VPA and PB in the CBZ group may increase the risk of hyponatremia. The diuretic response to a water load was previously tested and found to be significantly greater in those

taking CBZ and phenytoin in combination than in those on CBZ monotherapy[17]; in contrast to our findings PHT seemed to reverse the anti-diuretic effect of CBZ. Concomitant use of VPA and PB were previously described as risk factors for CBZ induced hyponatremia.[7] A previous study suggested OXC in combination with levetiracetam (LEV) was a risk factor[5], but we found that concomitant use of LEV did not influence hyponatremia risk in either group.

One limitation of this study is that there were no recorded sodium levels for a fifth of the cohort. This, however, may reflect clinical practice in which some people, due to pressure of time and dislike of venipuncture, do not have samples taken for assay. The study was conducted at a single tertiary referral centre and it is likely that levels were estimated more frequently than in the primary or secondary levels of care.

It is important for clinicians to be aware of the high prevalence of COIH and nonspecific symptoms. Mild to moderate COIH may cause lethargy, cognitive slowness, headache, dizziness and nausea. Severe COIH may lead to falls, seizure aggravation and hospitalization.[6,9] We found mild symptoms in almost half of those with hyponatremia although due to the design we used we can't be certain if these symptoms were due to hyponatremia or if another cause, such as high AED levels could be playing a role. Of interest, is that only 6% of the symptomatic had high levels of either CBZ or OXC at the time. We have not systematically collected data on levels of other concomitant AEDs or of metabolites of CBZ and OXC.

A recent population-based study found that CBZ use compared to no antiepileptic use was associated with a 8.2 higher relative risk of hospitalization with hyponatremia within 30 days of drug initiation in people over 65 years.[18] To prevent this, physicians should have a low threshold of suspicion for this common adverse effect and checking sodium levels should be routine in clinical practice for people taking either of these drugs. Mild hyponatremia can be treated with fluid restriction; in case of severe hyponatremia we would recommend the introduction of an alternative antiepileptic drug with the gradual withdrawal of either CBZ or OXC. Alternative antiepileptic medication also needs to be considered especially in the elderly, females and in those on multiple AEDs, before hyponatremia develops. Prospective studies are warranted to establish the true frequency of symptomatic hyponatremia.

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CHAPTER 4

Symptomatology of carbamazepine- and oxcarbazepine-induced hyponatremia in people with epilepsy

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Symptomatology of carbamazepine- and oxcarbazepine-induced hyponatremia in people with epilepsy

Abstract

Objective To ascertain whether adverse effects (AEs) experienced by people taking carbamazepine or oxcarbazepine could be attributed to carbamazepine- or oxcarbazepine-induced hyponatremia.

Methods We performed an observational study collecting data between 2017 and 2019 on serum sodium levels and AEs retrospectively in people with epilepsy while on treatment with either carbamazepine or oxcarbazepine. We defined hyponatremia as Na^+≤134 mEq/L and severe hyponatremia as Na^+≤128 mEq/L. AEs experienced were compared between groups of individuals with and without hyponatremia.

Results 1,370 people using CBZ or OXC were identified, of whom 410 had at least one episode of hyponatremia. We checked for symptoms related to the use of CBZ and OXC in 710 people (410 with and 300 without hyponatremia), and found relevant information in 688. AEs occurred in 65% of people with hyponatremia compared to 21% with normal sodium levels (OR 7,5, *p*=<0,001) and in 83% of people with severe hyponatremia compared to 55% in those with mild hyponatremia (*p*=<0,001). Significant predictors of AEs were the drug (OXC vs CBZ), and the number of concomitant anti-seizure medications. Dizziness (28% vs 6%), tiredness (22% vs 7%), instability (19% vs 3%) and diplopia (16% vs 4%) were reported more often in the hyponatremia group than in those with normal levels.

Significance People with COIH had a seven-fold increased risk of developing adverse effects during treatment. Clinicians should consider ascertainment of sodium levels in those taking carbamazepine and oxcarbazepine and to act upon findings.

Introduction

The anti-seizure medications (ASMs) carbamazepine (CBZ) and its keto-analogue oxcarbazepine (OXC) are frequently prescribed for the pharmacological treatment of focal epilepsy. Both are also used to treat trigeminal neuralgia and bipolar disorders. Their use is limited by adverse effects (AEs) including hyponatremia as both seem to influence water reabsorption via stimulation of the vasopressin 2 receptor/aquaporin pathway causing a sodium dilution.[1] The prevalence of CBZ or OXC-induced hyponatremia (COIH) varies greatly; for CBZ the reported estimates are between 4 and 40% whilst for OXC they are between 23 and 73%.[2-5] High serum levels of CBZ or OXC, concomitant use of other ASMs and being female are risk factors for COIH, as well as age over 40 years.[5] A genetic predictor for COIH has not yet been identified.[6]

COIH is often assumed to be asymptomatic, but it can lead to symptoms ranging from unsteadiness and mild confusion to acute symptomatic seizures and coma. We previously found that almost half of people with COIH were symptomatic and in 3% this led to hospital admissions.[5] The type of symptoms were not very specific for hyponatremia and often COIH was not recognized by the clinician as a potential cause. We aimed to determine whether symptoms experienced by people taking these ASMs could be attributed to COIH. We assessed symptoms which could potentially be AEs in a cross-sectional cohort of people with epilepsy treated with CBZ and OXC previously described[5] and compared their occurrence in individuals with and without hyponatremia.

Methods

Study design: An electronic database designed for pharmacogenomic studies (www.epipgx.eu), capturing relevant clinical data with an emphasis on ASM history, has been in use since 2010 (http://www.sein.nl/en/). It was used to identify all individuals who were prescribed CBZ or OXC and who had a serum sodium level recorded during therapy at a tertiary referral centre. We defined hyponatremia as a sodium level ≤134 mEq/L, and severe hyponatremia as ≤128 mEq/L, in line with previous studies.[2, 7] Levels were measured as part of routine monitoring. For each

sodium level measurement, we recorded the date, serum level of CBZ or OXC (samples collected in the morning before taking the ASM) and concomitant use of other ASMs. Most individuals had several measurements, and we used the lowest recorded sodium level. Clinical characteristics, including the effect of treatment, were retrieved from case notes. Treatment outcome was recorded in three categories; failure of ASMs was defined as less than 50% seizure reduction with CBZ or OXC, response as seizure freedom for at least a year and moderate as seizure frequency reduction >50% but not seizure-free. We scored symptoms of AEs (Table 4) present at the time of hyponatremia, which could not be explained by another cause or comorbidity. From those with normal sodium levels, we selected the 300 individuals with most recent measurements (between 2006 and 2016) and scrutinized for AEs during the use of CBZ/ OXC at times when sodium levels were known. We used the same strategy for both groups. The starting point was the date of when the lowest sodium level was measured. We checked the records of visits/contacts prior and following this date. In case of several measurements in a continuous period, records were checked over this time for AEs. The individual must have been continuously on CBZ or OXC over the period, but the dosage could vary. If dosage changed, records were included only if sodium levels were available for the different dosages. For the hyponatremia group also only when all the sodium levels were l ≤134 mEq/L.

Usually, with normal sodium levels, the measurements were scattered and not close in time. When measurements were performed within one year with no dosage change between measurements, all records of the continuous period in between were included. When measurement intervals were over one year, only the records prior and following the date of assay were included.

In people who trialled CBZ and OXC (n=13) only the period with the lowest sodium level was used in the analysis. In the subgroup analysis (stratified by CBZ/OXC use) the ASM trial appropriate to the group was used.

Statistics: Having AEs or not was modelled as a dichotomous variable. Hyponatremia was modelled either as a dichotomous variable or as a categorical variable. The association between hyponatremia and the risk of having AEs was analysed with chi-squared tests. The association between hyponatremia and

different specific symptoms were also analysed with chi-squared tests. To correct for multiple comparisons, we used the Bonferroni method.
A stepwise logistic regression model was used to analyse the significance of clinical variables influencing the risk of having AEs. Hyponatremia, use of CBZ or OXC, treatment outcome, sex, age and number of concomitant ASMs use were included as covariates. The type of ASM co-used was modelled separately with hyponatremia to test the influence on the risk of having AEs. In a final model only the significant covariates were included.
Serum drug level was included as a covariate to analyse the influence of hyponatremia on the risk of having AEs in the subgroups of both CBZ and OXC use.
Relationships between dichotomous variables were assessed with 2*2 tables and Anova was used to compare means. Those with missing AEs data were excluded.
Statistical analysis was carried out using SPSS version 22.0 for Windows (SPSS Inc., Chicago, IL).

Ethics: The Ethical Committee of UMC Utrecht approved the study, and all participants provided written informed consent for data retrieval.

Results

We identified 1,370 people using CBZ or OXC, of whom 410 had at least one episode of hyponatremia. We checked for CBZ/OXC-related AEs in 710 people (410 with and 300 without hyponatremia) and found pertinent information in 688. Reports of AEs were identified in 313 people (45%). Thirteen individuals had trials of treatment with OXC and with CBZ. People who developed hyponatremia were significantly older than those with normal levels. Mean drug levels did not differ between symptomatic and non-symptomatic individuals (Table 1).
Hyponatremia and having AEs were independently associated with a higher frequency of failure of ASM treatment and use of combination therapy instead of monotherapy (Table 1).
In those hyponatremic, 65% experienced AEs compared to 21% in people with normal levels (P<0.001). In those with severe hyponatremia, 83% experienced AEs, while this was 55% in mild hyponatremia (P<0.001, Table 2).

Subgroup analysis showed that hyponatremia was associated with a higher frequency (78%) of AEs when related to use of OXC rather than with the use of CBZ (59%) (Table 2, *P* = 0,007 Table 3).

We modelled the contribution of clinical cofactors to having AEs. We found that, apart from hyponatremia, which of the two drugs used (OXC higher risk than CBZ) and the number of ASMs used concomitantly were significantly predictive of outcome (adjusted R2= 0.28, Table 3). The type of ASM co-used did not influence the outcome of having AEs (data not provided).

Serum drug level was analysed as clinical cofactor within the subgroups of CBZ and OXC. In both ASM groups drug levels had no significant influence on the association between hyponatremia and having AEs. (suppl table 1)

Table 1 Descriptives

							Having symptoms				
		HypoNa (N=388)		Normal Na (N=300)		*P*-value	Yes (N=313)		No (N=375)		*P*-value
Sex, No. (%)	male	188	(48,5)	152	(50,7)	0,56	150	(47,9)	190	(50,7)	0,49
Treatment outcome[a] , No. (%) (missing 17)	failure	157/375	(41,9)	67/296	(22,6)		125/303	(41,3)	99/368	(26,9)	
	response	76/375	(20,3)	106/296	(35,8)		65/303	(21,5)	117/368	(31,8)	
	moderate	142/375	(37,9)	123/296	(41,6)	<0,001	113/303	(37,3)	152/368	(41,3)	<0,001
Concomitant ASMs[b] (missing 22)	monotherapy	74/371	(19,9)	99/295	(33,6)	<0,001	58/302	(19,2)	115/364	(31,6)	<0,001
Mean age (SD), years		47,3	(15,0)	40,9	(17,0)	<0,001	45,8	(16,2)	43,4	(16,1)	0,06
Mean Sodium level (SD), mEq/L		129,6	(3,9)	139,7	(6,0)		131,0	(5,9)	136,47	(4,9)	<0,001
Mean drug level (SD), mg/L (cbz missing 34, oxc missing 23)	CBZ	8,3	(2,2)	7,6	(2,1)	0,001	8,2	(2,3)	7,8	(2,1)	0,07
	OXC	22,0	(7,0)	20,1	(6,9)	0,12	21,8	(6,4)	20,8	(7,6)	0,38

ASM = anti-seizure medication, CBZ=carbamazepine, HypoNa = hyponatremia, OXC=oxcarbazepine

[a]Treatment outcome is a categorical variable with groups failure (<50% seizure frequency reduction), response (seizure freedom > 1 year), and moderate (seizure frequency reduction >50%, not seizure free).

[b]Concomitant ASMs=dichotomous variable (mono vs poly-therapy)

Table 2 Univariate analysis, showing the frequencies of adverse symptoms for each group.

No. (%)	N	Hypo Na		Normal Na		*P*-value	Na<128		Na 128-134		Na >134		*P*-value
Total	688	251/388	(64,7)	62/300	(20,7)	<0,001	111/134	(82,8)	140/254	(55,1)	62/300	(20,7)	<0,001
CBZ	524	163/276	(59,1)	52/248	(21,0)	<0,001	62/79	(78,5)	101/197	(51,3)	52/248	(21,0)	<0,001
OXC	177	98/125	(78,4)	10/52	(19,2)	<0,001	54/62	(87,1)	44/63	(69,8)	10/52	(19,2)	<0,001

HypoNa = hyponatremia, CBZ=carbamazepine, Na= sodium in mmol/L, OXC=oxcarbazepine

13 people trialled CBZ and OXC; in the total analysis each individual appeared only once

Table 3 Stepwise logistic regression with outcome having adverse symptoms.

	N=666	Odds Ratio	95% C.I.		*P*-value	R2
Step	Dependent variables		Lower	Upper		
1	Hyponatremia	7,348	5,152	10,479	<0,001	0,254
2	Hyponatremia	6,932	4,848	9,914	<0,001	0,265
	OXC/CBZ	1,716	1,149	2,561	0,007	
3	Hyponatremia	6,582	4,591	9,436	<0,001	0,277
	OXC/CBZ	1,775	1,185	2,660	0,004	
	Nr concomitant ASMs	1,308	1,077	1,588	0,007	

ASM = anti-seizure medication, Nr = number

Treatment outcome, sex and age had no significant influence

Nr concomitant ASMs = continuous variable with values from 0-5

Supplementary table1. Logistic regression analysis testing the influence of drug levels with having adverse symptoms as dependent variable.

	Carbamazepine (n=490)				Oxcarbazepine (n=154)			
		95% C.I.				95% C.I.		
	Odds Ratio	Lower	Upper	*P*-value	Odds Ratio	Lower	Upper	*P*-value
Drug level (mg/L)	1,081	0,995	1,175	0,065	1,016	0,971	1,063	0,491
Univariate analysis				R2= 0,009				R2= 0.004
Hyponatremia	5,539	3,704	8,283	<0,001	18,159	7,421	44,434	<0,001
Drug level (mg/L)	1,03	0,941	1,128	0,519	0,996	0,943	1,053	0,900
Mulitvariate analysis				R2= 0,204				R2= 0,40

Table 4 shows the frequencies of specific symptoms in those with hyponatremia and those with normal sodium levels. Table 4 also indicates frequencies of symptoms for severe and mild hyponatremia. Data stratified by CBZ or OXC use are in table 5.

Dizziness (28%), tiredness (22%), instability (19%) and diplopia (16%) were most frequently reported and significantly more often in the hyponatremia group than in those with normal levels (Table 4). Cognitive slowing, concentration problems, confusion, falling, headache, increased seizure frequency, nausea and somnolence were also reported significantly more often in the hyponatremia group. These were even more frequently seen in severe hyponatremia than in mild hyponatremia.

In the separate analysis for OXC use (Table 5) tiredness was the most frequent symptom in the hyponatremic individuals, reported in 40% compared to 4% in those with a normal sodium level.

Table 4 Frequencies of specific symptoms in people with hyponatremia vs normal sodium levels, and shown for 3 sodium level categories.

Symptoms No. (%)	HypoNa (N=388)		Normal Na (N=300)		*P*- value	Na<128 (N=134)		Na 128-134 (N=254)		Na>134 (N=300)		*P*- value
Behavioral disturbance	8	(2,1)	2	(0,7)	0,13	6	(4,5)	2	(0,8)	2	(0,7)	0,005
Cognitive slowing	31	(8,0)	0		**<0,001**	13	(9,7)	18	(7,1)	0		**<0,001**
Concentration problems	30	(7,7)	4	(1,3)	**<0,001**	15	(11,2)	15	(5,9)	4	(1,3)	**<0,001**
Confusion	19	(4,9)	2	(0,7)	**0,001**	11	(8,2)	8	(3,1)	2	(0,7)	**<0,001**
Diplopia	60	(15,5)	12	(4,0)	**<0,001**	27	(20,1)	33	(13,0)	12	(4,0)	**<0,001**
Dizziness	108	(27,8)	19	(6,3)	**<0,001**	47	(35,1)	61	(24,0)	19	(6,3)	**<0,001**
Falls	29	(7,5)	1	(0,3)	**<0,001**	13	(9,7)	16	(6,3)	1	(0,3)	**<0,001**
Gait disturbance	16	(4,1)	2	(0,7)	0,005	10	(7,5)	6	(2,4)	2	(0,7)	**0,002**
Headache	35	(9,0)	9	(3,0)	**0,001**	21	(15,7)	14	(6,7)	9	(3,0)	**<0,001**
Increased seizure frequency	37	(9,5)	0		**<0,001**	21	(15,7)	16	(6,3)	0		**<0,001**
Instability	75	(19,3)	8	(2,7)	**<0,001**	32	(23,9)	43	(16,9)	8	(2,7)	**<0,001**
Nausea/vomiting	36	(9,3)	1	(0,3)	**<0,001**	22	(16,4)	14	(5,5)	1	(0,3)	**<0,001**
Personality change	5	(1,3)	0		0,05	2	(1,5)	3	(1,2)	0		0,16
Somnolence	45	(11,6)	6	(2,0)	**<0,001**	24	(17,9)	21	(8,3)	6	(2,0)	**<0,001**
Tiredness	84	(21,6)	20	(6,7)	**<0,001**	40	(29,9)	44	(17,3)	20	(6,7)	**<0,001**
Other symptoms	53	(13,7)	18	(6,0)	**0,001**	27	(20,1)	26	(10,2)	18	(6,0)	**<0,001**

HypoNa = hyponatremia. Other symptoms were: allergy, hair loss, memory problems, mood disorders, skin problems, tremor, non-specific complaints.
Bonferroni correction for multiple testing; *P* significant at 0,003125 *(*0,05/16), significant *p*-values are marked bold.

Table 5 Frequencies of specific symptoms in people with hyponatremia vs normal sodium levels, stratified for CBZ and OXC use

	CBZ					OXC				
Symptoms No. (%)	HypoNa (N=276)		Normal (N=248)		*P*-value	HypoNa (N=125)		Normal (N=52)		*P*-value
Behavioural disturbance	3	(1,1)	1	(0,4)	0,37	5	(4)	1	(1,9)	0,49
Cognitive slowing	23	(8,3)	0		**<0,001**	11	(8,8)	0		0,03
Concentration problems	7	(2,5)	4	(1,6)	0,46	23	(18,4)	0		**0,001**
Confusion	8	(2,9)	1	(0,4)	0,03	11	(8,8)	1	(1,9)	0,10
Diplopia	34	(12,3)	9	(3,6)	**<0,001**	27	(21,6)	2	(3,8)	0,004
Dizziness	70	(25,4)	15	(6,0)	**<0,001**	42	(33,6)	4	(7,7)	**<0,001**
Falls	20	(7,2)	0		**<0,001**	9	(7,2)	1	(1,9)	0,17
Gait disturbance	12	(4,3)	2	(0,8)	0,01	6	(4,8)	0		0,11
Headache	20	(7,2)	8	(3,2)	0,04	16	(12,8)	1	(1,9)	0,03
Increased seizure frequency	13	(4,7)	0		**0,001**	25	(20,0)	0		**0,001**
Instability	43	(15,6)	5	(2)	**<0,001**	34	(27,2)	3	(5,8)	**0,001**
Nausea/vomiting	20	(7,2)	1	(0,4)	**<0,001**	19	(15,2)	0		**0,003**
Personality change	3	(1,1)	0		0,10	2	(1,6)	0		0,36
Somnolence	29	(10,5)	4	(1,6)	**<0,001**	20	(16,0)	2	(3,8)	0,03
Tiredness	40	(14,5)	18	(7,3)	0,008	50	(40,0)	2	(3,8)	**<0,001**
Other symptoms	22	(8,0)	15	(6,0)	0,39	33	(26,4)	3	(5,8)	**0,002**

HypoNa=hyponatremia, CBZ=carbamazepine, OXC=oxcarbazepine. Other symptoms were: allergy, hair loss, memory problems, mood disorders, skin problems, tremor, non-specific complaints.Bonferroni correction for multiple testing; *P* significant at 0,003125 *(*0,05/16), significant p values are marked bold.

Discussion

CBZ and OXC are widely used, and physicians should be aware of the high prevalence of COIH, which is often assumed to be asymptomatic. We found that those with hyponatremia experienced seven-fold increased odds of AEs.

The symptoms related to hyponatremia are not very specific. Hyponatremia signs, whether or not related to the use of ASMs, can include nausea, vomiting, malaise, headache, dizziness, confusion, drowsiness and fatigue.[8] Similar symptoms can be seen with higher CBZ/OXC drug levels or with individual intolerability for these drugs.[9] Reports about side effects caused by CBZ and OXC describe rash, dizziness, headache, fatigue and drowsiness, but sodium levels were not taken into account in these reports.[10, 11]

We cannot extricate whether hyponatremia is the direct cause of the AEs or whether low sodium levels increase vulnerability to AEs of the ASMs. The drug levels of the ASMs did not influence the association between hyponatremia and having AEs and they were not significantly different between those symptomatic and those asymptomatic. Does the finding that ASM levels were not associated with having symptoms tell us that the symptoms are more likely to be caused by hyponatremia rather than the direct AEs of the ASM itself? This would only be the case when we assume that these direct AEs are highly dose dependent. For OXC a relationship between dose and AEs has been described, but titration schedule and concomitant ASMs also played an important role.[12]

AEs were seen more frequently with OXC than with CBZ. Our earlier study suggests that OXC is associated with lower sodium levels and more frequent severe hyponatremia.[5] This could provide some support to the notion that lower sodium levels are more likely to cause symptoms and is in line with the finding of a higher frequency of AEs in the severe hyponatremia group.

In the hyponatremia group fewer individuals had a good response to their treatment and more were on poly-therapy. The outcome of epilepsy treatment did not influence the association between hyponatremia and having AEs, but the number of co-prescribed ASMs did (Table 3). A recent study showed that poly-therapy with three or more ASMs was associated with more AEs, with no difference between monotherapy or duo-therapy.[13] In earlier studies no association was found between the number or load of ASMs and AEs.[14, 15] We previously showed

that the number of concomitant ASMs influenced the risk of COIH. With increasing numbers of concomitant ASMs used, sodium levels dropped, suggesting a higher risk of hyponatremia related symptoms.[5]

As hyponatremia seems to be symptomatic in a considerable number of people treated with CBZ or OXC, the clinical importance of this finding needs to be understood. Mild chronic hyponatremia was described earlier as causing neurocognitive deficits, gait disturbance and falls.[16] Treatment of chronic mild hyponatremia improved neurocognitive and neuromuscular function.[17] This suggests the need to treat COIH, even if mild, to improve overall functioning. Management can be either by fluid restriction or switching to another ASM.

A limitation of our study is that there was no consistent information available on sodium levels prior to starting CBZ/OXC. For further studies a prospective cohort with baseline sodium levels, follow up measurements at regular intervals and monitoring the effect of treatment of COIH is recommended.

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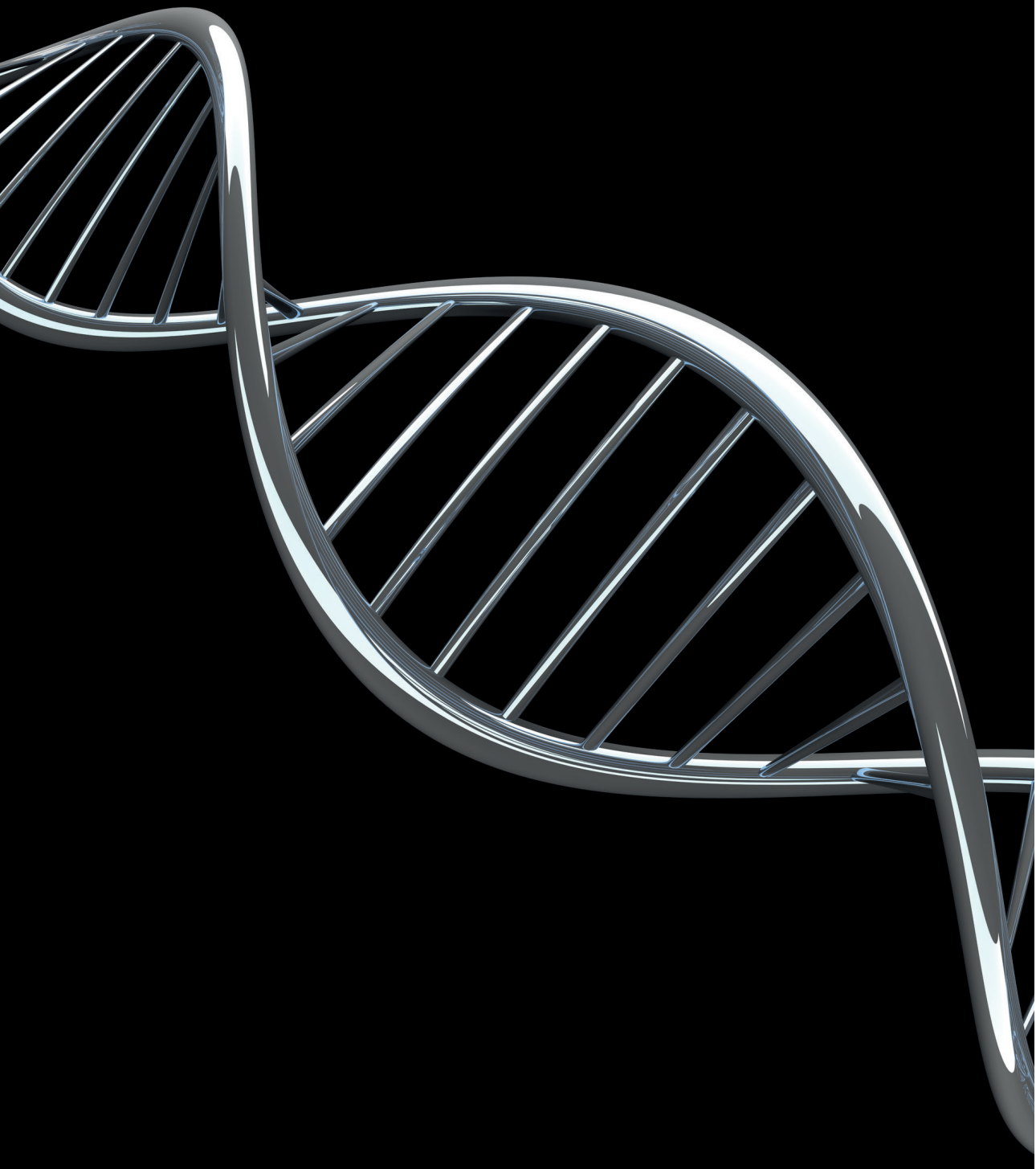

CHAPTER 5

A genome-wide association study of sodium levels and drug metabolism in an epilepsy cohort treated with carbamazepine and oxcarbazepine

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A genome-wide association study of sodium levels and drug metabolism in an epilepsy cohort treated with carbamazepine and oxcarbazepine

Abstract

Objective To ascertain the clinical and genetic factors contributing to carbamazepine and oxcarbazepine induced hyponatremia (COIH), and to carbamazepine (CBZ) metabolism, in a retrospectively collected, cross-sectional cohort of people with epilepsy.

Methods We collected data on serum sodium levels and anti-epileptic drug levels in people with epilepsy attending a tertiary epilepsy centre while on treatment with CBZ or OXC (oxcarbazepine). We defined hyponatremia as $Na^{+} \leq 134$ mEq/L. We estimated the CBZ metabolic ratio defined as the log transformation of the ratio of metabolite CBZ-diol to unchanged drug precursor substrate as measured in serum.

Results Clinical and genetic data relating to CBZ and OXC trials were collected in 1141 subjects. We did not observe any genome-wide significant associations with sodium level in a linear trend or hyponatremia as a dichotomous trait. Age, sex, number of co-medications, phenytoin use, phenobarbital use and sodium valproate use were significant predictors of CBZ metabolic ratio. No genome-wide significant associations with CBZ metabolic ratio were found.

Significance While we did not detect a genetic predictor of hyponatremia or CBZ metabolism in our cohort, our findings suggest the determinants of CBZ metabolism are multifactorial.

Introduction

Carbamazepine (CBZ) and its keto-analogue, oxcarbazepine (OXC), are routinely used as antiepileptic drugs (AEDs) and also used in the treatment of chronic pain conditions and in bipolar disorder. While effective, their use is limited by adverse drug reactions, including hyponatremia and hypersensitivity. Carbamazepine- and oxcarbazepine-induced hyponatremia (COIH) is reported in up to half of drug exposures. This is often assumed to be asymptomatic but it can lead to difficulties ranging from unsteadiness and mild confusion to seizures and coma. Careful dose titration and monitoring of sodium levels are recommended for reducing the risk of COIH while individual differences in drug metabolism can make titration difficult.

*HLA-B*1502* is strongly associated with CBZ-induced Stevens-Johnson syndrome (SJS) in people of Han-Chinese ethnicity, increasing the risk about 100 fold.[1] In individuals of European descent, *HLA-A*3101* is a clinically relevant predictor for the full spectrum of CBZ-induced hypersensitivity reactions.[2,3] To date, no genetic risk factors have been associated with COIH. Thiazide-induced hyponatremia is associated with two polymorphisms in the *KCNJ1* gene, encoding the renal outer medullary potassium channel (ROMK) which plays an important role in sodium reabsorption along the thick ascending limb of the Loop of Henle.[4] CBZ and OXC seem to influence water reabsorption, independent of salt retention, via stimulation of the vasopressin 2 receptor/aquaporin (AVPR2) pathway.[5] Mutations in the *AVPR2* gene, a regulator in water reabsorption, can cause a nephrogenic syndrome of inappropriate antidiuresis (NSIAD) with physiological similarities to the inappropriate antidiuresis induced by CBZ and OXC.[6] Studies of *AVPR2* copy number variation, however, did not explain variation in sodium levels in non-Hispanic Caucasian populations.[7]

We attempted to determine the clinical and genetic factors contributing to COIH and drug metabolism in a retrospectively collected, cross-sectional cohort of people with epilepsy of European descent treated with CBZ and OXC previously described.[8]

Methods

Study design and phenotypes

We followed a retrospective cohort study design. The majority of subjects were recruited at a Dutch tertiary epilepsy referral centre (SEIN) while the remainder were recruited around European tertiary referral clinics associated with the EpiPGX Consortium. Clinical information from medical records, with an emphasis on AED history, was recorded in an electronic database designed for retrospective pharmacogenomics studies.[9] The database was used to identify all individuals who were prescribed CBZ or OXC and who had a recorded serum sodium level during therapy. Most individuals had several measurements and the lowest sodium level recorded was selected for analysis. Our primary analyses were structured to test genetic variants for association with this lowest recorded sodium level per subject (mEql/L). Secondary analyses tested for genetic association with i) COIH (combined and per causal drug) and ii) CBZ metabolic ratio. For a subset of CBZ users, we calculated the metabolic ratio defined as the log transformation of the ratio of metabolite carbamazepine-10,11-diol (CBZ-diol) to unchanged drug precursor substrate as measured in serum. COIH cases were defined as having a blood sodium level ≤134 mmol/L attributed to CBZ or OXC as determined by their clinician. COIH controls trialled CBZ or OXC for at least three months with a sodium level ≥135 mmol/L. Epilepsy-specific cohort demographics are presented in Table 1.

Sampling and Genotype analysis

Serum drug and metabolite concentrations were measured during the course of routine monitoring in the morning prior to drug intake. For each sodium level measurement, we recorded subject age, serum level of CBZ or OXC and concomitant use of other drugs. Genotyping of all subjects was performed at deCODE Genetics on Illumina OmniExpress-12 v1.1 and OmniExpress-24 v1.1 single nucleotide polymorphism (SNP) arrays. Genotyping quality control was performed as described previously.[10] Principal components analysis (PCA) was performed with European-ancestral samples from the HapMap Project to assess cohort substructure and identify population outliers (Supplementary Figure 1). Eigenvectors were computed in GCTA for each subject for inclusion as covariates in genetic association testing.[11] Subjects were identified as outliers and removed if

greater than three standard deviations from the first eight principal components. We used FUMA to generate Manhattan and quantile-quantile (Q-Q) plots.[12]

Study power

We estimated from our recruited sample size that our study had 80% power to detect a genetic predictor of relative risk (approximated to odds ratio) ≥ 3 with an allele frequency ≥ 2% and an alpha level of $1.0x10^{-8}$, using the power calculator for case-control genetic association analyses PGA.[13]

Statistical analyses

Clinical cofactors influencing sodium levels and COIH in this cohort were previously reported and used as covariates in our models.[8] Association analyses were conducted using additive linear or logistic regression models in PLINK, including clinical covariates where appropriate and eight principal components from PCA. Dosage, number of co-medications and AED levels were excluded from genetic analyses due to missing information in the EpiPGX subcohort. We also analysed the significance of clinical variables influencing CBZ metabolic ratio using a stepwise linear regression model in SPSS. As before, significant clinical cofactors from the linear regression model were included as covariates along with eight principal components from PCA. For each association test, SNPs with < 90% call rate were excluded. The threshold for genome-wide statistical significance was set at $1.0x10^{-8}$, reflecting an empirical Bonferroni correction, for five tests, of the standard $5x10^{-8}$ genome-wide significance threshold.

Ethical considerations

All study participants provided written, informed consent for genetic analysis. Study protocols were approved by the research ethics committees listed in Supplementary Table 1.

Results

We collected clinical and genetic data relating to CBZ (n=1031 subjects) and OXC (n=297 subjects) trials. A subset (n=79 subjects) was trialled on CBZ and OXC. Of the total 1252 subjects, 1047 were recruited at SEIN while 201 were recruited through EpiPGX partner sites. Data on drug levels and compliance were available for 98% of the SEIN cohort, but not for the EpiPGX partner sites. In 5% of our SEIN cohort the drug levels or dosage was below therapeutic values (for CBZ< 4 mg/L or < 400 mg/day, for OXC <10 mg/L or <900 mg/day). We report 448 cases with COIH and 804 controls with normal serum sodium measurement. Within our cases there was a subset of 61 extreme hyponatremia. The incidence of OXC-induced hyponatremia (57%) was almost two-fold higher than that of CBZ (32%). Characteristics of our cohort are described in Table 1. A total of 25 subjects were removed after genotyping quality control.

Table 1. CBZ and OXC cohort characteristics.

Description	CBZ	OXC	Combined
Subjects	1031	297	1252[a]
% male	51.4%	48.1%	51.2%
Mean age (± SD)	42.9 ± 15.1	38.1 ± 15.9	41.9 ± 15.6
No. AED Co-medications (max)[b]	1.0 (5)	0.9 (4)	1.0 (5)
Hyponatremia (Na < 135mEq/L)	331 (32%)	170 (57%)	448[c] (36%)
Mean case serum sodium (mEq/L)	129.5 ± 4.1	127.5 ± 4.2	129.0 ± 4.2
Mean control serum sodium (mEq/L)	139.8 ± 2.5	139.4 ± 2.7	139.7 ± 2.5
Mean serum AED level (mg/L) (± SD) [b]	8.7 ± 2.3	17.8 ± 8.2	-
Metabolic ratio (± SD)[d]	0.35 ± 0.21	-	-

CBZ= carbamazepine, OXC= oxcarbazepine

[a] 79 subjects trialled both CBZ & OXC. [b] Calculated from SEIN subcohort (n=1074). [c] 53 subjects experienced hyponatremia on both CBZ & OXC. [d] Metabolic ratio calculated on subset of subjects with serum CBZ-diol level readings (n=468).

To test whether common genetic variants predict sodium levels, we performed a genome-wide linear regression adjusted for age, clobazam use, sex, plus eight principal components. We did not observe any genome-wide significant associations with sodium level. (Figure 1)

To test whether common genetic variants predict COIH, defined as a serum sodium level <135mEq/L, we performed a case-control genome-wide logistic regression adjusted for sex, age < 40, plus eight principal components. We did not observe any genome-wide significant associations when we considered COIH as a dichotomous trait. (Figure 2) There was a suggestive association signal ($p<1x10^{-6}$) from chromosome 5, in an intergenic region approximately 500Mb downstream of the gene *ANKRD55*, evident in the quantitative and dichotomous analyses of sodium. Further, we did not detect evidence for a genetic signal in a subset of 61 severe COIH cases, defined as serum sodium ≤125mEq/L, when compared to controls. Neither did we observe any significant associations when we differentiated hyponatremia by causal drug. (see Supplementary Figures 2-4) Given prior reports of an association with thiazide-induced hyponatremia, we looked closely within the genes *KCNJ1* and *AVPR2*, yet we did not observe any signals of association in our data.

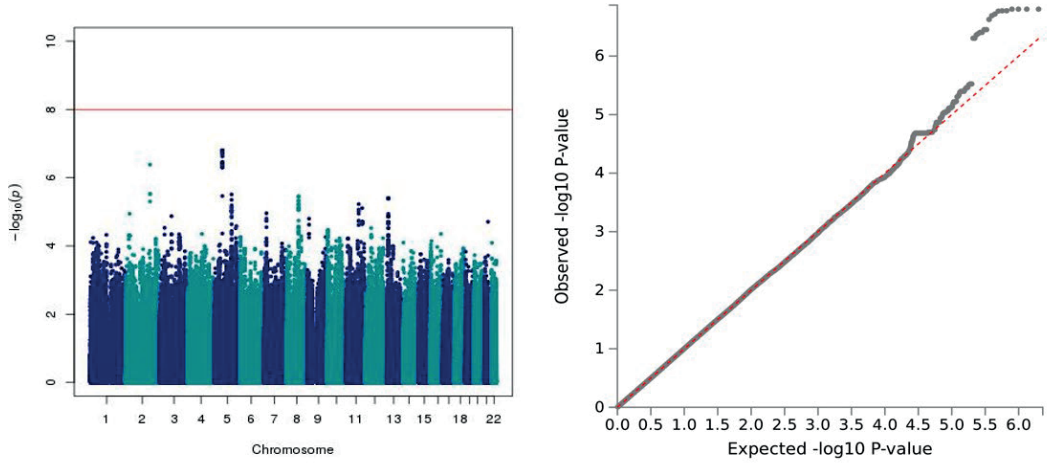


Figure 1 Manhattan and Q-Q plots of sodium levels (λ = 1.00).

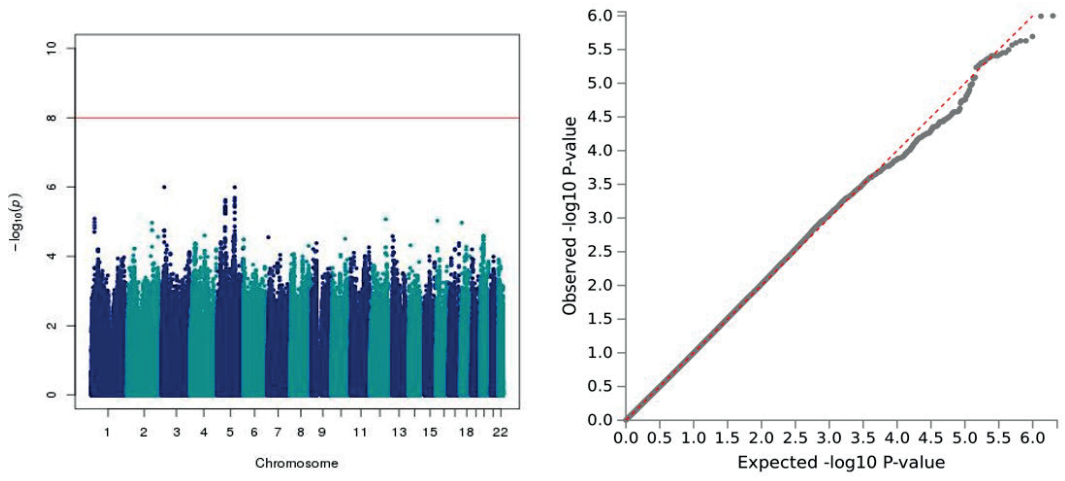


Figure 2 Manhattan and Q-Q plots of COIH (λ = 1.00).

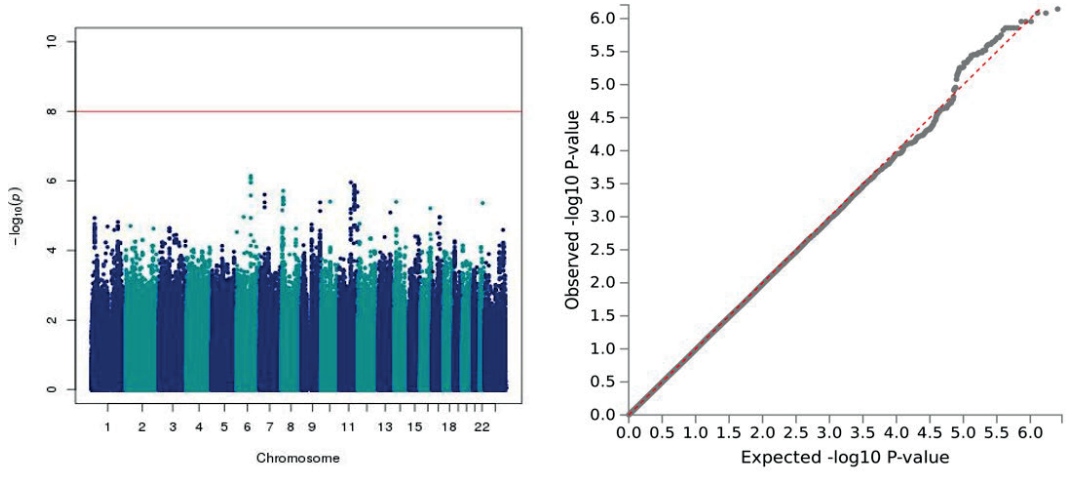


Figure 3 Manhattan and Q-Q plots of carbamazepine metabolic ratio (λ = 0.98).

Next, we explored whether clinical cofactors or genetic variants could predict the ratio of active drug to metabolite in our CBZ-exposed subjects. We modelled the contribution of clinical cofactors to CBZ metabolic ratio and found that age, sex, number of co-medications, phenytoin use, phenobarbital use and sodium valproate use were significantly predictive of outcome (adjusted r^2=0.236, Model 5 in Table 2).

Table 2. Stepwise linear regression of carbamazepine metabolic ratio.

Model	Factors	R	R^2	Adjusted R^2	Std. Error
1	PHT	.363[a]	.132	.130	.196
2	PHT, NoCoMed	.421[b]	.177	.174	.191
3	PHT, NoCoMed, Age	.458[c]	.210	.205	.188
4	PHT, NoCoMed, Age, PHB	.486[d]	.236	.230	.185
5	PHT, NoCoMed, Age, PHB, VPA	.493[e]	.243	.236	.184

PHB: phenobarbital, PHT: phenytoin, NoCoMed: number of co-medications, VPA: sodium valproate

To test whether common genetic variants predict CBZ metabolic ratio, we then performed a genome-wide linear regression adjusted for the covariates in Model 5, plus eight principal components. We did not observe any genome-wide significant associations with CBZ metabolic ratio. The top ten most significant GWAS markers for each analysis are listed in Supplementary Tables 1-5. Polymorphisms in *CYP3A4* and *EPHX1* have been shown to associate with inter-individual variability of CBZ metabolism.[14,15] We did not observe even nominally significant associations between SNPs in *CYP3A4* and CBZ metabolic ratio. It had been reported that homozygous carriers of the *EPHX1* c.416A>G SNP (rs2234922) seemingly show a reduced CBZ metabolism as measured by a significantly decreased metabolic ratio.[16] We did not replicate this finding (rs2234922; p= 0.303) but we observed a nominally significant association between an intronic *EPHX1* SNP (c.365-2139T>C) and CBZ metabolic ratio (rs4653689; p=1.1x10-4).

Discussion

While we did not detect a genetic predictor of hyponatremia in our cohort, we have demonstrated that the determinants of CBZ metabolism are multifactorial. Modelling the contribution of clinical variables showed there were strong non-genetic predictors of CBZ metabolism. Subject age, total number of co-medications and the concurrent use of either phenytoin, phenobarbital or sodium valproate were significantly associated with a higher CBZ-diol to CBZ ratio. Much of this can be explained by the induction of the cytochrome P450 enzyme CYP3A4. CBZ is metabolised in the liver by CYP3A4 to carbamazepine-10,11-epoxide which is further metabolised by microsomal epoxide hydrolase (mEH) to carbamazepine-10,11-diol.[17] Phenytoin and phenobarbital induce CYP3A4 and thus can lower plasma CBZ levels but leave the metabolite levels unaltered, which results in the observed higher metabolic ratio.[18,19] Sodium valproate inhibits epoxide hydrolase, potentiating higher levels of the active metabolite CBZ-10,11-epoxide which is associated with toxicity and adverse events,[20] but this was not directly measured in this study. Valproate has been shown to increase dose ratios between CBZ and its metabolites, for both the diol and epoxide forms.[21] Age has previously been found to contribute to pharmacokinetic variability in individuals using CBZ with increasing clearance until age 33 and a gradual decrease towards older age.[22]

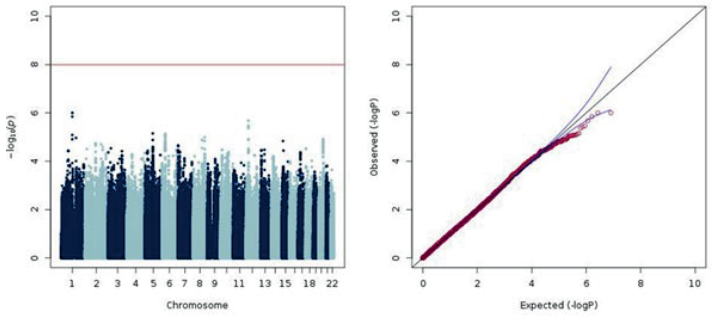
A limitation of the study is that AED dosage was not reliably recorded in our cohort and we had to make an assumption that the measurement of CBZ metabolic ratio was independent of the individual subject's dosage. In the subset of subjects for whom serum CBZ-diol and CBZ dosage information was available (n=40) we did not detect a significant effect of CBZ dose on the metabolic ratio (p=0.41).

CBZ and OXC are widely prescribed but their use coincides with a high prevalence of COIH. Within our cohort OXC-induced hyponatremia has a much higher prevalence than that of CBZ, which is consistent with previous estimates. [23,24] From clinical experience, susceptibility to COIH is individually variable. Experimental studies and a recent clinical report suggest COIH is caused by a direct effect of CBZ/OXC on the kidney by stimulating the vasopressin receptor.[25,26] Mutations in the V2R/AQP2 pathway regulating water reabsorption can cause disorders clinically similar to the syndromes of inappropriate antidiuresis associated with CBZ/OXC use. Meanwhile thiazide-induced hyponatremia has been associated with

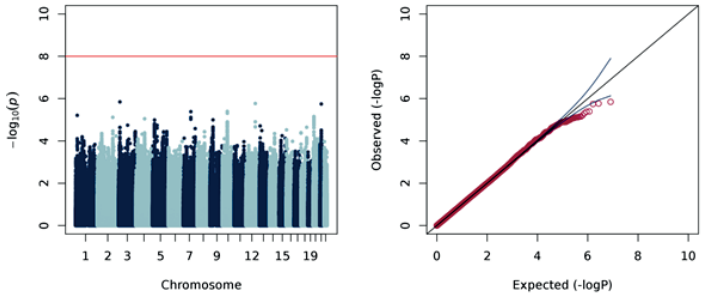
polymorphisms in the gene *KCNJ1* and a suggestive association with a variant in *SLCO2A1*, encoding a prostaglandin transporter; these signals did not show even nominal significance in our data.[4,27] We further looked for an effect from these markers within the subset of 53 subjects who experienced hyponatremia on both CBZ and OXC independently, but there was no significant enrichment.

Previously described clinical predictors of serum sodium levels only explain 11-14% of the variance in the SEIN cohort.[8] Therefore, it is hypothesized that genetic variation could in part explain the variation in susceptibility to COIH. Yet, after analysing sodium levels in a linear trend and hyponatremia as a dichotomous trait, we did not find genetic predictors for COIH. A recent report of variants in *NFAT5* and *SLC4A10* with suggestive association with plasma osmolality further imply a genetic component to hyponatremia but these variants showed no evidence for effect on serum sodium measurements in our study, albeit we were not as powered as the original discovery cohort.[28]

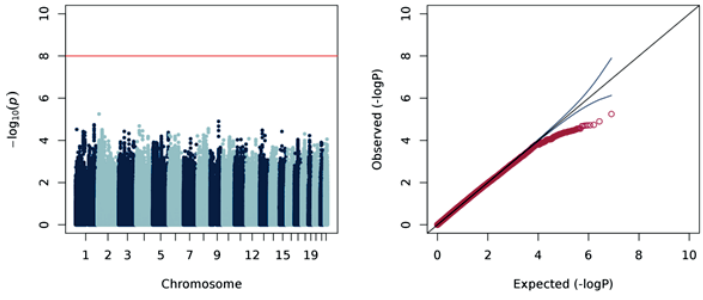
In summary, our study rules out common genetic variants of clinically relevant effect size, however genetic susceptibility for COIH cannot be ruled out completely, as rare variants and combinations of genetic variants of smaller effect size (polygenic risk) may contribute to overall risk. Further study, ideally in a prospective cohort with baseline sodium level measurements, is warranted to investigate the genetic contribution to CBZ and OXC-induced hyponatremia.



Supplementary Figure 2 Manhattan and Q-Q plots for severe hyponatremia (GIF = 1.03).



Supplementary Figure 3 Manhattan and Q-Q plots for CBZ-induced hyponatremia (GIF = 0.99).



Supplementary Figure 4 Manhattan and Q-Q plots for OXC-induced hyponatremia (GIF = 1.03).

Other supplementary figure and tables are available online.

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CHAPTER 6

General discussion

General Discussion

This thesis aimed to clarify the clinical importance of carbamazepine- and oxcarbazepine-induced hyponatremia (COIH) and identify biomarkers to improve the clinical management of epilepsy. In this chapter, we provide a brief overview of significant findings, discuss the relevance, and give recommendations for the future.

The occurrence of carbamazepine- and oxcarbazepine-induced hyponatremia

Despite the recent development of over 20 different anti-seizure medications (ASMs), carbamazepine (CBZ) and oxcarbazepine (OXC) are still essential drugs in the treatment of epilepsy. They are widely used and are among the most prescribed ASMs, as they are effective[1] and relatively cheap. Nevertheless, CBZ and OXC are associated with adverse effects (AEs), such as hyponatremia, limiting their use. COIH, caused by anti-diuresis, was reported as far back as 1966 and at the time used to treat people with diabetes insipidus.[2] The reported prevalence of COIH varied greatly; for CBZ, between 4 and 40%, whilst for OXC between 23 and 73%.[3,4] We wanted to establish the magnitude of COIH as a problem in the population we treat at our tertiary centre for epilepsy. People from this population have taken ASMs for many years, and seizure control is difficult to achieve in the majority. Is COIH so common that it complicates the treatment of epilepsy even further and negatively influences the lives of our patients?

Chapter three shows that hyponatremia occurred in 26% of those taking CBZ and 46% OXC. Hyponatremia was severe ($Na^+ \leq 128$ mmol/L) in 7% in the CBZ group and 22% in the OXC group. These numbers were in line with other studies, although the frequency of severe hyponatremia in OXC users was relatively high.[5,6] This higher rate of severe hyponatremia in OXC could not be explained by the composition of the cohort or the use of co-medication.

Our next question was: "Can we identify those people who are most at risk for COIH?" We found that ageing increased the risk of COIH. When analysed in age categories, we found that people over 40 had over twice the risk of developing

COIH. A slow deterioration of renal function and thirst sensation explains this and suggests we should prescribe CBZ or OXC more cautiously in the elderly.[7] We found that high serum levels of CBZ and OXC and the concomitant use of other ASMs were risk factors for hyponatremia in both treatment groups. It would seem logical that a higher dose of the drug would increase the risk of AEs, such as COIH. Though, most more extensive studies did not find this association.[4,5] A large Japanese study however reviewed 12,452 adults with epilepsy and found that a CBZ dose over 600 mg/day led to a 10.9 fold higher risk of hyponatremia. A CBZ dose below 600 mg/day leads to a 3.8 fold more elevated chance of hyponatremia.[8] In our cohort, the effect size of CBZ and OXC serum levels was meagre, with an OR just above 1.

Assuming the main pathway of developing COIH is by direct binding to the vasopressin receptor, dosage increase will increase the risk of COIH until CBZ or OXC binds all receptors. Any extra drug amount over this threshold probably does not increase the risk of COIH further. Our patients at the tertiary clinic for epilepsy are more likely to be taking higher drug dosages. When most use a dosage above a certain threshold above which all receptors are saturated, the association between dosage/ serum levels and risk of COIH is lost. This could explain why the role of high serum levels of CBZ and OXC as a risk factor was small. Saturation kinetic studies are not available for CBZ or OXC and V2R. Studies of nephrogenic diabetes insipidus did perform saturation binding assays and showed a flattening of the curve of healthy (wild type) V2R binding with increase of AVP serum levels,[9] supporting the above theory.

The concomitant use of ASMs, especially clobazam and phenytoin (PHT) in both groups and valproate (VPA) and phenobarbital in the CBZ group increased the risk of COIH. VPA inhibits hepatic epoxide hydrolase, leading to an increase in the serum level of carbamazepine-10,11-epoxide, which may elevate the risk of COIH.[10] Not all increased risk of COIH by concomitant use of ASMs can be explained by elevated serum levels caused by drug interactions. PHT and PB lower the serum levels of CBZ, and a water load test suggested that PHT (partially) reversed the antidiuretic effect of CBZ. The decrease in CBZ serum levels thoroughly explained the reversal.[11] So another path should explain how PHT and PB may contribute to COIH, despite their interactions with CBZ. PHT, PB, and CBZ are thought to decrease thyroid hormone levels by enzyme induction.[12] Hypothyroidism is associated with the decreased capacity of water excretion, which might add to the risk of COIH.[13]

Females on OXC were at a higher risk of hyponatremia than males. We explained this by escape from inactivation of the *AVPR2* gene coding for the vasopressin 2 receptor (V2R), located on the X chromosome (Xq28).[14] This inactivation escape is not seen in all women, and the amount of activation will also vary between women. This variation may explain different outcomes about this determinant in other studies. It will also make it hard to predict which woman will experience an additional risk.
Chapter three concludes that hyponatremia is a pervasive AE, especially in women over 40 treated with CBZ/OXC combined with other ASMs.

COIH: Is it a clinical problem?

Data on symptomatic COIH is limited. Case reports warn about mild symptoms concerning (sometimes severe) hyponatremia induced by ASMs. For example, a 44-year-old woman presented with fatigue and lower limp cramps after using CBZ 600 mg/day prescribed to treat a painful knee. Her sodium level was 119 mmol/L. After discontinuation of CBZ and fluid restriction, her symptoms resolved.[15] Two earlier mentioned studies reported an 8.2 relative risk of hospitalisation with hyponatremia within 30-90 days of CBZ initiation in people over 65 years.[16],[17] These case reports and extensive epidemiological studies about hospitalisation provide some information about clinical problems related to COIH. Still, they cannot tell us how often persons using CBZ or OXC experience symptoms or complaints caused by COIH, or what those symptoms could be.

The occurrence of AEs in COIH
In our cohort, we searched medical records for AEs reported by the patient when hyponatremic and not explainable by other causes. We found that COIH was symptomatic in 48% (35% in people with mild hyponatremia and 72% in severe hyponatremia) and lead to hospital admissions in 3% (Chapter 3). Symptoms included dizziness, diplopia, unsteady gait, lethargy, cognitive slowness, tiredness. These symptoms were not specific and difficult to attribute with certainty to the hyponatremic state. Kim and his colleagues reported the same problem. They classified hyponatremic symptoms into mild symptoms (lethargy, headache, dizziness, nausea, vomiting, restlessness, and disorientation) and significant

symptoms (seizure aggravation, respiratory failure, and death). Symptomatic hyponatremia was found in 6,8% of a cohort of 1,009 people with epilepsy treated with OXC, 4.1% mild and 2.8% significant. From the data presented in tables, 22 % (69/311) of patients with hyponatremia experienced symptoms. In the severe group, this was over half of the patients. As a study limitation, they stated they could not be sure that the symptoms scored were caused solely by hyponatremia.[5] There were no studies on the prevalence of mild symptoms in COIH, which provided certainty that those symptoms were caused by hyponatremia. Therefore, we designed the study described in chapter 4. We compared CBZ and OXC users with and without hyponatremia and scored all the AEs reported in the medical records and not attributable to other comorbidities. We found a significantly higher amount of AEs in people with hyponatremia than without (65% vs 21%) and significantly more AEs in people with severe hyponatremia than in people with mild hyponatremia (83% vs 55%*)*.

More AEs were reported by people with hyponatremia induced by OXC rather than CBZ. We already discussed that hyponatremia was more often found in the OXC users and that it was also more severe in OXC users. This may further imply that the rate and severity of hyponatremia are associated with more AEs. The number of ASMs used concomitantly was also a predictor of AEs in patients with COIH. So, both the type of drug (CBZ vs OXC) and concomitantly used ASMs were determinants in predicting the occurrence of hyponatremia and experiencing AEs. This raised the question of whether these determinants influenced AEs just by their influence on sodium levels or independently.

In the multivariate analysis, the type of drug (OXC, CBZ) and the number of concomitant ASMs were significant predictors of AEs, with hyponatremia as a binary variable in the equation. Would this also be the case if we would replace hyponatremia by the linear variable sodium level? If these two factors had their effect on AEs entirely explained by the amount and severity of hyponatremia, one would expect these would not be significant anymore in such a multivariate analysis. In this post-publication analysis with sodium level (Na^+, table 1) instead of hyponatremia in the model, the type of drug (OXC, CBZ) was no longer a significant covariate in predicting AEs. So, the effect of the drug type we found in the analyses with the categorical variable hyponatremia was entirely explained by its impact on the sodium levels. Concomitant ASMs remained a significant risk factor for AEs

(table 1). So, the influence of concomitant ASM on AEs could not be entirely explained by its effect on sodium levels. It feels intuitive that using more different ASMs with each its own set of AEs together gives a higher risk of AEs, although there is no supportive evidence for this.[18,19]

Table 1 logistic regression with outcome having adverse symptoms.

Dependent variables			95% C.I.			
	N	Odds Ratio	Lower	Upper	*P*-value	R^2
Na^+	667	0,838	0,806	0,872	<0,001	0,285
OXC/ CBZ		1,437	0,955	2,162	0,082	
Na^+	666	0,835	0,808	0,864	<0,001	0,287
Nr concomitant ASMs		1,255	1,034	1,524	0,022	

Now that we know that the risk of the type of drug (CBZ/ OXC) for developing AEs was explained by the drug's effect on sodium levels, we will have another look at the subgroup analysis. The subgroup analysis, where the sodium levels were divided into three categories, showed that in people with normal sodium levels, the rate of AEs is quite similar in the OXC and CBZ groups. The most significant difference is found in the mild hyponatremia group. This could be because most OXC users are at the low end (Na^+ close to 128 mmol/L), and CBZ users are more at the high end (close to 134 mmol/L) within the group. Perhaps, hyponatremia duration also plays a role, and maybe OXC use induces more extended periods of hyponatremia than CBZ use. COIH may already occur three weeks after starting therapy.[20] Still, in Kim's study, hyponatremic symptoms that occurred in 59.4% of OXC users in the study of Kim, were found within 2 years after initial treatment.[5] More severe hyponatremia will expose symptoms probably within weeks. Still, the mild ones will develop more slowly and will take time to get recognised by patients and physicians.

In following our study, the earlier mentioned cohort study from Japan reported that 34,3% of patients with sodium levels <130 mmol/L had symptoms of fatigue, headache, vomiting, anorexia or coma and 4,2% were hospitalised for the treatment of hyponatremia. In this study, symptoms were not systematically investigated in all patients. Sixty-four % of the patients with hyponatremia had a

mild to severe intellectual disability or dementia, making it difficult to report AEs. So, it's likely these numbers were underestimated. [8]

The alert reader of this thesis might wonder why in chapter 3, a different percentage/prevalence of symptoms of COIH was reported compared to chapter 4 within apparently the same cohort. In the epidemiology study (chapter 3), we looked at the whole cohort of patients using CBZ or OXC. Symptoms were only scored in patients with COIH and only when other causes were excluded. They were not scored when symptoms seemed to directly result from high drug serum levels or interaction with another ASM. Percentages described in this chapter can be interpreted as the prevalence of symptoms in COIH. In chapter 4 (the clinical study) we evaluated all people with COIH and 300 epilepsy controls without COIH. In this study, all possible AEs of ASM treatment were scored, not just symptoms attributable to hyponatremia. Patients with no report about the response to treatment with the ASMs were classified as missing. So, from our clinical study, we can conclude that persons with COIH experience more AEs than persons without COIH, but the percentages found cannot be interpreted as the prevalence of symptoms of COIH. The specific AEs found significantly more in the group with COIH might be caused by the hyponatremia. They were dizziness, tiredness, instability, diplopia, cognitive slowing, concentration problems, confusion, falling, headache, increased seizure frequency, nausea and somnolence. All these clinical problems have been described both as AEs of ASMs and as symptoms of hyponatremia in general. When AEs were described for CBZ and OXC in literature, hyponatremia was not considered as a possible cause of the symptoms.[21,22] Sodium blockers like lamotrigine and lacosamide are also associated with AEs like dizziness, diplopia, tiredness and headache but without the occurrence of hyponatremia.[23,24] The sodium blocking properties of CBZ and OXC might explain part of these AEs. Still, it will also do so in the group without COIH. The difference in frequency of the specific AEs is explained by the difference in sodium levels between the groups with and without COIH.

This study design offered the most certainty about AEs attributable to COIH we could have shown, derived from retrospective data. Only in a prospective experiment with inducing and correcting COIH by water loading and inducing diuresis, respectively, you can genuinely assess symptoms caused by the hyponatraemic state. Perucca et al. performed such an experiment long ago in a

small number of individuals. A water loading test was performed in six people on chronic treatment with CBZ and six healthy controls. Free water clearance was two to three times lower in the CBZ treated individuals than in controls. In two CBZ treated patients, water clearance did not change at all after water load. These two became hyponatraemic and complained of malaise and drowsiness, one of them had an epileptic seizure at the end of the test. These symptoms cleared after the profuse diuresis, followed by oral administration of furosemide.[25] This test showed a causal relationship between the symptoms described and the COIH. As water loading does not resemble natural circumstances, performing such experiments in larger cohorts will not help better understand the impact of COIH on the lives of our patients. Thus far, no prospective studies have been done to test whether the correction of hyponatremia reduces AEs in the group with COIH to the level of AEs without COIH. These types of studies are available on chronic mild hyponatremia in general (not associated with ASMs).

In large population-based cohorts, hyponatremia was an independent predictor of mortality and caused neurocognitive deficits, gait disturbance, falls, bone fractures and osteoporosis.[26] Treatment of chronic mild hyponatremia without clinically apparent symptoms improved neurocognitive function after 14 days. Gait did not improve after 2 weeks, as shown in a prospective case-control study.[27] Apparently, most of the symptoms experienced by hyponatremia affect the brain's functioning and seem to be reversible to some extent. But how does hyponatremia affect the brain?

In a rat model, sustained reduction of serum sodium levels induced gait disturbances and cognitive impairment associated with elevated extracellular glutamate concentrations in the hippocampus. Glutamate, moving extracellular, works as an organic osmolyte, correcting the initial water movement into the cell caused by the hypo-osmolar state due to the hyponatremia. The extracellular glutamate concentration is kept low in physiologic conditions to avoid excessive receptor activation and glutamate neurotoxicity. The rise in glutamate due to hyponatremia was thought to affect neurotransmission. These abnormalities were reversible with correcting the sodium levels in the rat model.[28] Basic research showed that even in mild chronic hyponatremia, reduced extracellular Na^+ was associated with harmful effects on cellular homeostasis, elicited by oxidative stress. As described in the rat model study, high levels of extracellular glutamate result in

neuronal Ca^{2+} overloading and oxidative stress. Oxidative stress appears to be a common denominator of degenerative processes.[29] So, although symptoms of mild chronic hyponatremia seem to be partially reversible, these rodent data suggest that it is potentially damaging the brain.
Our studies taught us that people might suffer from COIH symptoms. As a physician, you will only find them when you know they exist and if you know where to look.

Now we can answer the question: "Carbamazepine and oxcarbazepine induced hyponatremia, is this a clinical problem?"
Yes, it is!

COIH is a very common adverse effect and mild chronic hyponatremia is not as benign as previously thought.

Genetics and considerations on the pathogenesis of COIH

Genetic markers for CBZ-induced Stevens-Johnson syndrome have been identified and have directly impacted treatment management.[30-32] For thiazide induced hyponatremia polymorphisms were found in the *KCNJ1* gene encoding for the renal outer medullary potassium channel (ROMK), which plays a role in renal reabsorption of sodium.[33] Just like these two drug-induced AEs, from clinical experience, susceptibility to COIH seems to vary individually. Experimental studies and a recent clinical report suggest COIH is caused by a direct effect of CBZ or OXC on the kidney by stimulating the vasopressin receptor (AVPR2) and thereby initiating water reabsorption.[20,34] Mutations in the *AVPR2* gene can cause a nephrogenic syndrome of inappropriate antidiuresis (NSIAD) with physiological similarities to the inappropriate antidiuresis induced by CBZ and OXC.[35] Variations in genes related to the AVPR2/AQP2 pathway would be logical candidates to explain individual variability in COIH. Also, genes causing variation in metabolism of CBZ and OXC influencing individual differences in serum levels of these drugs could be candidate genes for susceptibility to COIH. Appreciating that several pathways might affect the individual susceptibility to COIH, we performed a genome-wide

association study (GWAS) to ascertain genetic factors contributing to COIH, as described in chapter 5.

We did not find a genetic predictor of COIH in our cohort. However, genetic susceptibility for COIH cannot be ruled out completely. It could be argued that our retrospective cohort was not suitable to find a possible genetic predictor. With a prospective design where those with low sodium levels before the start of CBZ of OXC therapy are excluded, it might be possible to identify genes playing a role in COIH. Conversely, susceptibility to COIH is unlikely a binary but rather a linear variable. This AE may not be an expression of pathogenicity but a normal response of the body to stimulation of the vasopressin receptor inhibiting diuresis. Ten out of twelve healthy subjects given therapeutic doses of CBZ and who underwent a water loading test had a decreased ability to excrete water.[36] In a similar study with an intake of OXC, most of the subjects failed to eliminate 80% or more of the water load. The researchers, therefore, called this effect of OXC physiological.[20] So, for the susceptibility to COIH, one doesn't search for a defective gene but for a specific combination of genetic factors causing a relatively more severe response within a physiological path.

Individual variability in developing COIH is not only there at the response of the vasopressin receptor but also in the metabolism of CBZ or OXC and at the interaction with other drugs. Further, the AVPR2/AQP2 pathway relates to several different pathways with possible individual variability in various steps of these pathways. One example is the influence of prostaglandins discussed in chapter 2 (*review article*). Another is the interaction with the renin-angiotensin-aldosterone system (RAAS) that I like to discuss here. The role of RAAS in COIH was noticed in a study of ten people with epilepsy whose long-term treatment with CBZ was replaced by OXC monotherapy. Low serum precursor atrial natriuretic peptide (ANP) concentrations were found in all, reflecting decreased serum sodium levels. A compensatory aldosterone response may have prevented the development of hyponatremia in some patients. Serum aldosterone levels increased in six patients whose serum sodium concentrations did not decrease. Still, no increase was seen in four people with reduced sodium levels during OXC treatment.[37] Aldosterone increases sodium reabsorption, usually followed by water reabsorption to increase blood pressure. How does the RAAS system act in COIH? The water-retentive phase in SIAD(H) caused by drugs is generally relieved by a physiological process known

as “vasopressin escape”. This consists of natriuresis followed closely by diuresis of increasingly more dilute urine. Increased renal arterial pressure due to volume expansion during water retention appears essential for the process. Volume expansion usually occurs when a hypertonic state is compensated by water-reabsorption regulated by ADH (vasopressin). The increased renal arterial pressure induces the production of ANP and renin followed by aldosterone decrease resulting in natriuresis. In the case of COIH, there is a volume expansion with initially an average amount of sodium, later on evolving to a hypotonic state. In this study, the production of (precursor) ANP was decreased. Only patients with an increase in aldosterone, sodium reabsorption could compensate for the dilution induced by the increased water retention caused by the switch to OXC. An increased aldosterone activity has been reported in several studies as a direct result of low sodium levels. The rise in aldosterone excretion occurs with a delay of days.[38] It usually normalises after approximately a week. As long as the water-retentive phase stays, so does the elevated aldosterone excretion. So, individual differences in the response of aldosterone to sodium levels may be a further key factor in the development of COIH.

Concomitant use of an angiotensin-converting enzyme (ACE) blocking agent, which decreases aldosterone levels, will also increase the risk of hyponatremia. In chapter 3, we found that patients using OXC had significantly lower sodium levels with co-use of an ACE inhibitor. For patients on CBZ we did not see this, at least in part because the subgroup with detailed information on co-medication was small.

Vasopressin escape can also result from downregulation of the vasopressin V2R receptor due to decreased angiotensin II in combination with increased intrarenal nitric oxide and prostaglandin E2.[39] Hence the regulation of electrolyte balance is complex and the susceptibility to COIH most certainly will be genetically complex.

Relevance

Taking the oath of Hippocrates, physicians swear not to harm with their treatment. To fulfil this oath, one should be aware of possible harm and not miss a treatable disorder**.** We like to help physicians to achieve their oath by bringing COIH to their attention. When a patient using CBZ or OXC, reports an AE, the physicians' first response should be to measure sodium levels and serum drug levels. If hyponatremia is found, act upon it and check whether the patient is relieved from this AE. It remains difficult to prove whether COIH directly causes reported AEs, but the risk of experiencing AEs is seven times higher when the individual is hyponatremic (chapter 4). By normalising sodium levels of the person, one will improve their quality of life and in some cases, prevent hospitalisation.
The patient needs to be informed about COIH and explained that specific behaviour, like polydipsia, may cause problems.

Clinical recommendations

Now that we are aware of the clinical importance of COIH, it is equally important to know how to manage the problem and how to manage people suffering from this. First, when do you measure sodium levels? It is recommended to measure these before starting CBZ or OXC treatment, one month after the start and 3 to 6 months after starting, when the individual should be on a stable dose of the drug. Usually, COIH develops in weeks to months after the initiation of therapy. When the individual is already on regular drug use, measure sodium levels after increasing the dose, changes in co-medication, or when they report symptoms or possible AEs. With advancing age and on regular drug use, annual measurement of sodium levels is recommended. In case of finding hyponatremia, the first question should be about fluid intake. When the sodium level is between 134-128 mmol/L, and especially when the fluid intake is 2 litres or more per day, the first option is a mild fluid restriction (1,5 L/day). If this doesn't restore levels to normality, and the patient still has AEs, the next step is to lower the dose of the drug or switch it to another sodium channel blocker or to intensify fluid restriction to 1 L/day. Of course, this choice will also depend on how dependent the individual is on these

ASMs to control seizures. With sodium levels <128 mmol/L, we recommend substituting the ASM as the first option when this is possible regarding seizure control. The alternative is a fluid restriction to 1 L/ day. It is recommended to treat all COIH<128 mmol/L, not only when the individual reports AEs. Consult an internal medicine specialist when sodium levels do not increase (enough) following the interventions described above. Treatment with urea or a vasopressin receptor agonist (tolvaptan) can be helpful, but other causes should be excluded. Salt supplementation has no place in the treatment of COIH as the problem is an excessive amount of water, not a shortage of salt.

Measure sodium levels

- At the start, after 1 month and after 3-6 months of CBZ or OXC use
- After dosage increase, alterations in co-medication or reports of AEs
- In chronic CBZ users over 60 and OXC users over 40 years of age once a year

Treatment

Sodium level 134-128 mmol/L

1 fluid restriction (1,5 L/day)
2 not resolved and AEs: decrease dose/ substitute/ fluid restriction 1 L/day.

Sodium level<128 mmol/L

1 substitute ASM
2 restriction of 1 L/day
3 consult an internal medicine doctor

Future perspectives

Our findings and conclusions are based on retrospective data. Future research should be performed with a prospective design. This would allow measuring a baseline sodium level before the start of CBZ or OXC and measuring the decrease in sodium levels after initiation therapy. At chosen follow-up moments, for instance, after 1, 3, 6 and 12 months, serum sodium and aldosterone measurements, serum levels of the prescribed drug and direct questioning on symptoms/ AEs are recommended. It would also be interesting to study the impact of an intervention correcting hyponatremia. Do symptoms disappear or reduce? When patients don't report symptoms before the correction of COIH, do they still feel better, or is their functioning improved afterwards? A study on the effect of correction of sodium levels would give more information on which part of the symptoms we scored can genuinely be attributed to COIH.

For further genetic studies, a prospective design would enhance the chance to find a predictor or markers for the vulnerability to COIH.

CBZ and OXC are increasingly being replaced by modern sodium channel blockers like lamotrigine and lacosamide in the western world. The cost of older ASM might be cheaper per tablet. Still, the median total direct health care cost associated with enzyme-inducing ASM therapy was reported higher than with non-enzyme inducing ASMs by a long term study from the UK. There appears to be a higher risk of complications associated with enzyme induction.[40] Studies like this and the clinical advantages of prescribing non-enzyme inducers, for example, fewer interactions to consider, will reduce the use of CBZ and OXC, making it more challenging to carry out such a prospective study in Europe. Worldwide, CBZ remains among the two or three most prescribed drugs for focal epilepsy. OXC is among the first-choice options for the initial treatment of focal-onset seizures in the US and China.[41] So, although CBZ and OXC are currently less newly prescribed in epilepsy in western countries, many individuals are still on CBZ or OXC and often for a long time. For all of them, better knowledge about COIH could significantly impact the quality of life.

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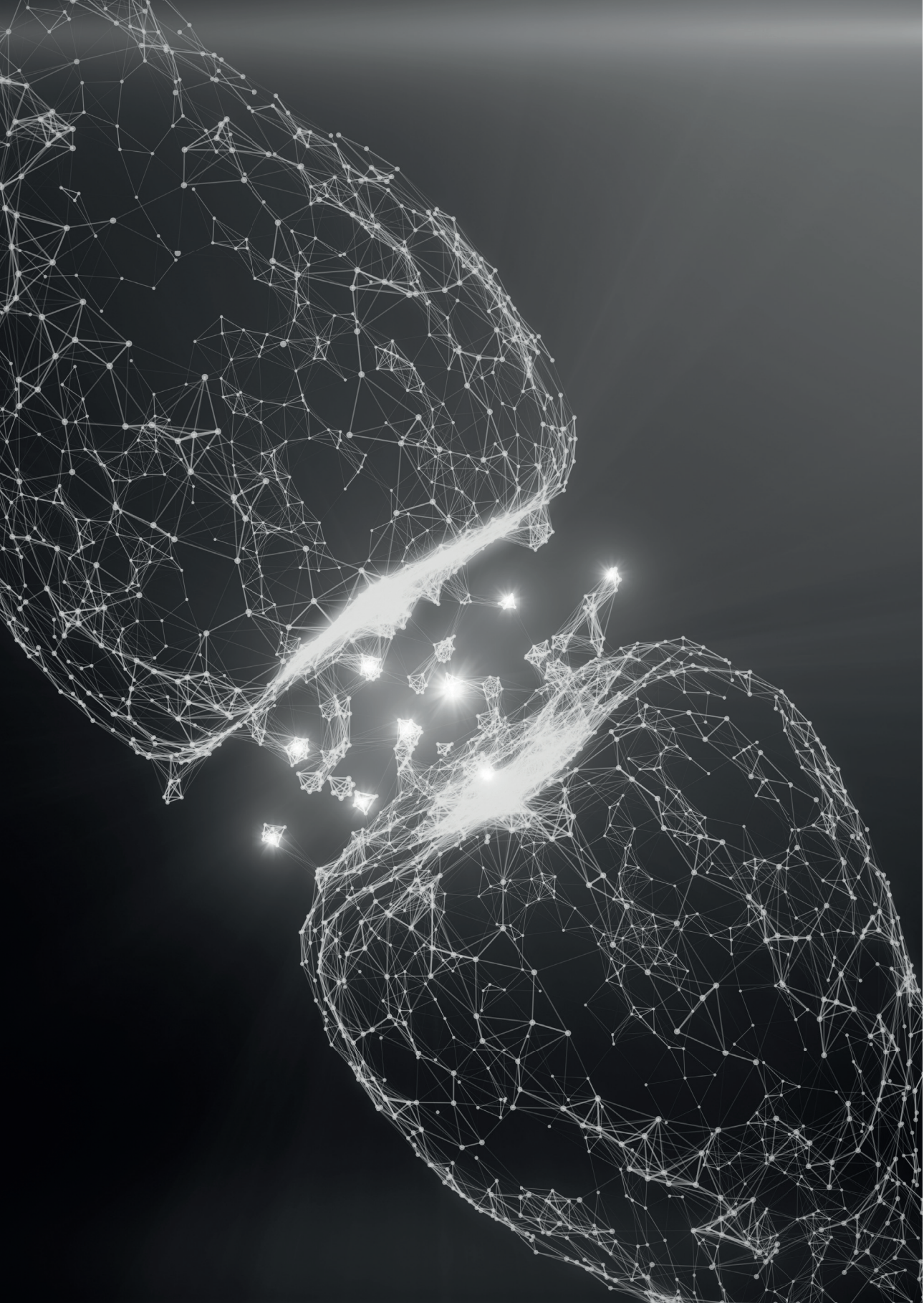

CHAPTER 7

Summary
Samenvatting

Summary

Epilepsy affects about 1 % of people and is mainly treated with anti-seizure medication (ASM). Unfortunately, ASM's adverse effects (AEs) affect many people, often limiting effective treatment. The use of carbamazepine (CBZ) and oxcarbazepine (OXC) as first-line ASM in treating focal epilepsy is limited by hyponatremia. Although often assumed to be asymptomatic, hyponatremia can lead to symptoms ranging from unsteadiness and mild confusion to seizures and coma. This thesis describes the association between CBZ or OXC and hyponatremia and the clinical impact that carbamazepine- and oxcarbazepine-induced hyponatremia (COIH) has on people with epilepsy.

Chapter 1 provides background information on the neurophysiology of epilepsy and the working mechanism of different types of ASM. It then focuses on the drugs CBZ and OXC and describes the current knowledge on COIH.

Chapter 2 reviews the epidemiology, pathophysiology and putative genetic basis of COIH. Hyponatremia occurs in up to half of people taking CBZ or OXC and is often assumed to be asymptomatic. Chronic hyponatremia causes subtle neurological symptoms that are often wrongfully attributed to underlying disorders, direct drug toxicity, or are not recognised. COIH was initially thought to be a syndrome of inappropriate antidiuretic hormone secretion. Still, clinical and in vitro studies have shown that the antidiuretic properties of CBZ and OXC are, at least partly, explained by the direct stimulation of the vasopressin 2 receptor (V2R)/Aquaporin 2 (AQP2) pathway. No known genetic risk variants for COIH have yet been identified, but genes that code for proteins in the vasopressin water reabsorption pathway are likely candidates.

In **chapter 3** we assessed the occurrence of COIH in a large cohort of people with epilepsy and looked for possible determinants. Since 2010, we have collected clinical data, including ASM history, as part of EpiPGX, an international collaboration performing pharmacogenomic studies. Over 2,600 people were

included from our tertiary epilepsy centre in the Netherlands, and we collected data on sodium level measurements in people who (had) used CBZ and OXC (available in 1,132 on CBZ and 289 on OXC). Our main finding was that hyponatremia (Na^+≤134 mmol/L) occurred in about a quarter of those taking CBZ and almost half of those taking OXC, in line with other studies. Severe hyponatremia (Na^+≤128 mmol/L) occurred in 7% in the CBZ group and 22% in the OXC group. Especially in those treated with OXC, we found a relatively high frequency of severe hyponatremia compared to others. Age over 40 years, high serum levels of CBZ and OXC and concomitant use of other ASMs were the main risk factors for hyponatremia in both treatment groups. Females on OXC were at a higher risk of hyponatremia than males. The gender difference was less clear from the currently available evidence. This may provide a clue for genetic predisposition to COIH as the vasopressin 2 receptor (*V2R*) gene is located on the X chromosome.
In a subgroup analysis we found that an individual with hyponatremia associated with CBZ is also likely to develop hyponatremia while taking OXC.
Symptoms present at hyponatremia, which could not be explained by another clear cause such as overt ASM intoxication or comorbidity were scored and found in almost half of people who had COIH. They lead to hospital admissions in 3%, primarily because of falls. Due to the study's design, we could not determine whether these symptoms could be attributed to COIH or to different causes, which led to our next study.

In **chapter 4** we assessed the AEs experienced by people taking CBZ or OXC and whether they could be attributed to COIH. We performed an observational retrospective study collecting data between 2017 and 2019 on serum sodium levels and AEs in 410 people with COIH and 300 with normal sodium levels from our previously described cohort.
Our main finding was the occurrence of AEs in 65% of people with hyponatremia compared to 21% with normal sodium levels (OR 7,5, p=<0,001) and in 83% of people with severe hyponatremia compared to 55% in those with mild hyponatremia (p=<0,001). Significant predictors of AEs were the drug (OXC vs CBZ), and the number of concomitant ASMs. Dizziness (28% vs 6%), tiredness (22% vs 7%), instability (19% vs 3%) and diplopia (16% vs 4%) were reported more often in the hyponatremia group than in those with normal levels.

Serum levels of the drug did not influence the seven-fold increased risk of developing AEs associated with COIH. Treatment of this form of chronic mild hyponatremia can improve the overall functioning of people with epilepsy.

Chapter 5 describes the search for genetic factors contributing to COIH. In 1,141 individuals of a CBZ/OXC treated cohort genetic data was collected for a genome-wide association analysis to scan for common genetic determinants of COIH. From our clinical experience, susceptibility to COIH varies individually. Previously described clinical predictors of serum sodium levels only explained 11-14% of the variance in the SEIN cohort. We did not observe any genome-wide significant associations, neither with sodium level in a linear trait, nor with hyponatremia as a dichotomous trait. This finding cannot rule out genetic susceptibility for COIH completely, as rare variants and combinations of genetic variants of smaller effect size may contribute to overall risk.
This chapter also assessed the clinical and genetic factors associated with CBZ metabolism. Age, number of co-medications, phenytoin use, phenobarbital use, and sodium valproate use were significant predictors of CBZ metabolic ratio. The association with the co-used ASM can be explained by either the induction of the cytochrome P450- enzyme CYP3A4, by which CBZ is metabolised in the liver, or by inhibition of epoxide hydrolase. We could not replicate the finding of polymorphisms in *CYP3A4* and *EPHX1* (gene encoding microsomal epoxide hydrolase) that have been associated with inter-individual variability of CBZ metabolism. Also, no genome-wide significant associations with CBZ metabolic ratio were found.

Chapter 6 provides an overview of our findings and discusses their relevance. COIH is a very common AE. We discuss whether this is a clinical problem. Even mild chronic hyponatremia causes oxidative stress in the brain. Besides the AVPR2/AQP2 pathway, the renin-angiotensin aldosterone system also plays a role in inter-individual differences in the susceptibility to COIH. Hyponatremia increases the risk of hospitalisation and causes a variety of seemly mild symptoms. Treatment of COIH, by fluid restriction, dose reduction or substitution of the ASM can relieve symptoms and improve quality of life.

Samenvatting

Epilepsie treft ongeveer 1% van de populatie en wordt voornamelijk behandeld met anti-epileptica (anti-seizure medication (ASM)). Helaas ervaren veel mensen bijwerkingen van ASMs, waardoor een effectieve behandeling wordt beperkt. Het gebruik van carbamazepine (CBZ) en oxcarbazepine (OXC) als eerstelijns ASM bij de behandeling van focale epilepsie wordt beperkt door het optreden van hyponatriëmie als bijwerking van deze middelen. Hoewel vaak wordt aangenomen dat deze hyponatriëmie asymptomatisch is, kan het leiden tot symptomen variërend van onvastheid ter been en lichte verwardheid tot toevallen en coma. Dit proefschrift beschrijft de associatie tussen CBZ of OXC en hyponatriëmie en de klinische impact die carbamazepine- en oxcarbazepine-geïnduceerde hyponatriëmie (COIH) heeft op mensen met epilepsie.

Hoofdstuk 1 geeft achtergrondinformatie over de neurofysiologie van epilepsie en het werkingsmechanisme van verschillende typen ASM. Vervolgens wordt ingegaan op de medicijnen CBZ en OXC en wordt de huidige kennis over COIH beschreven.

Hoofdstuk 2 bespreekt de epidemiologie, pathofysiologie en vermeende genetische basis van COIH. Hyponatriëmie komt voor bij ongeveer de helft van de mensen die CBZ of OXC gebruiken. Chronische hyponatriëmie veroorzaakt subtiele neurologische symptomen die vaak onterecht worden toegeschreven aan onderliggende aandoeningen, directe geneesmiddeltoxiciteit of helemaal niet worden herkend. Aanvankelijk werd gedacht dat COIH een syndroom was van inadequate secretie van het antidiuretisch hormoon. Klinische en in vitro-onderzoeken hebben echter aangetoond dat de antidiuretische eigenschappen van CBZ en OXC, althans gedeeltelijk, worden verklaard door de directe stimulatie van het vasopressine 2-receptor (V2R)/Aquaporine 2 (AQP2)-pad. Er zijn nog geen bekende genetische risicovarianten voor COIH geïdentificeerd, maar genen die coderen voor eiwitten in het vasopressine-waterreabsorptie pad zijn waarschijnlijke kandidaten.

In **hoofdstuk 3** hebben we het vóórkomen van COIH in een groot cohort van mensen met epilepsie onderzocht en zijn we op zoek gegaan naar mogelijke determinanten. Sinds 2010 hebben we klinische gegevens verzameld, waaronder de medicatie voorgeschiedenis, deel uitmakende van de EpiPGX, een internationaal samenwerkingsverband dat farmaco-genetische onderzoeken uitvoert. Meer dan 2600 mensen onder behandeling van ons tertiaire epilepsiecentrum in Nederland werden geïncludeerd. Er werden gegevens verzameld over natrium waarden in het bloed bij mensen die CBZ of OXC (beschikbaar bij 1.132 voor CBZ en 289 voor OXC) hadden gebruikt. Onze belangrijkste bevinding was dat hyponatriëmie (Na^+≤134 mEq/L) optrad bij ongeveer een kwart van degenen die CBZ gebruikten en bijna de helft van degenen die OXC gebruikten; dit was in overeenstemming met andere onderzoeken. Ernstige hyponatriëmie (Na^+≤128 mEq/L) trad op bij 7% in de CBZ-groep en bij 22% in de OXC-groep. Vooral bij degenen die met OXC werden behandeld, was de gevonden frequentie van ernstige hyponatriëmie relatief hoog in vergelijking met andere onderzoeken. Leeftijd ouder dan 40 jaar, hoge serumspiegels van CBZ en OXC en gelijktijdig gebruik van andere anti-epileptica waren de belangrijkste risicofactoren voor hyponatriëmie in beide behandelingsgroepen. Vrouwen op OXC hadden een hoger risico op hyponatriëmie dan mannen. Het geslachtsverschil als risicofactor was minder duidelijk terug te vinden in de beschikbare literatuur. Deze risicofactor kan een aanwijzing zijn voor een genetische aanleg voor COIH, aangezien het gen voor de vasopressine-2-receptor (*V2R*) zich op het X-chromosoom bevindt.

In een subgroep analyse vonden we dat iemand met hyponatriëmie tijdens CBZ gebruik waarschijnlijk ook hyponatriëmie zal ontwikkelen tijdens het gebruik van OXC.

Symptomen passend bij hyponatriëmie, die niet konden worden verklaard door een andere duidelijke oorzaak, zoals een ASM-intoxicatie of co-morbiditeit, werden gescoord en gevonden bij bijna de helft van de mensen met COIH. Ze leidden in 3% tot ziekenhuisopnames, voornamelijk door vallen. Vanwege de opzet van het onderzoek konden we niet bepalen of deze symptomen konden worden toegeschreven aan COIH of aan andere oorzaken, wat leidde tot ons volgende onderzoek.

In **hoofdstuk 4** evalueerden we de bijwerkingen die mensen ondervonden tijdens het gebruik van CBZ of OXC en of ze konden worden toegeschreven aan COIH. We hebben een observationele retrospectieve studie uitgevoerd waarbij we tussen 2017 en 2019 gegevens verzamelden over natrium serumspiegels en bijwerkingen bij 410 mensen met COIH en 300 met normale natriumspiegels van ons eerder beschreven cohort. Onze belangrijkste bevinding was het verschil in optreden van bijwerkingen bij mensen met een hyponatriëmie (65%) vergeleken met mensen met een normale natriumspiegel (21%) (OR 7,5, p=<0,001). Verder werden vaker bijwerkingen gevonden bij mensen met een ernstige hyponatriëmie (83%) dan bij degenen met een milde hyponatriëmie (55%)(p=<0,001). Significante voorspellers van bijwerkingen waren het type medicijn (OXC versus CBZ) en het aantal gelijktijdig gebruikte ASM's. Duizeligheid (28% versus 6%), vermoeidheid (22% versus 7%), instabiliteit (19% versus 3%) en diplopie (16% versus 4%) werden vaker gemeld in de hyponatriëmie-groep dan bij degenen met normale natrium waarden.
Serumspiegels van CBZ en OXC hadden geen invloed op het zevenvoudig verhoogde risico op het ontwikkelen van bijwerkingen geassocieerd met COIH. Behandeling van deze vorm van chronische milde hyponatriëmie kan het algehele functioneren van mensen met epilepsie verbeteren.

Hoofdstuk 5 beschrijft de zoektocht naar genetische factoren die bijdragen aan COIH. Bij 1.141 individuen die CBZ of OXC gebruikten werd DNA verzameld voor een genoom brede associatieanalyse om te zoeken naar gemeenschappelijke genetische determinanten van COIH. Uit onze klinische ervaring blijkt dat de gevoeligheid voor COIH individueel varieert. Eerder beschreven klinische voorspellers van COIH verklaarden slechts 11-14% van de variantie in het SEIN-cohort. We hebben geen genoom brede significante associaties waargenomen, noch met het natriumgehalte als lineaire variabele, noch met hyponatriëmie als dichotome variabele. Deze bevinding kan genetische gevoeligheid voor COIH niet volledig uitsluiten, aangezien zeldzame varianten en combinaties van genetische varianten met een kleinere effectgrootte kunnen bijdragen aan het algehele risico. Dit hoofdstuk beschrijft ook de klinische en genetische factoren die verband houden met het CBZ-metabolisme. Leeftijd, de hoeveelheid comedicatie, gebruik van fenytoïne, gebruik van fenobarbital en gebruik van natriumvalproaat waren significante voorspellers van de CBZ-metabolische ratio. De associatie met

gelijktijdig gebruikte anti-epileptica kan worden verklaard door de inductie van het cytochroom P450-enzym CYP3A4, waardoor CBZ in de lever wordt gemetaboliseerd of door remming van epoxide hydrolase. We konden de bevinding van polymorfismen in *CYP3A4* en *EPHX1* (gen dat codeert voor microsomaal epoxide hydrolase) die zijn geassocieerd met interindividuele variabiliteit van het CBZ-metabolisme, niet repliceren. Er werden ook geen andere significante associaties tussen genetische factoren en CBZ-metabolisme ratio gevonden.

Hoofdstuk 6 geeft een overzicht van onze bevindingen en bespreekt de relevantie. COIH is een veel voorkomende bijwerking. We bespreken in welke mate dit een klinisch probleem is. Zelfs milde chronische hyponatriëmie veroorzaakt oxidatieve stress in de hersenen. Naast het AVPR2/AQP2-pad speelt het renine-angiotensine-aldosteron systeem ook een rol bij interindividuele verschillen in de gevoeligheid voor COIH. Hyponatriëmie verhoogt het risico op ziekenhuisopname en veroorzaakt een verscheidenheid aan schijnbaar milde symptomen. Behandeling van COIH, door vochtbeperking, dosisverlaging of vervanging van CBZ of OXC kan symptomen verlichten en de kwaliteit van leven verbeteren.

Abbreviations

AE(s)	adverse effect(s)
AED(s)	anti-epileptic drug(s)
ASM(s)	anti-seizure medication(s)
	In earlier articles (H2,3,5) AED(s) was used instead of ASM(s).
AQP2	aquaporin-2
CBZ	carbamazepine
COIH	carbamazepine and oxcarbazepine induced hyponatremia
mEq/L	=mmol/L (sodium levels)
Na^+	sodium
OXC	oxcarbazepine
SIAD	syndrome of inappropriate antidiuresis
SIADH	syndrome of inappropriate antidiuretic hormone secretion
V2R	vasopressin receptor 2

List of publications

This thesis

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Bianca Berghuis was born February 5th 1978 in Rotterdam. In 1996 she graduated at the Comenius College in Capelle aan den IJssel and started medical school at the University of Rotterdam. During her studies in medicine she attended a summer school program (1998-2000) partly at the Erasmus University in Rotterdam and partly at the Harvard University in Boston, USA. The summer program resulted in a Master of Science degree in Clinical Epidemiology. As part of this program she did her first research, about genetics in hemochromatosis, at the genetic epidemiological unit, departments of epidemiology & biostatistics (prof. dr.ir. C.M. van Duijn). In 2002 she obtained her medical degree cum laude, and worked as a resident in Neurology at the Sint Franciscus Gasthuis, Rotterdam. January 2003 she started as a neurology resident at the Medical Centre Haaglanden, Den Haag (dr. J. Tans and dr. C. Vecht). The last 6 months of her neurology training she did at the University Medical Centre Groningen (prof. dr. O. Brouwer). Since 2009 she has been working as a neurologist at SEIN, Stichting Epilepsie Instellingen Nederland, Zwolle. At SEIN (prof. dr. J.W. Sander) she did her studies described in this thesis, in collaboration with the Centre of Molecular Medicine (dr. B.P.C. Koeleman) and the Department of Genetics (prof. dr. D. Lindhout) at the University Medical Centre of Utrecht. In 2019 she became a trainer in neurology at SEIN. Since 2021 she also works as a Chief Medical Information Officer (CMIO) at SEIN.

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