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Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) or Hyponatraemia Associated with Valproic Acid

Four Case Reports from the Netherlands and a Case/Non-Case Analysis of Vigibase

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Abstract

Background: The Netherlands Pharmacovigilance Centre Lareb received four cases of severe symptomatic hyponatraemia or syndrome of inappropriate antidiuretic hormone secretion (SIADH) in association with valproic acid use, in which a causal relationship was suspected. This study describes these cases and gives support for this association from Vigibase, the adverse drug reaction (ADR) database of the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre.

Methods: Cases of hyponatraemia in valproic acid users are described. In a case/non-case analysis, the strength of the association between reported cases of hyponatraemia and the use of valproic acid in Vigibase was established by calculating a reporting odds ratio, adjusted for possible confounding by concomitant medication.

Results: Four females aged 57, 67, 71 and 88 years developed symptomatic hyponatraemia or SIADH after starting valproic acid. Despite concomitant medication or co-morbidity, a causal relationship was plausible. In Vigibase, valproic acid is disproportionally associated with hyponatraemia and SIADH (corrected reporting odds ratio 1.83 [95% CI 1.61, 2.08]).

Discussion: Based on the described cases and the reports from Vigibase, a causal relationship between valproic acid use and hyponatraemia or SIADH can be suspected. The mechanism by which valproic acid could cause hyponatraemia or SIADH has not been fully elucidated. Valproic acid use could lead to reduced sensitivity of hypothalamic osmoreceptors. It also might

directly affect tubular cell function, thereby leading to SIADH. It might be expected that a combination of effects on the osmoreceptors and a lack of compensation of the salt-water unbalance by the nephrons causes SIADH in some patients using valproic acid. It could be a dose- or concentration-related adverse effect.

Conclusion: In this report, severe symptomatic hyponatraemia and SIADH have been associated with the use of valproic acid. With this study, not only is the number of published cases doubled, but also the data from Vigibase strongly support the association. Since hyponatraemia and SIADH have a high morbidity, health professionals should be aware of this potential ADR.

Background

Hyponatraemia is defined as a serum sodium level of <135 mmol/L.[1,2] Mild hyponatraemia is generally asymptomatic, but serious symptoms occur if sodium levels fall below 125 mmol/L or when the condition develops rapidly (within 48 hours). Because of hypotonicity in the extracellular space, water flows into the cells and leads to cellular swelling and cerebral oedema. These effects result in early symptoms of headache, nausea, muscular weakness, lethargy, ataxia and confusion, which can progress to seizures, irreversible neurological damage, coma and death.[1-3]

Hyponatraemia can be due to impaired capacity of renal water excretion, effective arterial blood volume depletion, primary polydipsia, reset osmostat syndrome, hyperlipidaemia or hyperparaproteinaemia.[4] Effective arterial blood volume depletion can be caused by several factors, for example vomiting, peritonitis, renal failure and the use of several drugs such as antidiuretic hormone (ADH) analogues, ADH-release agonists, or agents potentiating the action of ADH.[4,5] Hyponatraemia has also been associated with the use of antipsychotic drugs, antidepressants, certain anti-cancer agents and with several antiepileptic drugs.[1,5-12]

In the syndrome of inappropriate ADH secretion (SIADH), the ADH arginine vasopressin (AVP) is released despite plasma hypo-osmolality, which is inappropriate. The syndrome is characterized by a euvolaemic hyponatraemia, with concentrated urine represented by an excessive urinary sodium concentration (>20 mmol/L) and urine hyperosmolality (>100 mOsmol/kg).[5] An excess of ADH can be found in SIADH, mineralocorticoid deficiency and hypothyroidism.[3,4] Laboratory parameters, such as thyroid function, cortisol level, serum and urine osmolality, urine levels of sodium,[4] as well as cerebral and thoracic imaging, are useful tests in the differential diagnosis of hyponatraemia.

Only four case reports in the literature describe hyponatraemia or SIADH as a possible adverse drug reaction (ADR) associated with use of the antiepileptic drug valproic acid.[13-16]

In this study we describe four cases of symptomatic hyponatraemia or SIADH in association with the use of valproic acid, which have been reported to the Netherlands Pharmacovigilance Centre Lareb. Because in the literature only four case reports were found, Vigibase, the database of the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre, (WHO-UMC) was also searched for the association.

Methods

The reports submitted to the Netherlands Pharmacovigilance Centre Lareb are described. Subsequently, the reports submitted to the WHO-UMC, are analysed. Currently, over 4.7 million ADR reports from more than 90 countries are filed in this database. One of the objectives of the WHO-UMC is to receive, analyse and record

worldwide ADR data. ADRs are coded according to the WHO Adverse Drug Reaction Terminology. The suspected drugs are classified according to the WHO Drug Dictionary. For analysis purposes, the WHO Anatomical Therapeutic Chemical (ATC) classification system, which is linked to the WHO Drug Dictionary, can be used. An ADR can be attributed to one or more suspected drugs and to one or more concomitant drugs.

All ADRs reported to the WHO-UMC until September 2007 were taken into account for this analysis. The index group consisted of reports with the suspected drug being valproic acid (ATC code N03AG01). The control group consisted of all other reports in the database. Cases were defined as reports mentioning the preferred terms 'hyponatraemia' or 'syndrome of inappropriate ADH secretion'. All other reports were selected as non-cases. The presence of suspected or concomitant drugs that have been associated in the literature with hyponatraemia was used as a co-variate (see table I).[2]

The strength of the association between hyponatraemia and valproic acid compared with other drugs in the database was calculated using the ADR reporting odds ratio (ROR) as a measure of disproportionality.[17] Using the ROR, correction for co-variates can be easily made. An additional advantage is the fact that non-selective underreporting of a drug or ADR has no influence on the value of the ROR compared with the population of patients experiencing an ADR.[18] If more than four reports are received, the outcome of various methods is comparable. The Bayesian approaches are less likely to yield false positive results when low numbers (less than four reports) are involved. Given the high number of reports in this study, there is no reason to use this approach. In the present dataset, there is no advantage for using the proportional reporting ratio over the ROR or vice versa. Both methods yield similar results and are largely comparable.[18]

In this study we adjusted for the use of concomitant medication that had been associated with hyponatraemia in the past, calculated by means of logistic regression analysis and expressed as point estimates with corresponding 95% confidence intervals (CIs). In case the ROR is statistically significant, hyponatraemia is more frequently reported in association with valproic acid compared with the other drugs in the database.

Table I. Suspected or concomitant drugs that have been associated with hyponatraemia

ATC code	Name
A10BB02	Chlorpropamide
C01BD01	Amiodarone
C03A	'Low-ceiling' diuretics, thiazides
C03C	'High-ceiling' diuretics
C07B	Thiazides/β-blockers combination
C07D	Thiazides and other diuretics/β-blockers combination
H01BA01	Vasopressin
H01BA02	Desmopressin
J01MA02	Ciprofloxacin
L01AA01	Cyclophosphamide
L01CA01	Vinblastine
L01CA02	Vincristine
L01XA01	Cisplatin
N03AF01	Carbamazepine
N03AF02	Oxcarbazepine
N04BC01	Bromocriptine
N05A	Antipsychotics (without lithium N05AN)
N06A	Antidepressants
N07BA01	Nicotine

ATC = Anatomical Therapeutic Chemical classification system.

Results

Cases

Patient A

Patient A is a 67-year-old female. Her medical history showed two myocardial infarctions, a cerebrovascular accident (CVA) in January 2005 and epilepsy following this CVA, for which she was treated with valproic acid (Depakine®) 500 mg twice daily since January 2005. She had never used valproic acid before. In the last year she did not experience epileptic seizures. Fourteen months after the start of valproic acid treatment, the patient was sent to hospital because of inability to walk without help for 2 weeks. She also had an insufficient intake of fluid and food, and occasionally signs of confusion for several days. Before the present admission, the serum sodium concentration was normal; the last

sodium level was assessed in September 2005 (136–143 mmol/L).

Laboratory findings on the day of admission and concomitant medications are shown in table II. Other contributing factors besides the pre-existing CVAs were ruled out: nuclear MRI of the brain 1 week after admission revealed no pathology except ischaemic damage due to the CVA in 2005; a CT scan of the thorax revealed no relevant pulmonary pathology.

Sodium levels and actions taken are shown in figure 1. After normalization of the sodium level, this value remained stable and within the normal ranges (138–139 mmol/L).

Patient B

A 71-year-old female was admitted to the hospital because of hyponatraemia (125 mmol/L). She had a history of epilepsy and chronic leg pain due to a stenosis of the spine. A year before, she was also admitted because of hyponatraemia. During that admission, diuretic drugs were stopped. The effect of this cessation is unknown to the authors. Valproic acid and phenobarbital (phenobarbitone) were continued. At the present admission, her antiepileptic drugs were valproic acid 300 mg three times daily and phenobarbital 50 mg once daily. Concomitant medications are shown in table II, as well as the relevant laboratory findings.

To rule out continued diuretic use, despite official cessation of the medication a year before, a drug screening in urine of diuretics was performed, which was negative. A urinary tract infection due to *Escherichia coli* was diagnosed. Thoracic x-ray was normal. An MRI of the lumbar spine revealed the known stenosis of the spine.

SIADH was diagnosed based on the laboratory findings and the absence of other causes for SIADH. During hospitalization, the patient was treated with fluid restriction. The sodium level increased, but subsequently fell again to 124 mmol/L. Because other possible causes were ruled out, valproic acid was stopped, after which sodium level rose to 132 mmol/L. The patient was switched to topiramate to treat her epilepsy. She recovered fully and the concomitant medication was continued.

Patient C

An 88-year-old female was admitted to hospital because of sudden somnolence on the day of admittance. For about 2 days she experienced malaise, nausea and vomiting, and a weight loss of 4 kg in about 10 days was reported. She also had abdominal pain in the left lower quadrant. The patient had a history of asthma, epilepsy, hypothyroidy and cholecystectomy.

She was prescribed valproic acid 300 mg daily and phenobarbital 50 mg twice daily. Concomitant medication and laboratory findings are shown in table II. Her thyroid function was normal. Neither x-rays of the thorax and abdomen, nor abdominal echography or laboratory findings revealed other pathology. Gastroscopy revealed a diaphragmatic hernia. Colonoscopy showed a diverticulosis, without signs of inflammation or other further pathology. SIADH was diagnosed.

During admission the somnolence disappeared spontaneously. The sodium level increased to 125 mmol/L within a few days and then did not change any further, although vomiting had stopped. Because other causes for the hyponatraemia were ruled out, it was suspected that valproic acid might have caused the SIADH, with a latency of 2 years. Valproic acid treatment was therefore stopped. In the following days, sodium level normalized and remained constant. Concomitant medication was continued. An explanation for the abdominal complaints was not found, but these might have worsened the hyponatraemia.

Patient D

A 57-year-old female was admitted to hospital because of symptoms of confusion, memory impairment, increasing somnolence and severe hyponatraemia. She had a history of multiple sclerosis since the age of 46 years and epilepsy since the age of 56 years. Her antiepileptic drugs were lamotrigine 200 mg daily and valproic acid 1000 mg twice daily. Because of an insufficient effect on convulsion frequency, the lamotrigine

Table II. Clinical data and laboratory findings

Data	Normal range	Patient			
		A	B	C	D
VPA dose		500 mg bid	300 mg tid	300 mg od	1000 mg bid
Concomitant drugs		Amlodipine 5 mg od Aspirin (acetylsalicylic acid) 80 mg od Fusidic acid cream 20 mg/g Metoprolol 25 mg tid Olmesartan 20 mg od Ranitidine 150 mg od Thiamine 100 mg	Carbasalate calcium 80 mg od Esomeprazole 40 mg od Atorvastatin 10 mg od Vitamin B complex Ibuprofen 400 mg bid	Dipyridamole/salicylic acid 25/500 mg bid Oxazepam 10 mg bid Losartan 50 mg od Levothyroxine sodium 100 μg od Rabeprazole 20 mg od Salmeterol/fluticasone propionate inhaler 50/250 μg bid Tiotropium bromide inhalation powder 18 μg od	Atenolol/chlortalidone Oxybutynin Bisacodyl Potassium chloride (no dosages known)
VPA level (mg/L)	50–100				89
Sodium (mmol/L)	136–146	120	125	116	116
Serum osmolality (mOsmol/kg)	275–300	252	256	249	
Creatinine (μmol/L)	70–100	58	83	66	
Urea (mmol/L)	2.9–7.5	3.3		4.0	
GFR[a] (mL/min)	85–125	76			
Urine sodium (mmol/24 h)	130–200	46	94	28	
Urine osmolality (mOsmol/kg)	275–300	562	286	224	
AVP (ng/L)	0.2–4.7	0.37			
TSH (mU/L)	0.5–3.9	1.9	2.3	3.37	
FT4 (pmol/L)	9–24	14	26	16	
Cortisol (nmol/L)	0.15–0.70	0.64	0.66	0.26	

a Calculated with Cockroft-Gault formula.

AVP = arginine vasopressin; **bid** = twice daily; **FT4** = free thyroxine; **GFR** = glomerular filtration rate; **od** = once daily; **tid** = three times daily; **TSH** = thyroid-stimulating hormone; **VPA** = valproic acid.

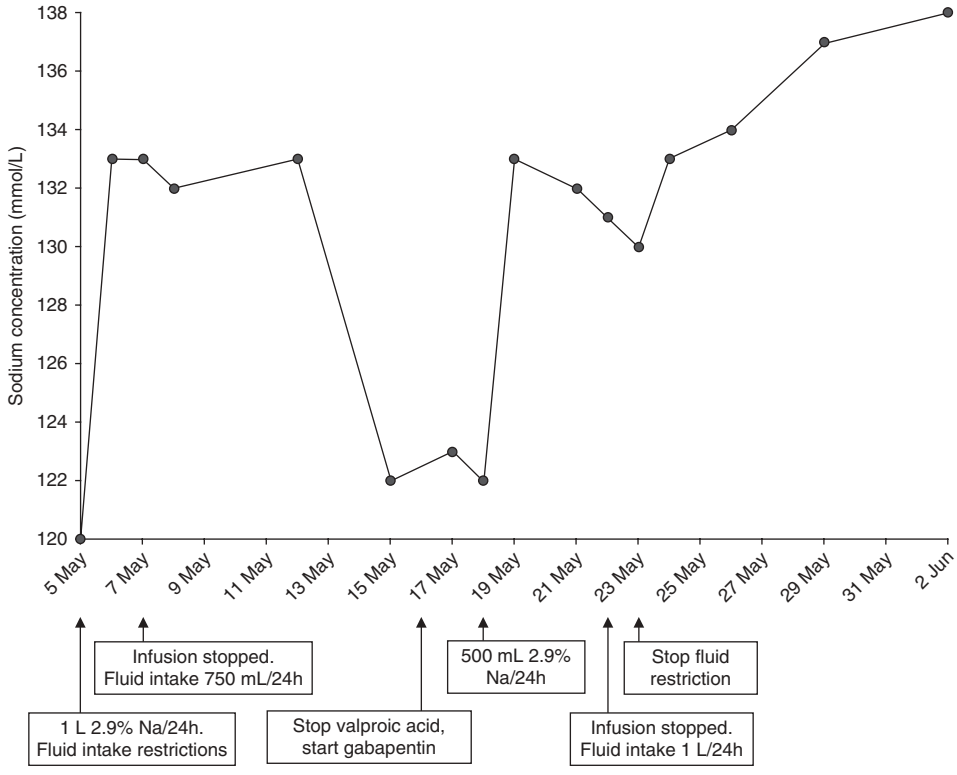

Fig. 1. Sodium levels and actions undertaken in patient A.

had been started in place of phenytoin about 5 months before the admission. Valproic acid dose was not changed. The plasma level of valproic acid after cessation of phenytoin was within the therapeutic range. Concomitant medication and laboratory findings are shown in table II.

During admission, the patient received extra salt, and fluid intake was restricted. Valproic acid dose was decreased to 1500 mg daily and the lamotrigine dose was not altered. The sodium level then increased to 133 mmol/L, despite continuation of diuretic treatment. The patient was discharged from the hospital.

Vigibase Analysis

Until September 2007, a total of 22 606 reports with valproic acid as the suspect medication were received. Hyponatraemia as the suspected ADR was reported in 238 (1.05%) of the reports. Concomitant medication also associated with hyponatraemia was present in 123 reports of these cases. Results are shown in figures 2 and 3. Logistic regression analysis showed that, in Vigibase, valproic acid use is statistically significantly associated with hyponatraemia (ROR 2.40; 95% CI 2.11, 2.73). The ROR corrected for the presence of concomitant medication associated with hyponatraemia is 1.83 (95% CI 1.61, 2.08).

Discussion

This study describes four patients who developed severe symptomatic hyponatraemia or SIADH requiring hospital admission, strongly suggestive of a causal relationship with the use of valproic acid. The data from Vigibase support this association.

Our study has its limitations. First, the described cases are derived from a spontaneous

reporting system. The information given by the reporter can be limited, for example on reaction outcome or on the patient's health status prior to the adverse event (e.g. fluid intake prior to the occurrence of hyponatraemia). To assess causality between the suspect drug and the reported adverse event, additional information is often needed, but not always provided.

Second, the patients used concomitant medication that has been associated with hyponatraemia. They also had other risk factors for the development of hyponatraemia. Furthermore, sodium level can normalize following fluid intake restriction or even without intervention. Taking these considerations into account, we considered the hyponatraemia in the described patients as probably due to valproic acid use. In patient A, all risk factors for hyponatraemia, except the cerebrovascular accident 14 months before, were ruled out. This patient only fully recovered after cessation of valproic acid.

Patient B was administered ibuprofen as concomitant medication. Hyponatraemia has been rarely described with the administration of ibuprofen.[19,20] Because the sodium level rose to 132 mmol/L after cessation of valproic acid, while ibuprofen was continued, a causal relationship with the valproic acid was considered the most plausible. Patient C concomitantly used losartan. Hyponatraemia has been reported during the postmarketing use of losartan,[21] but has not been reported in literature. However, she experienced vomiting at hospital admission and this can be either a risk factor for hyponatraemia, or a consequence of it. Her concomitant medicines (table II) also included levothyroxine sodium: hypothyroidism, the indication for levothyroxine sodium use, is associated with hyponatraemia.

	VPA present	VPA absent
Hyponatraemia or SIADH present	123	10 806
Hyponatraemia or SIADH absent	7 349	787 554

Fig. 2. Figures from Vigibase – reports in which concomitant medication associated with hyponatraemia or syndrome of inappropriate antidiuretic hormone secretion (SIADH) was present. **VPA** = valproic acid.

	VPA present	VPA absent
Hyponatraemia or SIADH present	115	6 139
Hyponatraemia or SIADH absent	15 019	3 039 982

Fig. 3. Figures from Vigibase – reports in which concomitant medication associated with hyponatraemia or syndrome of inappropriate antidiuretic hormone secretion (SIADH) was absent. **VPA** = valproic acid.

Plasma levels of thyroid function parameters were normal in patient C. It is unclear what role the abdominal pain might have played in the hyponatraemia. A causal relationship between valproic acid use and hyponatraemia was suspected, because the sodium level only normalized after cessation of valproic acid, and other common causes for hyponatraemia were ruled out. Patient D used atenolol with chlortalidone. This thiazide-related sulfonamide has been previously associated with hyponatraemia.[22] The multiple sclerosis in this patient is also a risk factor for hyponatraemia and SIADH.[23-25] Her sodium level did rise, but did not normalize after dose decrease of valproic acid. The time relationship between valproic acid use and the occurrence of hyponatraemia, however, was suggestive of a causal relationship.

In cases originating from spontaneous reporting systems, not all information is available at time of reporting. For this reason, retrieving additional information is often needed, but not always are all clinical details provided, such as fluid intake prior to admission. Information on fluid intake was not provided in any of the cases.

Third, using Vigibase also has its shortcomings. The WHO-UMC collects ADR reports from over 90 countries. A known limitation of ADR databases is that they can include duplicate reports, leading to a statistically generated false signal if there are a high number of duplicates. Features about duplicate reports were not available to the authors. However, the role of duplicate reports does not play a significant role in this particular association, because the number of reports associating hyponatraemia to valproic acid is 238. Furthermore, the existence of duplicate reports has its influence on both the numerator

and the denominator of the ROR. Only if the duplicate reports within the cases of valproic acid/hyponatraemia were higher compared with the other reports in the database, could an increase in the ROR be expected. We have no indication for this.

Using the ROR might not be familiar to readers. It is, however, a method used in the statistical approach of spontaneous reporting systems. One of the advantages of using the ROR is the possibility to correct for co-variates in logistic regression analysis. Moreover, the ROR is less sensitive for non-differential misclassification or under-reporting than other measures.[26]

Finally, to calculate the strength of the association between hyponatraemia and SIADH and valproic acid in Vigibase, as a co-variate we corrected for the presence of suspected or concomitant drugs that have been associated in the literature with hyponatraemia. We have limited our selection to the relatively common associated drugs in order to keep the calculation clinically relevant.

The mechanism by which valproic acid could cause hyponatraemia or SIADH has not been fully elucidated. SIADH due to drugs can be caused by stimulation of the release of ADH by the hypophysis, by enhancing ADH action on the kidney, by acting directly on the kidney, or by inhibiting the vasopressinase activity, resulting in prolonged vasopressin half-life.[7,11,14] The AVP level in patient A was within the normal range, but not suppressed. This was seen in patients with SIADH in the literature as well.[2,14,27] In one case report of a patient with hyponatraemia after treatment with valproic acid, AVP levels were low, but the AVP levels of this patient did not respond to water loading when combined with a high dose of valproic acid.[14] Another patient, however, showed an AVP increase to 14.1 pmol/L after treatment with valproic acid, which returned to normal after valproic acid was changed to another antiepileptic drug.[15]

Valproic acid could make hypothalamic osmoreceptors less sensitive, which was also suggested for carbamazepine and oxcarbazepine.[7,28] This could explain the inappropriate but inter-individually fluctuating ADH levels and the lack of response of AVP to water loading during valproic acid treatment, as described in the case reports.

The high AVP level during valproic acid treatment in one patient is more likely caused by a reaction of valproic acid on the renal tubular system, since the tubules do not seem to respond by reabsorbing sodium.[15] In children, valproic acid has shown to alter the renal tubular system, possibly leading to interference with kidney function, causing hypersensitive interstitial nephritis or Fanconi syndrome.[29,30] The effect of valproic acid on the renal tubular system suggests that it may directly affect tubular cell function, thereby causing SIADH. Possibly a combination of effects on the osmoreceptors and a lack of compensation of the salt-water imbalance by the nephrons causes SIADH in some patients using valproic acid.[28]

Hyponatraemia due to valproic acid could be a dose- or concentration-related adverse effect. In two cases, the study of Branten et al.[14] and our case patient D, showed that a dose decrease of valproic acid resulted in less severe hyponatraemia.

Conclusions

This study describes hyponatraemia and SIADH as a possible ADR of valproic acid, based on four patients and support from Vigibase. This association between valproic acid use and hyponatraemia and SIADH has been recognized before. It is not yet described in all summaries of product characteristics worldwide. With this study, not only have the number of published cases doubled, but the data from the Vigibase strongly support the association.

Since hyponatraemia and SIADH have a high morbidity and mortality,[3] health professionals should be aware of this possible ADR associated with valproic acid. Electrolytes should be monitored closely during treatment with valproic acid in patients with risk factors for hyponatraemia or SIADH, such as the elderly.

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