

Valproic acid in association with hyponatremia and SIADH

Introduction

Valproic acid is an antiepileptic drug which has been approved for the treatment of *the primary form of generalized epilepsy* and for the treatment of *the secondary form of generalized epilepsy and partial epilepsy if other antiepileptics do not have a positive effect* [1].

Hyponatremia is a condition in which serum sodium levels are decreased below the normal range (135-145 mmol/l). Several clinical states may lead to hyponatremia: volume depletion, edema, renal disease, inappropriate anti diuretic hormone (ADH) secretion, psychogenic polydipsia or accumulation of osmotically active solutes, as in uncontrolled diabetes mellitus [2]. Numerous drugs can cause hyponatremia by increasing the release of ADH from the posterior pituitary, by enhancing ADH action on the kidney or by acting directly on the kidney [3]. The syndrome of inappropriate ADH secretion (SIADH) results from persistent ADH release. This may result from an ectopic production of ADH, like in small cell lung cancer, by CNS disorders, by hypothyroidy or by medication [3].

Reports

Up to June 28, 2006 the Netherlands Pharmacovigilance Centre Lareb received six reports of hyponatremia and/or SIADH in association with valproic acid.

Table 1. reports of hyponatremia and/or SIADH associated with the use of valproic acid

Patient, Sex, age	Drug Indication for use	Concomitant medication	ADR	Time to onset, outcome, remarks
A F, 67	valproic acid Chrono 500 mg bid post-CVA epilepsy	amlodipine, fucidin cream, metoprolol, olmesartan, ranitidine, salicylic acid, thiamine	hyponatremia (Na 122 mmol/l; serum osmolality 252 mOsm/kg [N 280-295])	14 months, recovered after cessation (Natrium 138 mmol/l)
B F, 71	valproic acid Chrono 300 mg td epilepsy phenobarbital 50 mg od epilepsy	alendronate, atorvastatin, calcium, oxazepam, paracetamol, potassium 'durette', salicylic acid, vitamin B complex,	Hyponatremia (Na 125 mmol/l; serum osmolality 256 mOsm/kg)	months, not recovered at time of reporting
C F, 88	valproic acid Chrono 300 mg od epilepsy	aspirin/dipyridamole, fluticasone, levothyroxine, losartan, phenobarbital, oxazepam, rabeprazole, tiotropium,	SIADH (Natrium 116 mmol/l; serum osmolality 249 mOsm/kg [N 275-300])	2 years, recovering at time of reporting
D F, 57	valproic acid Chrono 1000 mg bid epilepsy lamotrigine 200 mg od epilepsy	atenolol/chlorthalidone, oxybutynine, bisacodyl, potassium 'durette'	SIADH (Natrium 116 mmol/l)	5 months, recovering at time of reporting; severe multiple sclerosis in medical history
E F, 70	valproic acid Chrono 300 mg od pain hydrochlorothiazide 25	amlodipine 5 mg od	hyponatremia	one day, recovered after cessation of suspect drugs

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Patient, Sex, age	Drug Indication for use	Concomitant medication	ADR	Time to onset, outcome, remarks
	mg od not reported			
F	valproic acid 500 mg bid	unspecified	SIADH	6 years, unknown
F, 60	generalized epilepsy		hyponatremia	

In patient A other contributing factors were ruled out: an MRI showed no pathology, except the pre-existing ischemic damage due to the CVA. A CT-scan of the thorax showed no pulmonary abnormalities. Thyroid functions were normal: TSH 1,9 mU/l (N 0.35-5.00) and fT4 14 pmol/l (N 9-27).

In patient B other contributing factors, like diuretic misuse and hypovolemia, were excluded.

In Patient C no malignancies or other contributing factors were identified, thyroid function was normal with an fT4 of 16 pmol/l (N 9-24).

In patient D the diagnosis of SIADH was made after laboratory findings of hyponatremia, low serum osmolality and high sodium level in urine. No values, except the sodium level, were reported.

Other sources of information

Literature

In literature four case reports discuss the association between hyponatremia and/or SIADH and valproic acid [4-7].

One patient is a 50-year-old male with hyponatremia of 128 mEq/l, hypoosmolality of 261 mOsm/kg and an impaired excretion of water, all features of SIADH, following valproic acid with a latency of two years after start. Other contributing factors were ruled out [4].

Another patient is a male aged 62 years with SIADH following valproic acid 660 mg per day with a latency of six years. Laboratory findings showed a decreased serum sodium level of 127 mEq/l and a decreased serum osmolarity of 265 mOsm/l. ADH was elevated to 14.1 pg/ml and an increase in urinary sodium excretion and slight elevation of urinary osmolarity were observed. Serum level of valproic acid was 10.5 µg/ml. He recovered after cessation of valproic acid [5].

In the American SPC of Depacon[®] SIADH and hyponatremia are mentioned as possible ADRs [8].

Databases

On June 28, 2006 the Lareb database contains six reports of hyponatremia and/or SIADH in association with valproic acid. In total the database contains 130 reports of hyponatremia and 27 reports of SIADH. Hyponatremia as well as SIADH in association with valproic acid are disproportionately present in the Lareb database: ROR 4.9 (95%CI 1.8-13) respectively ROR 20 (95%CI 5.9-65).

The database of the Uppsala Monitoring Centre of the WHO contained 19358 reports on valproic acid and associations with hyponatremia and SIADH are disproportionately reported (table 2).

Table 2. reports of hyponatremia and/or SIADH associated with the use of valproic acid in the WHO database

	valproic acid (n)	ROR (95%CI)
hyponatremia	171	2.3 (2.0-2.7)
SIADH	18	3.2 (2.0-5.1)

Mechanism

The mechanism of hyponatremia and SIADH due to valproic acid is not clear. One hypothesis postulates that valproic acid has a direct effect on tubular cell function, because a few cases of tubular dysfunction (Fanconi syndrome) in association with valproic acid with a positive dechallenge have been described [4].

Discussion

In the cases reported to Lareb other factors might play a role. Patient D has a severe multiple sclerosis, which has been associated with SIADH very rarely. Three case reports concerning this association are present in literature [9-11]. Nevertheless, patient D recovered after dose reduction of valproic acid. Patient E was using hydrochlorothiazide for five years and valproic acid for only one day when she developed symptomatic hyponatremia. Although it is possible that hydrochlorothiazide could cause hyponatremia, it is striking that only one day after the addition of valproic acid symptoms occur. No further details were reported.

Conclusion

In the Lareb database 359 reports of valproic acid are present, of which six concern hyponatremia and/or SIADH. The number of reports in the Lareb and the WHO database and the case reports in literature support the association.

References

1. Dutch SPC Depakine® (version date 1999) <http://www.cbg-meb.nl/IB-teksten/06175-07419-08659-08660-08661.pdf>. access date 30-06-2006.
2. Van Amelsvoort TH, Bakshi R, Devaux CB, Schwabe S. Hyponatremia associated with carbamazepine and oxcarbazepine: a review. *Epilepsia* 1994;35(1):181-88.
3. Miller M. Hyponatremia and arginine vasopressin dysregulation: mechanisms, clinical consequences, and management. *J Am Geriatr Soc* 2006;54(2):345-53.
4. Branten AJW, Wetzels JFM, Weber AM, Koene RAP. Hyponatremia duet o sodium valproate. *Ann Neurol* 1998;43(2):265-7.
5. Miyaoka T, Seno H, Itoga M, Kishi T, Ishino H, Horiguchi J. Contribution of sodium valproate to the syndrome of inappropriate secretion of antidiuretic hormone. *Int Clin Psychopharmacol* 2001;16(1):59-61.
6. Ikeda K, Moriyasu H, Yasaka M, Oita J, Yamaguchi T. Valproate related syndrome of inappropriate secretion of antidiuretic hormone (SIADH) -a case report. *Rinsho Shinkeigaku* 1994;34(9):911-3.
7. Corda C, Beuriat P, Sgro C, Giroud M, Escousse A, Dumas R. Hyponatremia under sodium valproate: search a drug interaction. *Therapie* 1991;46(2):169.
8. American SPC Depacon® (version date 01-11-2006) <http://www.fda.gov/cder/foi/label/2006/018081s42,18082s26,18723s32,19680s19,20593s11,21168s9lbl.pdf>. acces date 30-06-2006.
9. Nakasaka Y, Atsumi M, Saigoh K, Yamada A, Hirose N, Ishikawa K. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) associated with relapsing multiple sclerosis. *No To Shinkei* 2005;57(1):51-5.
10. Liamis G, Elisaf M. Syndrome of inappropriate antidiuresis associated with multiple sclerosis. *Neurol Sci* 2000;172(1):38-40.
11. Sakai N, Miyajima H, Shimizu T, Arai K. Syndrome of inappropriate secretion of antidiuretic hormone associated with multiple sclerosis. *Intern Med* 1992;31(4):463-6.