Lack of efficacy of phenytoin in the syndrome of inappropriate anti-diuretic hormone secretion of neurological origin

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Summary: Phenytoin has been proposed in the management of patients with the syndrome of inappropriate secretion of anti-diuretic hormone (SIADH) of neurological origin who fail to respond to water restriction.

We have conducted a prospective study in order to evaluate the role of phenytoin in the management of seven consecutive patients with SIADH of neurological origin which could not be controlled by limited water intake. Only one patient was successfully treated with chronic phenytoin regimen. This patient, like one previously reported, had suffered a basal skull fracture. It seems likely that in the majority of cases of SIADH of neurological origin phenytoin is ineffective on a long-term basis.

Introduction

Various treatments have been proposed^{1–4} in the management of patients with hyponatraemia related to the syndrome of inappropriate secretion of anti-diuretic hormone (SIADH), when water restriction appears ineffective. Demeclocycline,¹ urea³ and frusemide⁴ have been used successfully.

For SIADH of neurological origin, a trial with phenytoin has been suggested.^{2,5} However, although phenytoin acutely decreases ADH secretion,⁶ effective chronic management has been reported in only one case.² The drug can however reverse the carbamazepine-induced water intoxication.^{7,8} We have conducted a prospective study in order to evaluate the role of phenytoin in the management of seven consecutive patients with SIADH of neurological origin which could not be controlled by limited water intake.

Patients and results

Over a 3-year period we studied seven cases of chronic SIADH of neurological origin which could not be controlled by simple water restriction ($\text{Na} < 128 \text{ mmol/l}$ after 5 days). All the patients fulfilled the criteria of SIADH,⁹ namely (1) hyponatraemia (nor-

mal range 135–145 mmol/l) and hypo-osmolality (normal range 270–300 mOsm/kg H_2O) in the presence of inappropriately high urine osmolality; (2) urinary sodium greater than 30 mmol/l and (3) absence of volume depletion, oedema, cardiac and hepatic disease. All patients had normal renal, adrenal and thyroid function, and normal blood glucose levels. None of the patients took a medication known to interfere with water metabolism.

Details of the patients are shown in Table I. They received orally 900 mg of phenytoin on the first day and subsequently 300 mg/day, and continued water restriction ($< 1 \text{ litre/day}$). Blood concentration of phenytoin was measured after one week.

After one week, with phenytoin blood levels within the therapeutic range for seizure control (10–20 $\mu\text{g/ml}$), treatment was stopped when serum sodium concentration failed to reach 135 mmol/l. In the two patients with tuberculosis meningitis, phenytoin was maintained for a few months in order to control seizure. Despite this prolonged administration, no effect of phenytoin on hyponatraemia could be observed.

Only one patient clearly responded to the phenytoin trial (case no. 3). This patient was a 30 year old man with a basal skull fracture in 1979. He was admitted in November 1987 with a serum sodium concentration of 116 mmol/l. A computed tomographic scan of the brain was normal. After 5 days of severe water restriction ($< 500 \text{ ml/day}$), serum sodium concentration increased to 126 mmol/l.

Subsequently, a standard oral water loading test (20 ml/kg body weight) was performed, showing that

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Table 1 Clinical and laboratory observations in seven patients with SIADH treated with phenytoin

Sex-age (years)	Diagnosis	Serum Na ⁺ before water restriction (mmol/l)	Serum Na ⁺ after water restriction (mmol/l)	Before treatment Blood/urine osmolality (mOsm/kg H ₂ O)	Serum Na ⁺ during phenytoin (mmol/l)	During treatment blood osmolality (mOsm/kg H ₂ O)	Blood phenytoin (µg/ml)
1 F-60	Brain haemorrhage	119	124	259/402	122	252	15
2 F-70	Cerebral thrombosis	123	123	254/618	121	248	13
3 M-30	Basal skull fracture	116	120	245/500	136	285	19
4 M-50	Tuberculous meningitis	115	125	256/700	126	258	14
5 M-49	Tuberculous meningitis	119	124	255/500	125	260	16
6 F-70	Cortical atrophy	120	125	260/540	123	255	17
7 F-75	Cortical atrophy	122	127	258/400	123	255	13

the patient could excrete only 30% of the water load within a 5-hour collection period (normal response: >80% of the water load excreted in 4 hours). The minimal urine osmolality achieved during this period was 500 mOsm/kg H₂O (normal <100 mOsm/kg H₂O). A second water loading test was performed after phenytoin administration (blood level 16 µg/ml) with a serum sodium concentration of 136 mmol/l. The patient this time excreted 50% of the water load in 5 hours with a minimal urine osmolality of 189 mOsm/kg H₂O at the fifth hour. During the follow-up, the serum sodium level remained within the normal range, with 24-hour urine output being as high as 2800 ml. At each attempt to decrease phenytoin dosage (200 mg/day, blood level <10 µg/ml), serum sodium decreased after a few days (<130 mmol/l) and returned to normal range when a full dose was readministered. The patient is still successfully treated on a long-term basis with more than 10 months of normal serum sodium levels despite free water access.

Discussion

It has been demonstrated that phenytoin, when acutely administered, (intravenously or intramuscularly) can suppress ADH release by the post-hypophysis.⁶ Fichman *et al.* describe the capacity of phenytoin given intravenously to increase the free water clearance and to lower the minimal urine osmolality in patients with SIADH of neurological origin.⁶ However, they conclude that phenytoin is

probably not effective for long-term management of this syndrome, as the effect of ADH suppression occurs mainly during the rising phase of blood phenytoin concentration. It has to be noted that one previously published case with a SIADH related to a basal skull fracture, was also successfully treated chronically with phenytoin.²

The results of our study show that phenytoin was effective in chronically inhibiting the secretion of ADH in only one of the seven patients studied, although even here complete inhibition could not be achieved as reflected by a subnormal excretion of oral water load. The others were treated either by urea or frusemide.^{3,4}

These data suggest that phenytoin is ineffective in the chronic control of SIADH of neurological origin in a majority of cases. We can but speculate why phenytoin had an action only in the patient with a SIADH following basal skull fracture. It has been reported that SIADH with this condition results from a constant, non-suppressible release or 'leak' of vasopressin under hypotonic conditions despite otherwise normal osmoreceptor function (the so called SIADH of type C¹⁰). Such non-suppressible central secretion of vasopressin may be due to hyperfunction of stimulatory neurones, hypofunction of proposed inhibitory neurones or injury to the neurohypophysis itself.¹¹ As phenytoin is known to inhibit the calcium influx,¹² which plays a key role in the neurosecretion mechanism of ADH,¹³ it is possible that in this type of SIADH phenytoin could significantly inhibit ADH release.

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