Unexpected outcome (positive or negative) including adverse drug reactions

Syndrome of inappropriate antidiuresis in doxylamine overdose

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Summary

Doxylamine succinate, an H₁-antihistamine drug, is commonly used as sleep-inducing agent as well as therapy for nausea and vomiting in pregnancy. At usual doses, it may cause impairment of cognitive and psychomotor performance, anticholinergic effects, agitation and postural hypotension. Besides, since this drug is frequently involved in either accidental or intentional overdoses, it seems relevant to bear in mind other possible toxic effects. We report a case of acute severe hyponatremia in the setting of a syndrome of inappropriate antidiuresis (SIAD), an apparent new adverse effect linked to doxylamine overdose. The Naranjo adverse drug reaction probability scale indicated a probable relationship between doxylamine intake and SIAD development. SIAD may be considered as a potential, serious adverse reaction of doxylamine overdose. Clinicians should consider this aetiological possibility when attending patients suffering from hyponatremia.

BACKGROUND

Doxylamine succinate, an oral first-generation H₁-antihistamine drug,^{1 2} is commonly used as sleep-inducing agent² as well as therapy for nausea and vomiting in pregnancy.³ At usual doses, it may cause impairment of cognitive and psychomotor performance, anticholinergic effects, agitation and postural hypotension.¹ Since this drug is frequently involved in accidental or intentional overdoses, it seems relevant to bear in mind its possible toxic effects after overdose such as delirium, hallucinations, seizures, rhabdomyolysis and other.^{1 4 5} In this regard, we report the first case, to our knowledge, of a syndrome of inappropriate antidiuresis (SIAD) apparently induced by doxylamine overdose.

CASE PRESENTATION

A 69-year-old white woman was carried to our emergency department (ED) because of 1-day history of worsening drowsiness and confusion. Her medical history was relevant for chronic insomnia and bilateral hip osteoarthritis. The patient had been receiving aceclofenac (100 mg once daily), ranitidine (150 mg once daily), folic acid (10 mg once daily) and zolpidem (5 mg at night) for the last 4 years. Two months before admission, her serum sodium concentration was within normal limits on an ordinary laboratory check-up. Forty-eight hours before entry, the patient took 16 tablets of 25 mg of doxylamine on a non-coformulated presentation due to recently increased insomnia (the therapeutic recommended dose of doxylamine as sleep-inducing agent is 25 mg once daily). This time was the only one she received doxylamine. Some 8 h after swallowing this drug, she started showing 'slowness when speaking and walking'. Over the last 24 h before admission, the patient developed progressive somnolence and finally, she was brought to the ED since she appeared 'very weakly reactive'. There was no evidence of seizures

(her husband denied to have seen abnormal movements and there was no sialorrhea, micturition, visible faeces or cutaneous or tongue haematomas). Upon arrival in the ED, blood pressure was 133/76 mm Hg, heart rate 90 beats/min, temperature 37.1°C and respiratory rate 12 breaths/min. The patient showed marked drowsiness and had an initial Glasgow Coma Scale score of 10 (she opened her eyes to pain, emitted inappropriate words and localised pain). There was mild bilateral reactive mydriasis. Skin colour and turgor as well as oropharyngeal mucosa looked normal. Physical examination was otherwise unremarkable. Her husband referred she had taken neither extra-doses of the other four medications nor additional new drugs. In fact, he showed us four nearly full drug bottles, each one corresponding to each concomitant medication and one empty bottle of doxylamine that he had recovered from their bedroom.

INVESTIGATIONS

The results of initial laboratory tests included a serum sodium concentration of 110 mmol/l, a serum effective osmolality of 226 mOsm/kg of water, urinary sodium concentration of 206 mmol/l and urinary osmolality higher than 400 mOsm/kg of water. Plasma uric acid level was of 1.2 mg/dl and serum level of aspartate aminotransferase, alanine aminotransferase and lactic dehydrogenase was of 50, 55 and 500 U/l, respectively. The serum concentration of creatine kinase was 4386 U/l (normal, ≤185). Serology for HIV infection was negative. We also screened the patient's urine for drugs using the TOX/See Drug Screen Test (Bio-Rad Laboratories Inc, Hercules, California, USA). It is a lateral flow chromatographic immunoassay for the qualitative detection of the following drugs: amphetamine, barbiturates, benzodiazepines, cocaine, marijuana, methadone, methamphetamine, methylenedioxymethamphetamine, opiate, tricyclic antidepressants. The test was negative for all these drugs. The serum level of doxylamine

was not measured. Laboratory results were otherwise unremarkable and thyroid and adrenal function were normal. There were no electrocardiographic abnormalities. A CT scan of the head revealed only mild generalised atrophy. Finally, CT scan of the thorax and abdomen displayed normal findings.

TREATMENT

Concomitant medications were discontinued and saline infusion as well as restriction of fluid intake were prescribed. The correction of hyponatremia was begun with 0.9% saline infusion at ≈ 1 ml/kg/h and furosemide, 20 mg intravenously. Her serum sodium level rose to 114.5, 118.2 and 125 mmol/l in the first 12, 24 and 48 h, respectively. On hospital day 5, the serum sodium level was 135.2 mmol/l and her serum level of creatine kinase had decreased to 400 U/l.

OUTCOME AND FOLLOW-UP

The patient was discharged asymptomatic on hospital day 8. At a follow-up 2, 6 and 8 months after discharge, she remained well and her serum level of sodium, liver enzymes and creatine kinase was normal.

DISCUSSION

We think the crux of the matter in this report includes the development of a SIAD in a patient who had received a doxylamine overdose and the need of establishing a suitable causality link between doxylamine and SIAD. The term SIAD is used instead of SIADH (syndrome of inappropriate secretion of antidiuretic hormone) because not all patients with the disorder show increased circulating levels of arginine vasopressin, the antidiuretic hormone. In fact, SIAD has been proposed as a more accurate description of this condition.^{6 7} The case described herein strictly fulfils all essential features needed to make a diagnosis of SIAD, that is, hyponatremia, effective plasmatic osmolality <275 mOsm/kg of water, urinary osmolality >100 mOsm/kg of water, urinary sodium >40 mmol/l, clinical euolemia, normal thyroid and adrenal function and no recent use of diuretic agents.^{6 7}

Potential causes of SIAD other than drugs were convincingly ruled out in our patient (ie, pulmonary disorders, malignant diseases, HIV infection, disorders of the central nervous system and others^{6 7}). Concerning medications, several facts seem to militate against other concomitant drugs than doxylamine to explain the development of SIAD. First, the patient had been receiving the four associated medications until admission without untoward effects and her serum sodium level had been within normal limits prior to hospital admission. Second, there was a close temporal relationship between the intake of doxylamine and both onset of symptoms and appearance of hyponatremia. Third, there are no reports on SIAD or SIADH induced by any of the concomitant medications that our patient had been taken. Indeed, there have been reported cases on SIAD induced by some non-steroidal anti-inflammatory drugs (NSAIDs),⁸ but in none of them aceclofenac appears as causative agent. NSAIDs may produce water retention by potentiating the action of the antidiuretic hormone though it has been suggested that this is not a class effect.⁸ Fourth, there are no recognised interactions between doxylamine and aceclofenac,

Figure 1 Potential mechanisms for doxylamine-induced rhabdomyolysis. SIAD, syndrome of inappropriate antidiuresis.

ranitidine or folic acid.⁹ With regard to zolpidem, there is only a caution that concurrent use with other central nervous system depressants may result in enhanced central nervous system depression but nothing is stated about a hypothetical influence over sodium homeostasis.⁹ Finally, the patient went on receiving aceclofenac, folic acid, ranitidine and zolpidem at the same doses after discharge with good tolerance. The Naranjo adverse drug reaction probability scale¹⁰ also indicated a probable relationship between doxylamine overdose and the appearance of SIAD (see online supplementary material). Drug-associated SIAD can be induced by: (1) increasing the hypothalamic, eutopic production of arginine vasopressin (eg, antipsychotics, antidepressants, bromocriptine and some chemotherapeutics), (2) enhancing the antidiuretic hormone action on the renal collecting ducts (eg, chlorpropamide and carbamazepine) or (3) exogenous administration of the antidiuretic hormone or its analogues.^{6 7} We hypothesise that doxylamine-induced hyponatremia could be attributable to a SIAD originated through eutopic, nonosmotic release of antidiuretic hormone such as it has been described for antipsychotics and selective serotonin-reuptake inhibitors.¹¹ In this regard, it would be a serious adverse effect not related to the pharmacological action of the drug—so infrequent and unpredictable.

Moreover, and particular to our case, is the coexistence of hyponatremia and rhabdomyolysis. Since hyponatremia is a known cause of muscle breakdown,⁵ it is possible that direct toxic effect of doxylamine on striated muscle⁴ and drug-related hyponatremia could act jointly to produce muscular injury (figure 1).

We suggest that SIAD may be an adverse reaction probably related to doxylamine toxicity. Thus when dealing with patients suffering from hyponatremia, clinicians should keep in mind this additional aetiological possibility. Clearly, studies are needed to explore the apparent association between doxylamine overdose and hyponatremia.

Learning points

- Severe hyponatremia in the setting of a syndrome of inappropriate antidiuresis (SIAD) is a probable new adverse effect of doxylamine overdose.
- We hypothesise that doxylamine-related SIAD may be induced by non-osmotic, hypothalamic release of antidiuretic hormone.
- Clinicians should not discard doxylamine overdose when attending patients suffering from acute hyponatremia if no other causes are evident.

Competing interests None.

Patient consent Obtained.

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