It should be noted, however, that the best diagnostic test in each case is difficult to establish because of the heterogeneity and low prevalence of pheochromocytoma and paraganglioma, and will depend on the individual patient characteristics in terms of the secretory profile, suspected location, the histological characteristics of cell differentiation, biological behavior, and potential association with a genetic mutation.[6,11]

An adaptation to advances in imaging procedures is required, which includes the possibility that in hospitals where ^{18}F-DOPA-PET is available, it may replace ^{123}I-MIBG, at least partly, because of its greater precision, convenient performance, and less adverse effects for patients, although cost-effectiveness studies assessing its use will be required.

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Acute severe hyponatremia induced by aceclofen in a male patient with central diabetes insipidus

Hiponatremia aguda grave inducida por aceclofeno en un paciente varón con diabetes insípida central

Introduction

The side effects of desmopressin are headache, lethargy, obtundation and seizures all of which are due to severe and rapid hyponatremia caused by water intoxication. These symptoms have been described in patients treated with this drug for central diabetes insipidus, primary nocturnal enuresis and nocturnal polyuria.

Non-steroidal anti-inflammatory drugs (NSAIDs) in combination with desmopressin can induce symptomatic hyponatremia, though this effect is very rare and has seldom been described in the literature.

In this report, we describe the case of a 46-year-old man with central diabetes insipidus undergoing long-term treatment with a constant dose of desmopressin who developed acute severe symptomatic hyponatremia when desmopressin was combined with aceclofen.

Case report

A 46-year-old man was admitted to the Emergency Department of the Dr. Peset University Hospital (Valencia, Spain) with lethargy, obtundation and loss of consciousness. He had been diagnosed with central diabetes insipidus at the age of 28 and was being treated with desmopressin at a dose that he denied having altered. Three days prior to admission the patient had experienced dizziness, headache, nausea and vomiting.

A physical examination revealed normal blood pressure (130/80 mmHg), pulse rate of 90 bpm and body temperature of 36.9 °C. A neurological examination gave a Glasgow coma score of 14 (E4 V4 M6) and otherwise normal results.

On admission, the most relevant laboratory parameters were as follows: sodium (Na) 113 mequiv./L (reference value 135–145 mequiv./L); potassium (K) 4.3 mequiv./L (reference value 3.5–5 mequiv./L); creatine phosphokinase (CPK) 3576 UI/L (reference value 30–200 UI/L); creati-

nine 0.68 mg/dl (reference value 0.7–1.20 mg//dl); urea 31 mg/dl (reference value 19–50 mg/dl); and normal blood count. Urine analysis showed Na 200 mequiv./L (reference value 40–220 mequiv./L) and K 101 mequiv./L (reference value 25–125 mequiv./L).

A brain CT scan revealed no signs of intracranial bleeding or other abnormalities.

Further information indicated that the patient had not altered the prescribed dose of desmopressin (10 μg per day of intranasal solution administered divided in two doses) and had not experienced any previous complications. Additionally, several previous blood chemistry controls revealed that his plasma sodium concentration was within a normal range (the last, performed 45 days before hospital admission, showed a result of 139 mequiv./L). At the time of admission, the patient had also been taking 200 mg of aceclofen per day for one week as a pain killer for lumbar pain caused by weight lifting.

Desmopressin treatment was discontinued and the patient was treated with hypertonic saline infusion. The symptoms disappeared within 24 h. Serum sodium concentration increased to 123 mequiv./L 24 h later and to 136 mequiv./L on the second day after admission. On the third day desmopressin treatment was reinstated at the usual dosage and normonatremia persisted (discharge sodium concentration 139 mequiv./L). One month later, the patient's blood sodium concentration continued within the normal range (141 mequiv./L).

Discussion

Headache, dizziness, nausea, vomiting and uneasiness are mild, non-specific initial symptoms of hyponatraemia. Severe symptoms do not usually appear until blood sodium levels fall below 125 mequiv./L or drop abruptly. In such conditions, patients can experience loss of consciousness, seizures, obtundation and progressive lethargy.

Desmopressin is a structural analog of vasopressin (antidiuretic hormone) that increases water reabsorption via vasopressin V2 receptors in the renal tubules, thereby increasing urine osmolality and decreasing urine volume. This results in an increase of intravascular volume and a decrease in plasma osmolality, effects that last between 6 and 24 h.

This drug is more potent and much longer-acting than human vasopressin, and has several indications (central diabetes insipidus, nocturnal enuresis, haemophilia A and mild-to-moderate von Willebrand disease). Water intoxication with severe hyponatraemia is a potential risk of intravenous or intranasal administration of desmopressin. This adverse effect often occurs on initiation of therapy, until the appropriate daily dosage is determined.

Renal prostaglandins are important regulators of urinary dilution, as they partially antagonize the antidiuretic effects of vasopressin in the collecting tubules and impair sodium reabsorption in the loop of Henle and cortical collecting tubule.[1] By inhibiting glomerular cyclooxygenase, NSAIDS diminish renal synthesis of prostaglandins, thus increasing urinary concentrating ability. In patients with diabetes insipidus, the net effect can be a 25–50 per cent reduction in urine output, leading to water retention and consequent hyponatremia.[2,3] However, despite the well-known renal effect of these drugs and their frequent use, hyponatraemia as a result of water intoxication has seldom been described.[1,4,5]

To our knowledge only one other case of severe symptomatic hyponatremia as a result of the combination of non-steroidal anti-inflammatory drugs and desmopressin has been reported to date.[6]

The fact that our patient had been taking the same dosage of intranasal desmopressin for 18 years without developing clinical symptoms of hyponatraemia pointed to an additive effect of co-administration with aceclofen. It is well known that non-steroidal anti-inflammatory drugs constitute a widely used pharmacologic group, and are consumed with medical prescription and also through self-medication. In fact, in recent years, NSAID consumption has increased considerably. For instance, in 2008 ibuprofen was the third most prescribed drug in the Spanish Public Health System, while nearly 30 million persons worldwide are currently using non-steroidal anti-inflammatory drugs on a daily basis.[7]

The use of these agents is not free of risks: the most frequent adverse reactions are gastrointestinal (perforation, ulcer, bleeding), but there are many other potential complications and pharmacologic interactions that must be considered, especially in patients with comorbidities in whom NSAIDs may cause acute decompensation, thus leading to hospital admission, increasing mortality and morbidity rates and putting extra pressure on the resources of health systems.[8]

Hyponatremia can be induced by any NSAID, although it is proposed that with a low dose of aspirin (about 40 mg per day) the inhibition of glomerular cyclooxygenase is partial and transient, avoiding a significant reduction in glomerular prostaglandins.[8] Sulindac, another non-selective non-steroidal anti-inflammatory agent, appears to be safer than other NSAIDs, since some studies suggest that it spares prostaglandins by inhibiting cyclooxygenase to a lesser degree.[9] However, careful monitoring is recommended in all cases.

To conclude, although non-steroidal anti-inflammatory drugs are not contraindicated in central diabetes insipidus patients treated with desmopressin a priori, doctors should be aware of the potential risks in prescribing them and take the necessary precautions.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Dissociated cholestasis: An uncommon complication of thioamide therapy☆

Colestasis disociada: una complicación infrecuente del tratamiento con tionamidas

Introduction

Hyperthyroidism is caused by inadequate thyroid hormone synthesis and/or secretion due to different causes. The prevalence of hyperthyroidism is approximately 1%. The most common cause of thyrotoxicosis is primary autoimmune hyperthyroidism (Graves' disease), in which stimulation by anti-TSH receptor antibodies (TRAb) causes an increased production of thyroid hormones. In Europe, thioamides are the treatment of choice for Graves' disease, while radioiodine therapy and surgery are considered as second line treatments. Methimazole, like carbimazole and propylthiouracyl, is a member of the thioamide class, and is one of the main drugs used to treat hyperthyroidism.[1]

As with any other drug, adverse effects of different severity have been reported for antithyroid drugs. The most common and mildest adverse effects include skin reactions (4–6%), joint pain (1–5%), and gastrointestinal changes (1–5%). The most commonly reported serious adverse effects include agranulocytosis (0.1–0.5%) and hepatotoxicity (0.1–0.2%). The abovementioned mild changes are assumed to be dose-dependent with methimazole and carbimazole, while the hepatotoxicity of these two drugs, unlike as occurs with propylthiouracyl, is idiosyncratic.[2–5]

The prevalence of acute hepatitis induced by antithyroid drugs ranges from 0.1% to 1%, and most cases reported in the literature were due to propylthiouracyl. Data from 2003 reported a total of 83 cases of acute hepatitis induced by propylthiouracyl, although it has been suggested that the condition may occur in up to 1.2% of patients treated with propylthiouracyl.[3,7]

To date, less than 40 cases of acute hepatitis secondary to methimazole or carbimazole have been reported in the literature.[6] Acute cholestatic hepatitis[4–6] was reported in most cases, but there was a case each with a predominant cytolysis pattern,[8] granulomatous hepatitis,[9] and hepatic steatosis.[10]

Case report

We report the case of a 68-year-old male, a former smoker with no alcohol consumption and a history of high blood pressure, dyslipidemia, ischemic heart disease, and secondary dilated cardiomyopathy. The patient had had a pacemaker implanted in 2008 for a bradycardia-tachycardia syndrome. Since then, he had experienced multiple episodes of atrial flutter and fibrillation (AF), which led to treatment being started with amiodarone 200 mg/day three years before the start of the condition. His usual treatment included: bisoprolol 5 mg, olmesartan 20 mg, fluvastatin 80 mg, ezetimibe 10 mg, acetyl salicylic acid 100 mg, nitroglycerin patches 5 mg, acenocoumarol 1 mg, omeprazole 20 mg, and escitalopram 15 mg.

During a hospital admission in May 2011 for a new atrial fibrillation episode, the endocrinology department was consulted because of findings consistent with primary hyperthyroidism: FT4 4.21 ng/dL (0.89–1.76), FT3 6.59 pg/mL (2.3–4.2), TSH 0.009 mcU/ml (0.55–4.78). When questioned, the patient did not report other symptoms suggesting thyroid hyperfunction. Palpation of the anterior neck region was unremarkable, as was the rest of the physical examination. Autoimmune thyroid tests showed anti-TPO antibody levels of 60.6 U/mL (0–60), anti-thyroglobulin levels of 213 U/mL (0–60), and negative anti-TSI antibodies. A thyroid ultrasound showed no significant changes. Type 2 versus mixed hyperthyroidism secondary to amiodarone was suspected, and treatment was therefore started with prednisone 20 mg daily and methimazole 10 mg every 8 h. The dose of both drugs was doubled due to lack of response (FT4 5.23 ng/dL, FT3 6.15 pg/mL, TSH 0.015 mcU/mL) and a new AF episode with rapid average ventricular response two months later. One month later, laboratory tests provided the following results: total bilirubin 0.4 mg/dL (normal 0.2–1.4), GOT/AST 73 U/L (normal 17–59), GPT/ALT 200 U/L (21–72), GGT 1163 U/L (11–73), alkaline phosphatase 367 U/L (38–126), LDH 598 U/L (313–618). These results were consistent with a pattern of dissociated cholestasis which was not present in the tests performed in May 2011 (total bilirubin 0.5 mg/dL,

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