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Severe multifactorial hyponatremia in a lung transplantated patient: case report

Hiponatremia severa multifactorial en un paciente de transplante de pulmón: reporte de caso

Ángel Blanco, Alfonso Moreno, Elba Parodi, Cristina del Pozo, Javier García

Department of Anesthesiology, Critical Care and Pain at Hospital Puerta de Hierro Majadahonda, Madrid, España.

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Abstract

Hyponatremia is a common electrolyte disorder in clinical practice. It is sometimes difficult to identify the causes. We present a case about severe multifactorial hyponatremia in a patient with a history of lung transplantation on regular tacrolimus who complained of back pain being treated with tramadol. Possible causes are analyzed and discussed.

Resumen

La hiponatremia es una alteración habitual en la práctica clínica. En algunas ocasiones es difícil identificar la causa. Presentamos el caso de una hyponatremia multifactorial en un paciente con historia de trasplante pulmonar en tratamiento con tacrolimus que inició tratamiento con tramadol debido a una lumbalgia.

Se analizan y discuten las posibles causas.

Introduction

Hyponatremia is the most frequent electrolyte disorder. The exact incidence is unknown. Mortality rate is increased in admitted patients suffering this condition.[1]

There are many causes that lead to sodium abnormalities either fluid retention or solute increase.

Hyponatremia is classified according to hyper, hypo, or euvolemic state of the patient. Syndrome of inadequate secretion of anti-diuretic hormone (SIADH) is included in the euvolemic group and drugs are one of most frequent causes of this syndrome.[2] Sometimes, the probability of occurrence of SIADH does not depend on drug doses and might be increased by a pre-disposing patient baseline situation.

Case report

We report a case of a 54-year-old male who had undergone bilateral lung transplant 4 years ago due to chronic obstructive pulmonary disease (COPD) with a history of femoral artery embolism (treated with endarderectomy and anti-clotting agents). He was on acenocumarol, micofenolate, tacrolimus, prednisone, and omeprazole as usual medication. He consulted his family doctor for mechanic non-radiating lumbar pain without any other

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Correspondence: Departamento de Anestesiología, Cuidados Críticos y Dolor del Hospital Puerta de Hierro Majadahonda, C/Manuel de Falla 1, Majadahonda, Madrid, España. E-mail: angelblanco30@gmail.com

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symptoms. Neurological compromise was ruled out and he started taking tramadol 50 mg 6 times a day and paracetamol 1 g 4 times a day. No improvement was noticed and he went back to his doctor after 11 days. A blood test was performed, the result of which showed serum sodium 128 mmol/L. He did not have edema or other features of increased extravascular volume. Tramadol-induced hyponatremia was suspected, so it was stopped, and oxicodone/naloxone and tetrazepam were started. The patient showed no clinical improvement after 5 days of treatment. Another blood test performed revealed serum sodium of 117 mmol/L; hence, the patient was referred to Accident and Emergency Department and admitted to General Medicine ward.

After being admitted, the blood test showed serum Na^+ 113 mmol/L, serum osmolality 244 mmol/L, K^+ 3.8 mmol/L, urine Na^+ 57 mmol/L, urine osmolality >498 mmol/L. Differential diagnosis included hypothyroidism and suprarenal insufficiency and both of them were ruled out as thyroid hormone and cortisol levels were within normal range.

SIADH due to tramadol was the most likely diagnose, so water restriction and hypertonic fluids were given with a good response.

The patient continued feeling a severe back pain, so computed tomography (CT) and magnetic resonance imaging (MRI) spine were performed. They did not show abnormalities that justified sodium misbalance, but a left foraminal disc herniation was seen.

Pain was difficult to manage and endocrinologist involved the Pain team.

Increasing doses of intravenous (IV) oxycodone and gabapentin were needed to control pain. When pain relief was achieved, oral conversion of IV oxycodone was given with good response. Finally, patient was discharged after 26 days with corrected Na^+ and no clinical symptoms.

Discussion

SIADH is defined by some diagnostic features:

- Decreased effective serum osmolality (<275 mOsm/kg).
- Urinary osmolality >100 mOsm/kg with serum hypotonicity.
- Clinical euvolemia (no edema, orthostatic hypotension, or heart failure).
- Urinary sodium >40 mmol/L with normal dietary salt intake.
- Normal thyroid and adrenal function.
- No recent use of diuretics.

Many medications such as opiates, anti-depressants, anti-psychotic, or anti-epileptic drugs have been reported to cause SIADH. This effect is most common in certain predisposed patients, either because they usually take other medications that may produce it or because they are suffering from other conditions such as pain or surgery that might enhance it.[3]

Naranjo Scale was applied to this event, and it was classified as probable drug reaction, scoring 5 points.[4]

We found several factors in our patient that could have caused this situation.

First of all, pain produces an increase in stress hormones such as anti-diuretic hormone (ADH), hence a decrease in natremia due to water retention.

High levels of ADH have been reported in postoperative patients in relation to stimulation of pain afferents.[5,6]

In case of tacrolimus, also known as FK-506, it is an immunosuppressive anti-calcineurinic drug. Its mechanism of action is to reduce the peptidil-prolil isomerase activity joining an inmunophilin (FK506 junction protein), and thus limiting the transmission of signals from the lymphocytes and transcription of IL-2.[7] It is metabolized in the liver through cytochrome CYP3A4, although there is also evidence of gastrointestinal metabolism through CYP3A4 from the intestinal wall.

Tacrolimus-induced hyponatremia is frequent. It is produced because of an upregulation of the $Na^+/K^+/2Cl^-$ transporter in the distal tubule of the nephron, and it is supposed to be related to hyperkalemia or a salt wasting nephropathy.[8] Tacrolimus-induced hyponatremia due to SIADH is much less frequent, and there are only a few cases reported.[9,10] The mechanism of production is unknown, although it might be independent of the dosage and plasma levels. One theory refers to a pituitary–hypothalamic damage which produces an increase in ADH levels, and, therefore, a decrease in water excretion.[11]

An important factor in our patient was the addition of tramadol. It acted as a trigger, decreasing the sodium levels below the normal range.

Tramadol is a synthetic opioid belonging to the aminocyclohexanol group. It is metabolized in the liver through CYP3A4 and CYP2D6 enzymes where it undergoes *O*-desmethylation and *N*-desmethylation as well as conjugation of *O*-desmethylated glucuronide derivatives. It has dual actions as an analgesic.

It is a weak non-selective pure agonist of μ, δ, and κ receptors, although it is more selective for μ receptor. It directly increases ADH production in the hypothalamus through the same mechanism as the rest of the opioids.

On the other hand, it inhibits neuronal reuptake of norepinephrine and serotonin in the synaptic cleft, increasing serotonin levels. The same mechanism is shared by serotonin reuptake inhibitors, which are one of the most common drug-related causes of SIADH. This appears to be due to the stimulation of α-adrenergic receptors.[12]

Consequently, it is very important to be aware that we could induce a serotonergic syndrome when we give tramadol to a patient who is taking other drugs with the same effect as serotonin reuptake inhibitors, monoamine oxidase inhibitors, amphetamines, or tricyclic antidepressants.

There are a few cases of severe SIADH reported in patients taking tramadol. In some of them, there were no

other pre-disposing factors. In those cases, the dosages of tramadol were high either by prescription or overdose. This means that tramadol dosage might be relevant in anti-diuretic effect.[13–15]

We got in contact with World Health Organization (WHO) Collaborating centre for international drug monitoring in Sweden, but no assessment of tramadol and hyponatremia has been done.

They could not find any information about hyponatremia in the United Kingdom Supplementary Protection Certificate (UK SPC) or in the Food and Drug Administration (FDA) product label for tramadol.

A national pharmacovigilance follow-up of tramadol was done by the French Drug Agency in 2010–2011, and they identified that several "unlabeled" serious adverse drug reactions, and some of them, like hyponatremia or hypoglycemia, are poorly known by health professionals.[16]

Conclusion

It is important to take into account that the production of ADH could be increased due to a number of different factors. Therefore, it is recommended to evaluate other aspects that can contribute to cause SIADH, like taking other medications or stressful situations.

Transplanted patients usually take immunosuppressant drugs such as tacrolimus or cyclosporine that can increase the risk of SIADH.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics commit-tee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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Conflict of interest

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