Hyponatremia and Confusion Caused by Pregabalin

Arnon Blum MD, Claudia Simsolo MD and Imad Tatour MD

Department of Internal Medicine, Padeh Poria Medical Center, Lower Galilee, and Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

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Pregabalin is a relatively new drug for the treatment of neuropathic pain in adults. The most common adverse events include dizziness and somnolence followed by peripheral edema and weight gain. We present a 74 year old man who was admitted with drowsiness and disorientation and severe hyponatremia (110 mmol/L). He was treated with pregabalin for a month to alleviate neuropathic pain after undergoing below-knee amputation of the left leg.

PATIENT DESCRIPTION

A 74 year old man was admitted with weakness and confusion. He had suffered from diabetes mellitus type II (insulin dependent) for many years, accompanied by diabetic retinopathy, nephropathy and neuropathy. He had ischemic cardiomyopathy with congestive heart failure (left ventricular function of 27%). A DDDR pacemaker was transplanted in 2002 due to a complete atrioventricular block. For several years he had been taking dimeticone, angiotensin-converting enzyme inhibitors and loop diuretics, but without aldospirone. He was referred for a below-knee amputation because of chronic osteomyelitis. Before the amputation (and later on before admission to the rehabilitation center) his electrolytes were within normal limits.

After the amputation he was given pregabalin for neuropathic pain and continued to take it for several weeks after discharge from the rehabilitation center. One week before the present admission he started to feel weakness and became confused and disoriented.

The physical examination was normal with no signs of peripheral edema or pulmonary congestion. Hematological analysis demonstrated hemoglobin 10.1 g/dL, white blood cell count 8300/µl, and platelet count 245,000/µl. Biochemical analysis demonstrated sodium 110 mmol/L, potassium 4.40 mmol/L and osmolality 232 mOsm/kg (normal values 265–275 mOsm/kg). Liver function tests and renal function tests were normal, and lipid profile was normal. Thyroid function tests were normal – with free thyroxine 1.79 IU/ml and thyroid-stimulating hormone 2.970 IU/ml. Cortisol level (fasting 8 am) was 34.30 µg/dl. Urine level of sodium was 145 mmol/L, potassium level 29.40 mmol/L, and urine osmolality 650 mOsm/kg. Chest X-ray showed very mild pulmonary congestion with minimal left pleural effusion.

After the pregabalin was stopped, followed by fluid restriction and isotonic saline 0.9% for 2 days the sodium level increased to 125 mmol/L and the confusion was resolved. After another 2 days the patient’s sodium level increased to 130 mmol/L.

COMMENT

Our patient developed severe clinical confusion secondary to hyponatremia caused most probably by pregabalin. This is the first report of such an adverse reaction to this medication. Several articles reported decompensation of patients with chronic heart failure, edema and weight gain – all caused by pregabalin. The decompensated heart failure was resolved after discontinuation of the drug [1].

Pregabalin is an analog of the neurotransmitter gamma-aminobutyric acid that has analgesic, anticonvulsant and anxiolytic properties. It is now widely used in the management of diabetic peripheral neuropathy, post-herpetic neuralgia, generalized anxiety disorder and social anxiety disorder [1]. Although central nervous system disturbances account for most of the side effects (dizziness and somnolence) [2], there have been reports of dose-dependent peripheral edema and weight gain, at least in six patients with heart failure whose condition deteriorated after taking pregabalin. In all of them the heart failure was stabilized after discontinuation of the drug [1-3].

To determine whether an adverse drug reaction was due to pregabalin we used the Naranjo algorithm and found that the confusion and worsening of the heart failure with hyponatremia were most likely related to the drug’s side effects [4]. According to the laboratory analysis, our patient had low sodium osmolality with decreased extracellular fluid volume and high urine sodium concentration. It seems that pregabalin caused sodium-wasting nephropathy.

To the best of our knowledge this is the first report of a patient with ischemic cardiomyopathy and poor left ventricular function with clinical heart failure and who developed severe hyponatremia that was clinically expressed by confusion and disorientation. All his symptoms were resolved after the drug was discontinued and he regained a
sodium level > 125 mmol/L. We assume that the mechanism of hyponatremia was pregabalin-induced sodium wasting nephropathy that was resolved after discontinuation of the medication.

Correspondence:
Dr. A. Blum
Dept. of Medicine, Padeh Poria Medical Center, Lower Galilee 15208, Israel

tel/fax: (972-4) 665-2687
e-mail: ablum@poria.health.gov.il

References

Capsule

Peptide-MHC specificity is acquired during positive selection in the thymus

T cells are carefully calibrated in the thymus to react to invading pathogens and to ignore the self. This occurs through interactions between the T cell receptor and major histocompatibility complexes (MHCs) expressing self-peptides. A Goldilocks-like selection process is carried out whereby T cells that do not react or react too strongly to self-peptide MHCs are deleted, whereas those with interactions that are "just right" are allowed to survive. The result is T cells highly specific for a particular foreign peptide-MHC complex. Receipt of survival signals from "just-right" interactions (positive selection) and deletion of cells that are too reactive (negative selection) are spatially and temporally segregated in the thymus, and it is unclear at which stage T cells acquire their high degree of peptide-MHC specificity. By using mice expressing a single peptide-MHC complex, Wang and co-researchers now show that this single complex is sufficient for selection of a CD8+ T cell repertoire with a broad range of specificity. Importantly, recognition of peptide MHC by these cells was highly specific, demonstrating that peptide-MHC specificity is acquired during positive selection in the thymus.

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Capsule

Polymerase III is required for proper immunity both to bacterial and to viral infection

One way the immune system recognizes infection is by sensing the presence of foreign nucleic acids in the cytoplasm. Although it had been established that microbial double-stranded DNA (dsDNA) triggered the production of the inflammatory cytokine interferon-β, the identity of the dsDNA sensor remained elusive. Chiu et al. (Cell 2009; 138: 576) and Ablasser et al. (Nat Immunol 2009; 10: 1065) suggest that RNA polymerase III (Pol III) is the culprit. Pol III, which transcribes genes encoding several kinds of RNA (such as transfer and ribosomal), has been shown to be present in the cytoplasm, but what it did there was unclear. These authors show that cytoplasmic Pol III transcribes AT-rich microbial dsDNA into 5' triphosphate-containing RNA that is then detected by the retinoic acid-induced gene I (RIG-I), which proceeds to switch on the production of interferon-β. In the absence of Pol III, infection with Legionella pneumophila or Epstein-Barr virus does not induce interferon-β, indicating that Pol III is required for proper immunity both to bacterial and to viral infection.

Eitan Israeli

“Literature becomes the living memory of a nation”

Alexander Solzhenitsyn (1918-2008), Russian novelist, dramatist and historian. He made the world aware of the Gulag, the Soviet Union’s forced labor camp system, through his writing – particularly The Gulag Archipelago and One Day in the Life of Ivan Denisovich. Solzhenitsyn was awarded the Nobel Prize in Literature in 1970. He was exiled from the Soviet Union in 1974 and returned to Russia in 1994

“You talk when you cease to be at peace with your thoughts”

Khalil Gibran (1883-1931), Lebanese American artist, mystic and writer. He is chiefly known for his 1923 book The Prophet, a series of philosophical essays written in English. An early example of inspirational fiction, the book sold well despite a cool critical reception, and became extremely popular in the 1960s counterculture