Syndrome of inappropriate antidiuretic hormone secretion caused by proton pump inhibitor use

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To the Editor,

I write you upon the rising concern of possible side effects of chronic use of proton pump inhibitors (PPI) as we believe that our patient developed the Syndrome of Inappropriate Antiduretic Hormone Secretion (SIADH) secondary to the use of PPI.

We present to you an euvolemic 70 year old male that was admitted to the emergency ward with aspecific complaints just two weeks after the initiation of pantoprazole 40 mg daily in association with methylprednisolone (32 mg) because of a PET confirmed polymyalgia rheumatica (no vasculitis).

His serum sodium level was 115 mmol/L (normal 135-145 mmol/L), a serum osmolality of 242 mOsm/kg (normal 275-295 mOsm/kg), a urinary sodium level of 63 mmol/L (normal 54-150 mmol/L) and urinary osmolality of 528 mOsm/kg (normal 400-800 mOsm/kg).

SIADH was diagnosed following the Bartter- Schwarz criteria. The patient fulfilled this criteria except for one: hypertonic saline was administered because of a symptomatic severe hyponatremia. Serum sodium level two weeks before initiating PPI was normal (140 mmoL/L).

There was no evidence of adrenal insufficiëncy nor malignancy on CT as also no evidence of cerebral lesions or elevated intracranial pressure.

Pantoprazole was ceased and replaced by Ranitidine 300 mg daily. His hyponatremia recovered and remained normal afterwards.

SIADH is the most frequent cause of hyponatremia and the use of PPI has multiplied over the last decades. In 2015 738 922 elderly patients (≥65 years) were prescribed PPI in Belgium (1). Hyponatremia occurs during hospital stay in 38.2% of patients who were admitted with a serum sodium level above 138 meq/L In hospital acquired hyponatremia leads to higher in hospital mortality and overall poor prognosis (2,3)

The first cases that suggested a relationship between the use of PPI and hyponatremia were described more than two decades ago.

In a study of Rudge et al (4), evaluating 254 patients, hyponatremia occurred after surgical intervention for traumatic hip fracture in 27% in a moderate degree (serum sodium <135 mmol/L > 130 mmol/L) and 9% in severe degree (<130 mmol/L). An increased release of antidiuretic hormone (ADH) is a normal response to surgery and this leads to water retention. However, in this retrospective study a significant association between the use of PPI and hyponatriemia was noticed with a p-value of 0.023 in the group with moderate hyponatremia and a p-value of 0.019 in severe hyponatremia. In this cohort the association was stronger than for the selective serotonine reuptake inhibitor (SSRI).

A retrospective analysis, performed by Correia et.al. (5) revealed a correlation between hyponatremia and the use of PPI. A significantly increased risk (with a p-value of 0.007) of progression to severe hyponatremia was seen when using PPI.

Especially in the frail and elderly patients there is some concern on the high prevalence of hyponatremia development while taking PPI, which ranges from 18.7 to 46.3% (6). The secretion of antidiuretic hormone increases with older age and the risk of inappropriate secretion is higher with chronic use of PPI (5,6).

So the common use of PPI can lead to a significant morbidity and mortality secondary to SIADH. Especially in elderly patients and perioperative it might be advised to rule out any electrolyte disturbances and to identify other agents that increase the risk of hyponatremia/SIADH. To further investigate the relationship of hyponatremia and PPI and the underlying mechanism of SIADH it might be useful to check the serum osmolality and urine sodium and osmolality as a screening test even in the event of a very mild hyponatremia to detect a possible SIADH early on and to stop PPI when possible.

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