

The use of demeclocyclin in the syndrome of paraneoplastic inappropriate secretion of anti-diuretic hormone: about one observation.

C. GARCIA(1), T. PONCIN(2), P. LE GARLANTEZEC(2), L. BORDIER(1), H. MAYAUDON(1), S. CREMADES(3).



French Military Hospital BEGIN
69 avenue de Paris - 94160 SAINT MANDE – FRANCE

1. Department of endocrinology
2. Department of pharmacy
3. Department of internal medicine

Introduction :

Hyponatraemia constitutes the most common hydro-electrolytic abnormality, and the determination of its cause is important for patient's management, which sometimes can include the use of a pharmacological agent.

Observation:

A 78 year-old woman was referred for cough, chest pain, shortness of breath and tiredness. Her past medical history was composed of high blood pressure and dyslipidemia. Blood tests revealed hyponatraemia, and computed tomography analysis led to the diagnosis of a right lung adenocarcinoma with T2N1bM1 staging, that could not be surgically removed, as metastases were present (fig.1).



Fig. 1: Patient's chest computed tomography. A and B: Node and tumor complex of the right hilum pulmonis and pulmonary apex measured at 88x70x13 mm (arrow) with mass effect on the right superior and medium lobar bronchi and pleural effusion. C: Metastase to the VIIth segment of the liver measured at 18 mm (arrow)

The characteristics of this hyponatraemia were as follows :

- Chronic hyponatraemia (ranging from 113 to 123 mmol/l)
- Low plasma osmolarity, calculated at 250 mosm/L
- High urine osmolality (sodium urinary concentration > 60 mmol/24h)
- These abnormalities could not be corrected by fluid limitation alone.

Clinical and biological assessment led to the diagnosis of a syndrome of paraneoplastic inappropriate secretion of antidiuretic hormone (SIADH) related to the lung cancer.

As dyspnea and tiredness increased, a chemotherapy with pemetrexed was initiated. However hyponatraemia was still observed.

A treatment with demeclocyclin 600 mg daily was initiated, with a response within 6 days as natraemia increased to 137 mmol/l, with persistent efficacy at 2 months and with good tolerance (fig. 2).



Fig. 2: Effect of the introduction of demeclocyclin (arrow) on patient's natraemia: quick and persistent correction of hyponatraemia .

Discussion:

SIADH is characterized by a hypovolemic hyponatraemia, and must be evoked if the following criteria are present : plasmatic osmolarity <280 mOsm/kg or natraemia <134 mmol/L, urinary osmolality >100 mOsm/kg, clinical normal volemia, sodium urine concentration >40 mmol/L with normal fluid and sodium intake, exclusion of hypothyroidism, adrenal insufficiency or diuretics intake. Additional criteria are low uricemia, low uremia, and normal creatinine, potassium and alkali reserve (1).

In the face of a SIADH, the clinician can use few therapeutic strategies. Aetiological treatment and fluid limitation constitute the first line treatment. However, there are some situations where fluid limitation is not effective, and a pharmacological agent has to be introduced.

Demeclocyclin chlorhydrate is a tetracyclin with antagonistic properties against ADH action. The most important series of patients lasts for more than 30 years and included 11 patients (2). It should be prescribed initially at 900 to 1200 mg/day associated with moderate fluid limitation during 8 to 10 days, then 600 mg/day without fluid limitation. However in the elderly it can be initiated at 600mg/day without any fluid limitation. This drug must not be used in case of renal impairment as it can also cause renal impairment. It can be highly effective, although its mechanism of action is still unclear. The drug decreases the transcription of the *AQP2* gene, associated with aquaporin-2 expression in the renal inner medulla (3). The activity is probably also due to a cyclic AMP pathway inhibition leading to a decrease in the activation of aquaporins.

Another family of drugs, V2 ADH-receptors antagonists called vaptans show interesting results in case of euvoletic or hypervolemic hyponatraemias (4).

Conclusion:

- The use of demeclocyclin has been very helpful for this lady suffering from an advanced stage lung adenocarcinoma, and who could not benefit from an aetiological treatment, which is usually associated with correction of hyponatraemias in these situations.
- Demeclocyclin is an old drug, but can be still highly effective in some situations, with good tolerance.
- The precise mechanism of the drug is however not well understood yet, and deserves to be elucidated in pharmacological studies.

References :

1. Chabre O, Muller M. Hyponatrémies par SIADH. *MCED*, 2013;62:7-14.
2. Perks WH et al. *Thorax* 1979;34:324.
3. Kortenoeven MLA, Sinke AP, Hadrup N, Trimpert C, Wetzels JFM, Fenton RA et al. Demeclocycline attenuates hyponatremia by reducing aquaporin-2 expression in the renal inner medulla. *Am J Physiol Renal Physiol*. 2013;305:F1705-18
4. Vantghem MC, Balavoine AS, Wemeau JL, Douillard C. Hyponatremia and antidiuresis syndrome. *Ann Endocrinol (Paris)*. 2011;72:500-12.