

Letters and Replies

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Insight on mechanism of hyponatraemia induced by low-dose intravenous pulse cyclophosphamide

Sir,

We read with great interest the recent contribution by Lee *et al.* [1]. The authors showed significant clinical data on hyponatraemia induced by low-dose intravenous pulse cyclophosphamide (CYP) [1]. However, they did not reveal precise and molecular-based mechanisms of hyponatraemia induced by CYP. We would like to add some possible mechanisms of CYP-induced hyponatraemia.

Firstly, they speculated that the antidiuretic effect of cyclophosphamide might be related to increased renal action of vasopressin by the alkylating metabolites [1], but did not suggest the possible mechanisms. It was shown that increased interleukin (IL)-1 and NF- κ B [a transcriptional factor of tumour necrosis factor (TNF)- α] by acute inflammation were significantly associated with reduced expression of vasopressin receptor (V2R) and aquaporin-2 (AQ2) [2,3]. McBride *et al.* demonstrated that CYP metabolites (mafosfamide and 4-hydroperoxycyclophosphamide) caused the decrease in production of IL-1 and TNF- α in a dose-dependent manner [4]. Therefore, there is a possibility that CYP might cause hyponatraemia by upregulating expression of V2R and AQ2 through suppression of IL-1 and TNF- α , which are effector molecules in the downregulation of VR2.

Secondly, they thought that water retention might involve a direct tubular effect of cyclophosphamide metabolite on the collecting duct epithelium [1], because it was demonstrated in a case with established diabetes insipidus that developed CYP-associated antidiuresis without vasopressin secretion [5]. Regarding this issue, we speculate that one article by Pouzet *et al.* might give us an insight in understanding the possible mechanisms of CYP-induced hyponatraemia [6]. They reported that small amounts of endogenous AVP, known to be produced by adrenal and testis in diabetes insipidus rats, could also contribute to V2 agonism, as well as a possible constitutive activation of the V2 receptors [6]. As we mentioned above, because the expressions of V2R and AQ2 are increased through suppression of IL-1 and TNF- α by cyclophosphamide use, small amounts of endogenous AVP from other sources might have induced water retention, causing hyponatraemia.

Therefore, further studies are necessary to evaluate the serial changes of serum sodium, IL-1 and TNF- α levels, and renal changes of V2R and AQ2 before and after cyclophosphamide therapy. The dose-dependent relationships of cyclophosphamide with the severity of hyponatraemia should also be further elucidated in the future.

Conflict of interest statement. None declared.

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Reply

Dear Sir,

We thank Park *et al.* for their interest in our work [1]. They postulated two possible mechanisms by which water excretion can be impaired by intravenous cyclophosphamide. One is the increase in endogenous vasopressin release, and the other is upregulation of type 2 vasopressin receptor (V2R) and aquaporin-2 (AQP2). These sound plausible because cyclophosphamide may affect water homeostasis either by increasing vasopressin secretion or by potentiating the effect of endogenous vasopressin at the kidney [2]. However, the former possibility is not substantial even though the contribution of vasopressin release from adrenals and testes is considered. As discussed previously [1], cyclophosphamide-induced hyponatraemia is not accompanied by an elevated plasma vasopressin level and can occur in a patient with central diabetes insipidus.

The authors specified the possible intrarenal pathway via which the effect of endogenous vasopressin is potentiated by cyclophosphamide administration. This possibility is con-