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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-κB [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-

ceivable because vasopressin–V2R–AQP2–cAMP pathway has the major role in water absorption in collecting duct principal cells. Cyclophosphamide-induced hyponatraemia may correspond to type D (nephrogenic syndrome of inappropriate antidiuresis) among the four subtypes of syndrome of inappropriate antidiuresis proposed by Robertson [3].

It is interesting that cyclophosphamide can suppress the production of interleukin-1 (IL-1) and tumour necrosis factor (TNF) from human monocytes through its metabolites. Nuclear factor kappa B (NF-κB) and pro-inflammatory cytokines may downregulate V2R and AQP2 in acute inflammatory conditions, and the authors proposed a hypothesis that cyclophosphamide-induced suppression of IL-1 and TNF-α may upregulate V2R and AQP2 in the kidney. According to Hasler *et al*., NF-κB is a negative regulator of AQP2 transcription at a post-V2R level [4]. However, it is not clear whether the expression of V2R may be altered by pro-inflammatory cytokines in other conditions than sepsis animal models. Studies are required to provide direct evidences showing that the vasopressin–V2R–AQP2–cAMP pathway in the renal collecting duct is affected by cyclophosphamide administration or cyclophosphamide metabolites and which level (V2R or post-receptor) is the major determinant.

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Proteinuria or albuminuria?

Dear Editor,

Methven *et al*. [1] present some interesting data concerning the use of urinary albumin to creatinine (ACR) and protein to creatinine (PCR) ratios in the detection of significant proteinuria. Their observation that PCR and ACR thresholds may need to be modified in relation to age and gender is particularly important.

In 1696 individual 24-h urine collections, they observed a better relationship between PCR and 24-h urinary protein than between ACR and 24-h urinary protein and concluded that PCR is a more sensitive screening test than ACR to predict clinically relevant proteinuria. We feel that their conclusion needs to be examined a little more closely, given that both PCR and 24-h total protein loss were based on the same total protein measurement and that the reference measure itself—total protein loss—is flawed. Given the study design, it is perhaps more remarkable that the differences between ACR and PCR in terms of predicting total proteinuria were so marginal. The converse comparative analysis, ability of PCR and ACR to predict 24-h urinary albumin loss, was not undertaken.

Some of the limitations of this study acknowledged by the authors are of central importance. The PCR and ACR estimates were obtained from a 24-h collection and may not, therefore, reflect the situation in a random or early morning 'spot' urine sample in which ACR and PCR would more usually be estimated [2]. The population studied was that attending a general nephrology clinic and the results may not be generalizable to primary care populations.

The authors also demonstrate, as others have before [3], that there is a poor relationship between ACR and total protein loss at lower levels of proteinuria. This should not be interpreted as a criticism of ACR measurement, which is based on specific immunoassay detection of a single protein in urine. Rather, it reflects imprecision of total protein measurement against a variable background of clinically insignificant proteins (e.g. Tamm–Horsfall glycoprotein), compounded by the non-specificity and susceptibility to interferences of the chemical reactions used to estimate total protein concentration.

Recommendations, including those from NICE [4], that ACR should replace PCR as the test of choice for proteinuria detection were not based solely upon their relative abilities to estimate total protein loss, but on factors including that albumin measurement can be standardized and is more precise at lower levels of proteinuria, that it is already the test of choice in people with diabetes and that it is the predominant protein in the vast majority of proteinuric kidney diseases [5]. It is noteworthy that ACR and PCR had equal diagnostic performance amongst the subset of patients of Methven *et al*. receiving renin–angiotensin system blockade, amongst whom the proportion of albumin to total protein was higher.

An overwhelming body of evidence is accumulating pointing to the significance of low-level protein loss in terms of morbidity and mortality: such data can only be gathered using urinary albumin assays. To persevere in assigning primacy to total protein loss misses the point.

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