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LETTER TO THE EDITORS/REPLY

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Lithium concentrations during cisplatin-based chemotherapy: evidence for renal interaction

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Sirs,

We read with interest the report of J. H. Beijnen et al. [1] concerning lithium pharmacokinetics during cisplatin-based chemotherapy [1]. However, we do not agree with their interpretation of the transient decrease in serum lithium concentration. Lithium clearance is widely used in view of estimating the distal tubular sodium delivery, because of its absorption at the same rate as sodium in the proximal tubule and, normally, no more beyond the thick ascending limb [2]. This is true only in normovolemic states. In case of water and/or sodium depletion, some lithium is reabsorbed in the thick ascending limb and the collecting duct. Under osmotic diuresis as usually done during cisplatin-based chemotherapy, these phenomena do not occur [3]. Therefore, the two major factors influencing renal lithium clearance include not only the glomerular filtration rate but also variations in the tubular reabsorption of sodium and water. It cannot be interpreted at face value because of its variation with creatinine clearance and sodium intake. The necessity of correction for total sodium excretion and creatinine clearance so as to obtain the true value has been established [4]. Large variations in sodium loading before, during, and after treatment of the patient as reported by Beijnen et al. [1] may account for variation in lithium concentrations without a significant difference in noncorrected lithium clearance.

As for sodium, the transport of lithium along the proximal tubule is due mainly to an active phenomenon [5]. The mechanism of renal dysfunction during cisplatin therapy remains unclear. In a recent report suggesting a protective effect of glycine [6], it has been proven that toxic intracellular platinum species are formed early after injection. The main site of such formation is the S3 part of the proximal tubule. Usual indices of functional proximal tubular damage, such as β2-microglobulin, *N*-acetyl-β-glucosaminidase, or leucine aminopeptidase, are increased in the first few hours following cisplatin administration [7]. Such a finding occurs without a fall in the glomerular filtration rate. Thus, active transport of sodium along the brush-border apical membrane is probably precociously altered. As lithium reabsorption occurs at the same place and in the same way, it must also be diminished early after cisplatin administration. This observation supports the concept of an increase in true lithium clearance (corrected for sodium loading) without an alteration in renal function.

Of greatest interest should have been the report of plasma and urinary osmolalities in the observation of Beijnen et al. [1]. Lithium is known to induce nephrogenic diabetes insipidus, a syndrome characterized by insensitivity of the distal nephron to both endogenous and exogenous vasopressin. After cisplatin administration polyuria occurs and urinary osmolality falls, seemingly due to resistance of the kidney to vasopressin [8], as is observed with lithium. Simultaneous administration of the two drugs might theoretically lead to severe hypernatremia and hyperosmolarity.

We thus think that the reasons for the decrease in lithium levels observed by Beijnen et al. are more complex than a simple dilution effect. Pretreatment with diuretics as a prophylactic measure during cisplatin administration must be avoided so as to prevent possible episodes of acute lithium toxicity and severe hyperosmolarity.

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Reply

J. H. Beijnen

Lithium pharmacokinetics and cisplatin-based chemotherapy

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I appreciate highly the interest that Dr. F. Vincent and colleagues took in our case report describing lithium pharmacokinetics in a patient treated with four courses of cisplatin-based chemotherapy and a vigorous hydration regimen [1]. One of our interesting observations was that within 24 h of the start of the first chemotherapy course the serum lithium level dropped from 0.61 to 0.22 mmol/l (64% decrease). During the three subsequent courses this initial decrease was observed again, but its depth seemed to diminish. The decrease in lithium serum concentrations was transient and the nadir was reached in the morning of the 2nd day of each course, after which the lithium concentration increased to reach starting levels. Theoretically, there are several factors that could have influenced the lithium pharmacokinetics as outlined in our communication [1] and indicated by Vincent et al. The clinical chémistry parameters (serum creatinine, electrolytes, blood urea nitrogen levels) showed no significant change. Early proximal tubular damage such as that mentioned by Vincent et al. may have occurred, although it is difficult to associate with the transient nature of the effects observed during each course, which even tend to diminish during consecutive courses. An initial dilution effect may, indeed, be too simple a representation for the observed phenomena, which are probably more complex; however, in our setting we did not find proof of this. Future research in similar cases incorporating the measurement of parameters as indicated by Vincent et al. may cast more light on this matter. The message remains and is very clear: cisplatin-based chemotherapy can have a distinct influence on lithium pharmacokinetics that can even lead to subtherapeutic levels; careful monitoring of serum lithium levels is thus very much warranted in these cases!

References

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