Correspondence

Cimetidine as an Organic Cation Transporter Antagonist

To the Editor-in-Chief:

The recent article by Ciarimboli et al[1] reports for the first time that the organic cation transporter 2 (OCT2) is present in hair cells of the cochlea in mice. They nicely showed that no ototoxicity occurred after cisplatin administration in OCT2 knockout mice as opposed to wild-type mice. They also used coadministration with the organic cation antagonist cimetidine and observed protection from ototoxicity, which we would like to discuss in more detail.

Platinum drugs have a large propensity to react with soft nucleophiles, eg, sulfur compounds, and this type of interaction has been the focus of a multitude of studies.[2–7] Recently, Buss et al[8] showed that oxaliplatin rapidly interacts chemically with cimetidine, a thioether-containing drug, with a concomitant drastic reduction of the cytotoxicity of the platinum drug. The rate constant for the interaction of cisplatin with the thioether compound methionine is about half of the value reported for oxaliplatin,[7] and we have established that this also holds for cimetidine (unpublished observations). Taking the chemical reactivity of cimetidine into account, two alternative hypotheses can be formulated concerning the otoprotective effect of the drug:

First, in the paper by Ciarimboli et al,[1] cimetidine was given i.p. immediately before i.p. cisplatin. We do not know how fast the drugs are absorbed to the general circulation, ie, we do no not know if part of the dose of cisplatin is consumed by reaction with cimetidine in the peritoneal space or if there is a chemical interaction between the drugs systemically. We have previously studied the interaction between cisplatin and the otoprotector methionine in a guinea pig model.[9] Administration of methionine i.v. caused a 30% decrease in the area under the concentration-time curve (AUC) of cisplatin. Dose adjustment of cisplatin in animals receiving methionine, ie, to obtain similar AUC as compared with the saline control group, resulted in similar ototoxicity in the two groups. It was concluded that the protective effect of methionine was explained by a lowered systemic exposure of cisplatin.

Second, because of the presence of OCT2 in the cochlea, one can envisage that the protective effect of cimetidine depends on an accumulation of the drug in critical parts of the cochlea ie, the hair cells and stria vascularis in the lateral wall, and that the protective effect is due to chemical neutralization of cisplatin in these parts. The ototoxicity is highly dependent on cisplatin exposure (AUC) in the perilymphatic compartment. A decrease in AUC from 515 to 202 μmol/L $\times$ min completely abolished the ototoxicity.[10] It should also be pointed out that the *in vivo* transformation product, the monohydrated complex of cisplatin, is more ototoxic than the parent compound.[11] The chemical reactivity of this complex with sulfur compounds is even higher as compared with cisplatin.[6]

It should be highly interesting to compare the otoprotective effect of cimetidine with other candidates where no chemical interaction can occur.[12]

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Author's Reply:

Ehrson and Wallin critically discuss in their response to our work, where we showed that the presence of the organic cation transporter 2 (OCT2) in the mouse cochlea is critical for the development of cisplatin-induced ototoxicity, the mechanism by which cotreatment of animals with cimetidine leads to protection against cisplatin ototoxicity. They suggest that cimetidine leads to chemical neutralization of cisplatin and thereby reduces its ototoxic effects, rather than competes with cisplatin uptake via OCT2, as suggested in our paper. They base their suggestion on published data demonstrating such neutralization of cisplatin by cimetidine *in vitro*. This observation certainly needs critical consideration when interpreting our results. However, we presented at least two findings that argue against such an interpretation.

1) In experiments with MOLT4 cells, which do not express OCT2, cell toxicity of cisplatin was not different among cells that were incubated with cisplatin alone or with cisplatin and cimetidine in equimolar amounts (see Figure 8, A and B). Similar findings had been recently published by others, showing that coincubation of cells that do not express significant amounts of OCT2 with cisplatin and cimetidine did not change cisplatin toxicity.[1]

2) Treatment of animals with cimetidine was fully effective in protecting from cisplatin ototoxicity, but only partially effective in protecting the kidney, as shown for example in Figure 1B, where a significant polyuria is observed in the presence of cimetidine. If this protection were due to chemical neutralization by cimetidine, it should work similarly in both organs.

In contrast to these observations, in several studies an interaction of platinum derivatives with soft nucleophiles, such as methionine, glutathione, cysteine, and cimetidine, is reported. A possible explanation of this apparent discrepancy may come from the consideration that these studies are generally conducted using a large excess of nucleophiles. For example, in their cytotoxicity experiments, Buss et al[2] used 20 μmol/L oxaliplatin with 1.5 mmol/L cimetidine and, in their chemical interaction experiments, 10 mmol/L oxaliplatin with 150 mmol/L cimetidine. Jerremalm et al[3] used 60 μmol/L oxaliplatin in 9.9 mmol/L glutathione for their degradation studies. Moreover, in an *in vivo* approach, chemical interaction was investigated in guinea pig receiving 8 mg/kg cisplatin and 300 mg/kg methionine.[4]

In our model, cisplatin and cimetidine were used at the same molecular concentrations (giving origin to doses of 15 and 12.6 mg/kg, respectively). Assuming that all of the administered drugs enter the circulation, one could expect a maximal blood concentration of 0.23 mg/ml cisplatin and 0.19 mg/ml cimetidine in a mouse with 30 g bodyweight. However, mouse body fluids and, in particular, blood contain physiological concentrations of glutathione[5] and cysteine,[6] which are higher (1 and 0.4 mg/ml blood, respectively) than the maximally expected cimetidine concentration in our experiments. Thus, if chemical neutralization of cisplatin by cimetidine is involved in our experiments *in vivo*, its contribution is certainly less important.

We agree with Ehrson and Wallin that it is of high interest to compare *in vivo* protective effects of cimetidine with other candidates where no chemical interaction can occur. However, it is certainly necessary to investigate whether the chemical inactivation of cisplatin observed in the studies mentioned by Ehrson and Wallin is also relevant *in vivo* with the doses used in our study. In addition, it is of primary importance to identify which form of cisplatin (cisplatin, monohydrated complex) is the substrate transported by OCTs.

In conclusion, we are convinced that the evidence presented in our publication on the one hand and the considerably higher concentrations used in the *in vitro* studies on the other hand support our interpretation of the mechanism of protection form cisplation toxicity by cimetidine.

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