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Population Pharmacokinetics and Dosing Recommendations for Cisplatin during Intraperitoneal Peroperative Administration

Royer et al.[1] have written an interesting paper on dose recommendations for cisplatin to minimize the risk of renal toxicity and to optimize the intraperitoneal exposure of the drug. Peroperative chemotherapy was administered by filling the peritoneal cavity with isotonic saline 3 L containing cisplatin 90 mg heated to 37°C. Gentle stirring was carried out by the surgeon. One hour after administration, the peritoneal cavity was cleared out, rinsed and refilled with the same cisplatin solution as the first bath. This second intraperitoneal bath lasted 1 hour, after which the peritoneal cavity was cleared out, rinsed and closed up. The risk assessment of the dose was based on the total serum protein concentrations of the patients. The authors state: ''For instance, for the same risk of renal toxicity of 50%, the administered dose should be 90 mg if the protein concentration is high and 92.5 mg if the protein concentration is median, but 105 mg if the protein concentration is low.'' I want to question that recommendation for the following reasons.

Clinical studies after intravenous cisplatin administration to 425 patients found that low serum albumin increased the risk of nephrotoxicity, even suggesting infusion of albumin to hypoalbuminaemic patients to reduce the risk of nephrotoxicity.[2] This approach has also been proposed by Royer et al.[3]

The recommendation by Royer et al.[1] is based on their previous study[4] demonstrating a threshold to distinguish between patients with a low risk of renal toxicity and patients with a high risk. Patients who displayed a total platinum area under the concentration time curve from 0 to 24 hours (AUC_{24}) of >25 mg • h/L had a higher risk of renal toxicity.

I will first comment on the concentration relationships between ultrafiltered and total platinum. When cisplatin reaches the general circulation, it rapidly reacts with serum proteins.[5] The AUC_{24} for ultrafiltered platinum is only about 10% of the AUC_{24} for total platinum, and the ratio between ultrafiltered and total platinum will decrease with time.[3]

When serum protein concentrations are low, protein-bound platinum concentrations will decrease and the concentration of ultrafiltered platinum will increase.

Several studies have investigated the cytotoxic and nephrotoxic effects of platinum-protein complexes. Animal studies in rats[6] and mice[7] revealed that cisplatin incubated in serum was virtually without nephrotoxicity. A clinical study in humans with a cisplatin-albumin complex showed no evidence of nephrotoxicity when patients were given 100 mg/m^2 (calculated as cisplatin), despite a lack of prehydration or forced diuresis.[8]

Most probably, the agent(s) causing the nephtotoxicity will be part of the ultrafiltered fraction. Cisplatin has a short terminal half-life of approximately 30 minutes *in vivo*[9-11] and is converted to its cytotoxic monohydrated complex.[10,11] The half-life of the monohydrated complex is governed by its rate of formation. In an animal model, the monohydrated complex has higher nephrotoxicity than the intact drug.[12] Thus, a few hours after the end of a cisplatin infusion, the concentration of cisplatin and its monohydrated complex will already be low and the major proportion of ultrafiltered platinum will constitute inactive reaction products with endogenous sulphur-containing compounds.[13] With this background, it would have been interesting to evaluate a correlation between nephrotoxicity and the AUC of ultrafiltered platinum during, for instance, the first 4 hours.

Finally, Royer et al.[1] used a fixed-dose regimen of cisplatin, and I was surprised to note that they did not observe any correlation between body surface area and clearance of total serum platinum. Their finding is in contrast to the observation by Salas et al.,[14] which established a strong correlation between total plasma platinum clearance and body surface area using fixed intravenous doses.

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The Authors' Reply

We read with interest the comments of Hans Ehrsson about our recent article on the population pharmacokinetics of cisplatin after peroperative intraperitoneal administration.[1] He questions the dose recommendation in view of the relation between cisplatin binding to proteins and the risk of renal toxicity. He argues that, following the dose recommendation described in our paper (higher doses when protein concentrations are lower), the concentration of ultrafiltered fraction of platinum will increase and therefore so will the toxicity. Finally, he has questioned the fact that body surface area was not a significant co-variate on the clearance of total platinum.

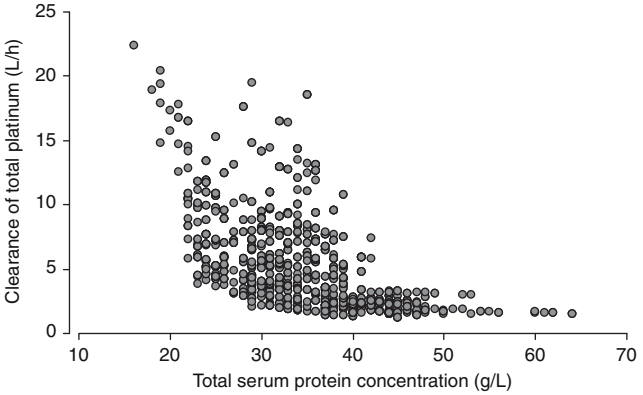

Fig. 1. Relation between clearance of total platinum from the central compartment and observed serum protein concentrations.

We firstly think that the dose recommendation described in the paper does not contradict the fact that the ultrafiltered fraction might be linked to the toxicity of platinum. Indeed, the relation between the clearance of total platinum and serum protein described in the paper clearly shows that the elimination of platinum is higher when protein concentrations are low (figure 1). This is especially the case at the beginning of the chemotherapy, when the protein concentration is lowest.[2] Thus, to maintain sufficient intraperitoneal exposition when protein concentrations are low, one should increase the dose administered, taking into account a given threshold of toxicity. Moreover, as total platinum is the source of ultrafiltered platinum, one can reasonably think that this fraction is also decreased even if its formation is increased when the protein concentration is low.

Secondly, the dose recommendation was built using previously used parameters, not physiopathological parameters, with the aim to optimize both efficacy and toxicity. The parameter of toxicity was the area under the plasma concentration-time curve (AUC) of total platinum, as previously described.[2] We previously compared the AUC of both total and ultrafiltered platinum with regard to toxicity and found that the AUC of total platinum was more relevant. The same conclusion was drawn with a greater number of patients (unpublished data). This confirms the rationale of the dose recommendation building, which was performed using known parameters but not physiopathological parameters for which we have no precise data.

Finally, the fact that body surface area was not observed as a significant co-variate on clearance and the clinical relevance of this co-variate were discussed in our article. It should,