Inhibition of Kidney Uptake of Radiolabeled Somatostatin Analogs: Amino Acids or Gelofusine?

TO THE EDITOR: With great interest we read the papers by Van Eerd et al. (*1*) and Vegt et al. (*2*) on the effects of the succinylated gelatin plasma expander Gelofusine (B. Braun Medical) on renal uptake of [^{111}In-diethylenetriaminepentaacetic acid (DTPA)]octreotide. We congratulate the authors on their innovative work, as we believe this is fundamental and interesting research.

The authors reported that Gelofusine significantly inhibited kidney uptake of [^{111}In-DTPA]octreotide to a level comparable to the level of inhibition by currently applied amino acid solutions. This finding further expands on the previous clinical observation that Gelofusine infusion results in tubular proteinuria (*3–5*) of both albumin and β_2-microglobulin. Although the mechanism for this proteinuria is not completely understood, involvement of the megalin receptor system is likely, because both β_2-microglobulin and albumin are ligands for this receptor. The megalin system was recently shown to be essential for kidney uptake of radiolabeled somatostatin analogs (*6*), making interventions at the megalin level interesting potential targets for renal protection during peptide receptor radionuclide therapy (PRRT). The new findings of the group in Nijmegen (*1,2*) offer an additional way to further research this subject. We would like to comment on some conclusions and statements brought forward in the 2 papers.

On the basis of several reports, the authors stated that amino acid infusion for kidney protection may have several side effects such as vomiting and potentially fatal hyperkalemia. We previously reported on the safety and side effects of different amino acid solutions (*7*). On the basis of that study, we now use a combination of 25 g of L-lysine and 25 g of L-arginine, dissolved in 1 L (LysArg), as a standard 4-h infusion protocol for kidney protection during PRRT. During infusion with LysArg, the highest serum potassium level measured was 6.0 mmol/L in 1 of 11 patients. No electrocardiography changes were seen. Vomiting occurred in 1 patient, but this was not drug related (*7*). We then concluded that this LysArg solution was safe enough to be used as the standard procedure in our PRRT protocols. In the years following this publication, we have infused the LysArg solution more than 2,000 times in the PRRT setting. In our clinical setting, we have not encountered severe side effects, underlining the good toxicity profile for LysArg. In particular, no symptoms of volume overload have occurred in patients and no drug-related emergencies or fatalities have been registered. Vomiting occurs in about 15% of patients and nausea in about 30% (*8*), but it should be noted that vomiting may be caused in part by other factors, as we reported vomiting in at least 6% of patients who did not receive an amino acid infusion (*7*).

The authors stated that lysine itself may produce renal failure, and they cited two studies indeed showing that administration of lysine produced significant renal impairment (*9,10*). However, the doses used in these animal studies were approximately 4−6 times higher than the dose of lysine used in our (*11*) and their (*1*) animal experiments (400 mg/kg). To our knowledge, no studies have been published that describe toxicity from lysine in our dose range or in human subjects.

Most publications on plasma expanders deal with administration to critically ill patients—for instance, patients in septic shock, in hemorrhagic shock, or after surgery. Little is known, however, about infusion of plasma expanders in healthy subjects and patients with a normal circulation. The authors reported that infusion of Gelofusine volumes did not cause side effects in 5 healthy volunteers; it was not stated, however, which parameters in addition to blood pressure and heart rate were investigated (*2*).

An important point is that the incidence of allergic reactions is 12-fold higher for Gelofusine than for human albumin infusion (*12*), possibly because of the bovine origin of the gelatin fluid. More than 40 reports have been published on anaphylactic reactions that were due to the use of gelatin-derived plasma expanders. Also, a cross reactivity exists between the different gelatin solutions (*13*). A 0.038% frequency of severe reactions (shock, cardiac, or respiratory arrest) has been reported for gelatin solutions (*14*). The incidence of all grades of allergic reactions is between 0.06% and 0.78% (*14–16*). Although this incidence is low, any anaphylactic reaction in the PRRT setting is unwanted.

In conclusion, lowering the renal uptake of radiolabeled peptides, such as somatostatin analogs, using the plasma expander Gelofusine may be a promising method to protect the kidneys in PRRT. Although no side effects were noted in 5 healthy subjects, we must be aware that infusion of gelatin-based plasma expanders may cause side effects, such as anaphylactic reactions, in the target group of patients. Further validation studies on larger groups of healthy subjects and patients must be performed and compared with the current method using amino acid solutions to find out whether this new strategy is also safe and effective in the PRRT setting.

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REPLY: We appreciate the interest of Rolleman et al. in our 2 papers (*1,2*) in which we showed that infusion of the succinylated gelatin plasma expander Gelofusine (B. Braun Medical) might be useful for protection of the kidneys during peptide receptor radionuclide therapy. We fully agree that the findings of our pilot study, that the radiation dose to the kidneys will be reduced by coinfusion of Gelofusine, need to be validated in randomized controlled trials. Particularly, an intrapatient comparison between the use of lysine/arginine and Gelofusine would demonstrate the relative effectiveness of Gelofusine in reducing uptake by the kidneys. Furthermore, we take the opportunity to respond to their specific comments.

Rolleman et al. have developed a protocol in which arginine and lysine are infused to reduce uptake of radiolabeled somatostatin analogs by the kidneys. Apparently, hyperkalemia is not a major problem, probably because of the fluid load of 1 L. Still, vomiting as a side effect occurred more frequently in the infused patients as indicated by the 10% difference in vomiting rate between the infused group and the control group. Moreover, in a recent therapy study using lysine (2.5%) and arginine (2.5%) in 1 L of 0.9% NaCl to reduce uptake of ^{177}Lu-1,4,7,10-tetraazacyclododecanetetraacetic acid Tyr^{3}-octreotate by the kidneys, nausea and vomiting occurred in 31% and 14% of patients, respectively, despite the use of the antiemetic granisetron (*3*).

In animal experiments, high doses of lysine are required to induce renal failure. However, the relevance of animal models in determining nephrotoxicity and extrapolation to humans are difficult, because toxicity data generally are based on a dose of mg/kg of body weight. In general, higher doses are needed in animals to induce drug toxicity. For example, the doses of aminoglycoside antibiotics to induce nephrotoxicity in mice and rats are much higher than the doses described for humans (*4*). Nevertheless, the toxicity of lysine in humans has been demonstrated. ten Dam et al. compared intravenous lysine (0.44 g/kg) with intravenous arginine in healthy volunteers. Infusion of lysine increased urinary excretion of the proximal tubular injury marker β-*N*-acetylglucosaminidase 20- to 100-fold compared with arginine, clearly illustrating the tubulotoxic effect of lysine (*5*).

Gelofusine is normally applied in critically ill patients. Therefore, we believe that induction of side effects in healthy subjects and patients with normal circulation may occur even more sporadically. We have used Gelofusine in a total dose of approximately 320 mL for a 70-kg adult. The duration of the infusion was 3 h. No major effect on extracellular volume is to be expected with this rather slow infusion rate, unless applied in patients with severe renal insufficiency or heart failure. We have used blood pressure and heart rate as hemodynamic parameters to evaluate volume status. Other parameters were not determined, but there were no complaints of dyspnea, edema, or headaches.

The authors point to the risk of anaphylactic reactions to Gelofusine. The 12-fold higher incidence compared with albumin is noteworthy but must be put into perspective: Barron et al. (*6*) stated that the incidence of severe reactions to albumin was 5 in 100,000, meaning that Gelofusine will cause a severe reaction in 6 of every 10,000 infusions. The latter figure is comparable to the reported incidence of severe anaphylactoid reactions of 0.028%−0.15% in large studies. To reduce the risk of anaphylactoid reactions, one should specifically ask patients about anaphylaxis after vaccination or during perioperative care (*7*). Certainly, we cannot exclude certain risks during infusion of Gelofusine. Further studies will indicate which compound in peptide receptor radionuclide therapy with somatostatin analogs is most effective in reducing the kidney radiation dose and has acceptable side effects.

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