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Letter to the editors

Human pharmacokinetics of carboplatin after oral administration

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Sir,

Carboplatin has proven to be the most promising second-generation platinum compound [1, 2]. Its spectrum of activity appears comparable with that of cisplatin, with a much more favorable pattern of toxic side effects. The risk for renal damage is very low for carboplatin and a hydration scheme is not required. In contrast to cisplatin, carboplatin has a stable chemical structure, suggesting a role for oral administration [5]. Therefore, we investigated the tolerance of carboplatin following oral administration and determined the pharmacokinetics of total platinum (Pt), non-protein-bound platinum (free Pt), and the parent drug in plasma for this route of administration in two patients.

The i.v. formulation of carboplatin (*cis*-diammine-1,1-cyclobutane dicarboxylate platinum II), as provided by Bristol Myers, was used for preparing the oral dose by adding 60 ml carboplatin solution (480 mg) to 180 ml water and 60 ml lemonade syrup. Each dose of carboplatin was taken within 5 min. Heparinized blood samples were obtained at 0, 15, 30, 45, 60, 75, 90, 120, 150, 180, and 210 min and at 4, 5, 6, 9, 11, and 24 h after administration. Plasma and plasma ultrafiltrate were prepared immediately after sampling. Pt and free Pt concentrations were determined by flameless atomic absorption spectrometry. Intact carboplatin concentrations were determined by HPLC, according to procedures previously described by us [3]. Both patients suffered from an advanced tumor of the mouth, progressive after previous therapies. The carboplatin solution was taken by the patients on an empty stomach: patient 1 received three oral doses of 300 mg/m^2 on 3 consecutive days; patient 2 received 300 mg/m^2 orally on day 1 and 187.5 mg/m^2 i.v. on day 2.

Clinical effects. A few hours after taking the carboplatin solution, both patients experienced nausea and several episodes of vomiting (WHO toxicity grade 2) over a period of 3–9 h after administration. Bone marrow suppression was not observed in the first patient, who received carboplatin orally (300 mg/m^2 daily $\times 3$). Late toxicity due to the oral administration of carboplatin could not be studied in patient 2, because of the i.v. administration of the drug on the 2nd day.

Pharmacokinetics. The concentration vs time curves of Pt, free Pt, and carboplatin in patient 1 are shown in Fig. 1. In both patients, peak levels of Pt, free Pt, and in patient 1, of carboplatin, were reached between 3.5 and 4 h after administration. These peak levels were 3.5, 3.2, and 2.9 μmol/l in patient 1, and 3.1 and 2.4 μmol/l in patient 2, respectively. Repeated oral administration of carboplatin on 2 subsequent days in patient 1 resulted in similar Pt peak values of 4.0 and 3.0 μmol/l, respectively.

Pt could be measured over at least 5 days after the third administration in patient 1. Free Pt was detectable until 24 h after each administration in patient 1 and until 11 h postadministration in patient 2. Carboplatin was detectable over the initial 9 h after the first administration in patient 1. The terminal half-life of Pt, calculated over days 1–5 after the last administration in patient 1, was 4.1 days. AUCs$^\infty$ (min × μmol/l) as calculated by the trapezoidal rule were 4104 and 4156 for Pt and 2131 and 790 for free Pt in patients 1 and 2, respectively, and 1538 for carboplatin in patient 1.

The AUCs after the oral administration of carboplatin were compared with those previously obtained from four other patients after i.v. administration [4]. Their AUC$^\infty$ values were normalized to a dose of 300 mg/m^2 (actual dose range, 280–400 mg/m^2). The mean values of these normalized AUCs$^\infty$, as used for the calculation of bioavailability, were 95241, 18160, and 15587 min × μmol/l for Pt, free Pt, and carboplatin, respectively. Bioavailabilities of Pt were 4.3% and 4.4%, and of free platinum, 11.7% and 4.4%, for patients 1 and 2, respectively. The bioavailability of carboplatin. as measured in patient 1, was 9.9%.

Pt and parent carboplatin were also determined in the urine. The bioavailabilities calculated from the CUE over the first 6 h after drug administration were 2.9 and 5.0% for Pt and 3.9 and 4.8% for carboplatin in patients 1 and 2, respectively. In patient 2 the bioavailability was also calculated from the CUE over 24 h. The values were 7.8% for Pt and 4.0% for carboplatin.

In this pilot study it was evident that an oral dose, in the range of those used for the i.v. route, caused at least the same acute gastrointestinal side effects as i.v. administration. It is not unlikely that these observed gastrointestinal effects are partly the result of local effects of carboplatin on the mucosa. In the two patients studied, plasma concentrations of Pt and free Pt were similar, indicating that only a limited amount of carboplatin is bound to proteins. In patient 1, the peak plasma concentration of the parent drug was also close to that of free and total Pt peak plasma concentrations, which means that the structure of

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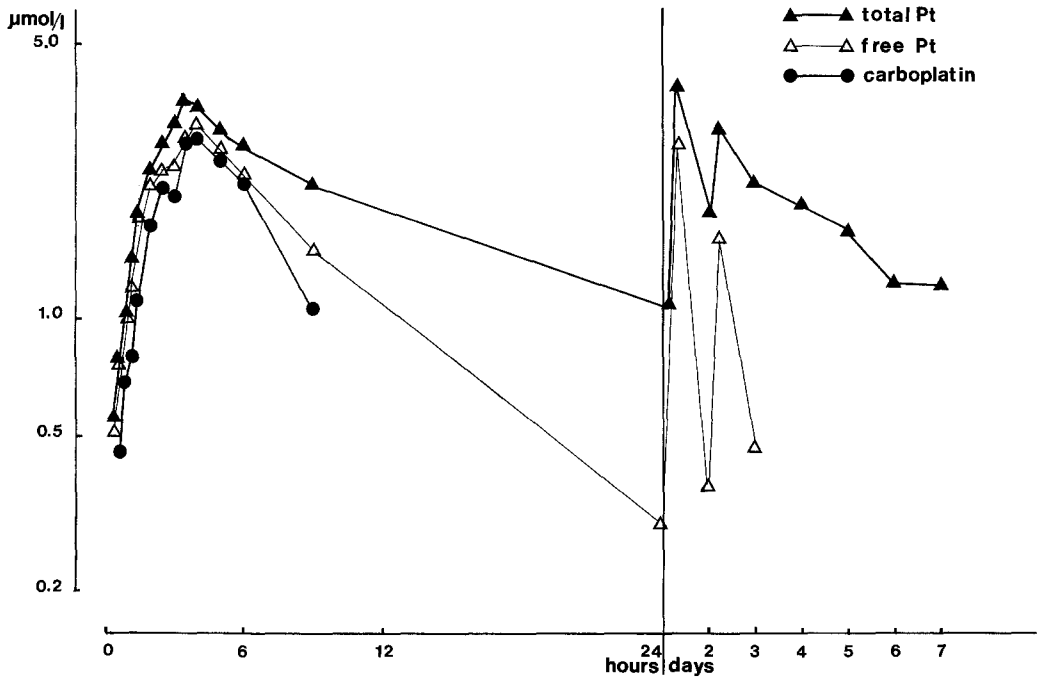

Fig. 1. Concentration vs time curves of total platinum, free platinum, and carboplatin after oral administration of 300 mg/m^2 carboplatin at days 1, 2, and 3 in patient 1

carboplatin remained intact during absorption from the GI tract. This finding is in accordance with the chemical stability of the drug.

It can be concluded that the very low bioavailability of free Pt and parent carboplatin, in combination with the observed gastrointestinal side effects, does not warrant further studies with orally administered carboplatin.

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