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LETTER TO THE EDITORS

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Cerebrospinal fluid concentrations of carboplatin in a patient without blood-brain barrier disruption

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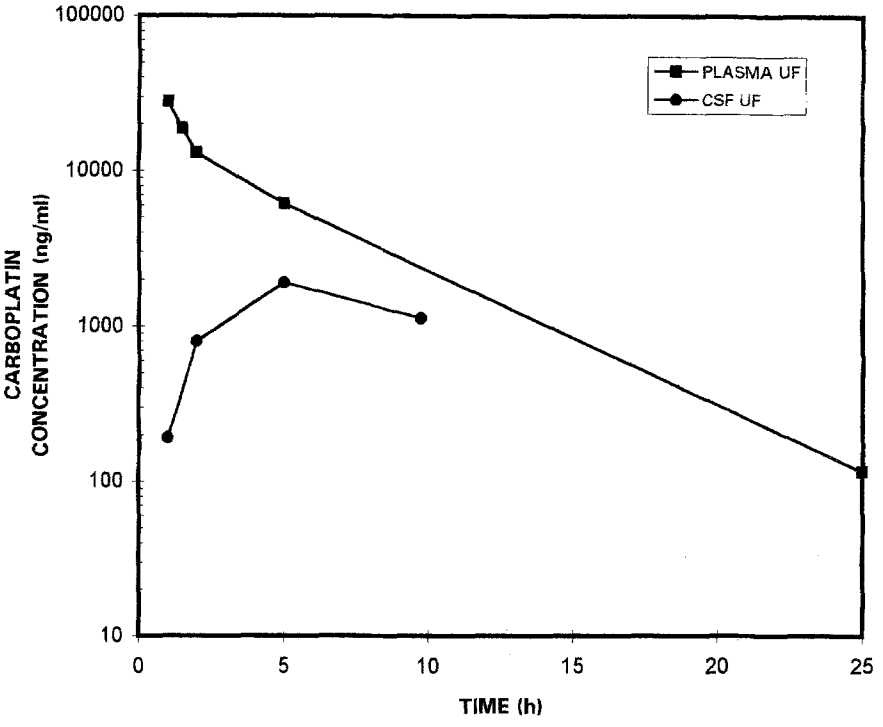

Fig. 1 Time course of plasma and CSF ultrafilterable carboplatin concentrations as determined in a 73-year-old women without blood-brain barrier damage

Sirs,

Carboplatin is an antineoplastic agent with the same spectrum of activity as cisplatin but with very different toxicological properties: carboplatin is less nephrotoxic but more myelosuppressive, especially in terms of thrombocytopenia [2, 4]. Thus, carboplatin can be an alternative treatment for elderly patients, patients with impaired renal function, or patients with cisplatin-induced toxicity. We report herein a pharmacokinetics study of carboplatin in cerebrospinal fluid and plasma in a patient without any blood-brain barrier damage.

In July 1993 a urothelial cancer with paravertebral extramedullary dorsal metastases was diagnosed in a 73-year-old woman. On admission, the physical examination was normal in view of her age and no other metastatic dissemination was observed. Because of the complaints of the patient, the first treatment was dorsal irradiation (30 Gy), resulting in a partial response. After 5 months, progression at the paravertebral dorsal metastatic site required the implantation of a lumbar catheter for administration of morphine chlorhydrate (2 mg per day). The metastatic site remained extraspinal, and the cerebrospinal fluid (CSF) values were close to normal (0.8 g/l protein without malignant cells). Then the patient received combination therapy with methotrexate (30 mg/m^2), vinblastine

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(4 mg/m^2), and carboplatin. The carboplatin dose was calculated according to the Calvert formula [3] with a target AUC of 5 mg ml^{-1} min and the patient received a total dose of 415 mg carboplatin given as a 1-h i.v. infusion. A pharmacokinetics study was performed over 24 h after the end of the infusion in the plasma; because of ethical reasons, the CSF could be studied for only 8.75 h after the end of the infusion.

Plasma and lumbar CSF ultrafilterable fractions were prepared immediately after sampling, and platinum concentrations were determined by flameless atomic absorption spectrophotometry. The time course of plasma and CSF ultrafilterable carboplatin concentrations are shown in Fig. 1. The peak concentrations of carboplatin in plasma and CSF were 27.6 and 1.9 μg/ml, respectively. Although plasma carboplatin levels fell rapidly after the completion of carboplatin administration, CSF concentrations increased to reach a maximum at between 1 and 4 h after the end of the infusion and remained significant for 10 h. The ratio of CSF AUC/plasma AUC was 0.16 from 0 to 9.75 h and 0.2 from 0 to infinity (CSF AUC extrapolation = 30%); these data, obtained in a patient with an intact blood-brain barrier, were comparable with those previously described for patients with blood-brain barrier disruption due to brain tumor but without meningitis [5]. The CSF/plasma ratio observed at the end of the infusion was 0.007; this value was lower than those previously described [5, 8]. By contrast, this ratio reached 0.31 at 4 h after the completion of the infusion, which was much larger than the reported values obtained in samples collected from the ventricular area (<0.02) [8]. It seems that in the lumbar subarachnoid space, concentrations of carboplatin reached the maximal value later but remained significant for a longer period than they did in the ventricles; indeed, it has been established that the flow of lumbar fluid is slower than that of ventricular fluid, which rapidly leaves the ventricles and circulates within the subarachnoid space [6, 7].

Finally, carboplatin crossed through the blood-brain barrier more extensively than did cisplatin; after an injection of 80 mg/m^2 cisplatin, the CSF maximal concentration was 10-fold lower than that shown in our study [1]. Carboplatin seems to have a pharmacological advantage over cisplatin for the treatment of primary or secondary brain tumors.

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