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Letter to the Editor

Pharmacokinetics of Brequinar Sodium (NSC 368390; DUP 785) in Cerebrospinal Fluid

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BREQUINAR SODIUM (NSC 368390; DUP 785) is a novel 4-quinoline carboxylic acid derivative which completed phase I trials within the framework of the Early Clinical Trials Group (ECTG) of the European Organization for Research and Treatment of Cancer (EORTC). This compound inhibits the mitochondrial enzyme dihydroorotate dehydrogenase, which catalyzes the fourth biochemical step in the pyrimidine *de novo* pathway [1–3].

The preliminary results of a pharmacokinetic study of Brequinar sodium in plasma, urine and feces of patients with solid tumors who received the drug by a 3-weekly schedule were reported elsewhere [4]. We describe the case of a patient in whom Brequinar sodium was studied concomitantly in plasma and cerebrospinal fluid (CSF).

The patient was a 57-year-old caucasian man with the diagnosis of metastatic adenocarcinoma of the nasal cavity. Brequinar sodium was given to the patient as a 1-h intravenous (i.v.) infusion every 3 weeks at a dose of 1200 mg/m^2. Plasma samples were collected for pharmacokinetic purposes during the first chemotherapy course. Up to day 3, a tri-phasic decay in the plasma drug concentrations was observed (Fig. 1). Subsequent half-lives were 11.6 min, 187.9 min and 25.0 h, respectively. The peak drug concentration in plasma was 421.4 μg/ml at the end of infusion; the area under the plasma concentration–time curve (AUC$^\infty$) was 2531.1 μg/h/ml and the total body clearance was 15.8 ml/min.

By that time, an intraspinal port-a-cath device was inserted for chronic intrathecal morphine therapy. The second chemotherapy course was given on day 22 and samples for pharmacokinetics were collected both from plasma and CSF.

Brequinar sodium was extracted from the plasma and CSF in dichloromethane after the addition of an ion-pairing agent, tetrabutylammonium chloride; and the samples were analyzed by HPLC as described previously [4].

Although the patient was sampled from 0 to 168 hrs, Brequinar sodium could be detected in the CSF from 3 h after the completion of drug infusion ([Breq.]$_{CSF}$ = 0.9 μg/ml, CSF/plasma ratio = 0.008) until 24 h ([Breq.]$_{CSF}$ = 1.8 μg/ml, CSF/plasma ratio = 0.12) (Fig. 1). Brequinar sodium reached its highest concentration in the CSF at 11 h after drug administration ([Breq.]$_{CSF}$ = 2.2 μg/ml, CSF/plasma ratio = 0.07).

This is the first time that the pharmacokinetics

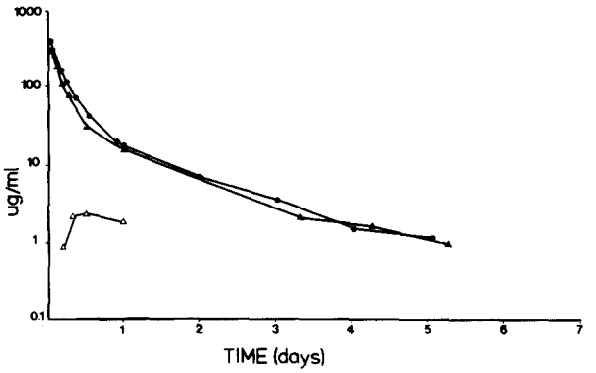

Fig. 1. Semilogarithmic concentration vs. time plot of Brequinar sodium in a patient who received the drug as a 1-h *i.v. infusion at a dose of* 1200 mg/m^2 [*plasma levels during the first chemotherapy course* (●); *plasma* (▲) *and CSF* (△) *levels during the second chemotherapy course*].

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of Brequinar sodium have been studied in the CSF of man. Preclinical studies have shown that the drug penetrates poorly through the blood–brain barrier [5]. In mice, the brain/plasma concentration ratio after i.v. administration of ^{14}C-labelled Brequinar sodium was much lower than the ratio for ther tissues except for the testis (brain/plasma ratios of 0.02, 0.03 and 0.04 at 1, 6 and 24 h after i.v. injection, respectively).

In the case of our patient, the levels of Brequinar sodium in the CSF were relatively low (0.9–2.2 μg/ml) compared to *in vitro* growth-inhibitory drug concentrations (1–10 μg/ml) [1–3]. However, the dose given to this patient during the phase I trial was 2/3 of the recommended dose for this risk-group in phase II trials by that schedule [4]. Moreover, as observed previously, the non-linear pharmacokinetics of Brequinar sodium could also lead to an extra increase of CSF levels at the recommended dose compared to that given to this patient [4]. Therefore, it would be useful to determine the range of drug concentrations in the CSF to be achieved in patients who enter phase II trials of Brequinar sodium in order to determine its potential usefulness for the treatment of malignant diseases in the central nervous system.

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