Human pharmacokinetics of 1-[2-[2-(4-pyridyl)-2-imidazolinyl-(1)]-ethyl]-3-(4-carboxyphenyl) urea (CGP 15720A)

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Summary

Pharmacokinetics of CGP 15720A have been studied in patients receiving this drug in a short I.V. infusion during its phase I clinical trial. Plasma decay was biphasic with a mean $t_{1/2}$ of 4.9 ± 2.47 h. The drug was cleared rapidly from plasma (7.02 ± 5.95 L/h). Renal clearance (4.13 ± 1.65 L/h) appears to be the major clearance pathway. The steady state volumes of distribution of the drug indicate limited tissue distribution for the drug. Studies with plasma and urine of patients receiving $^{14}$C GCP 15720A indicate that the drug is not metabolized. CGP 15720A could be measured in cerebrospinal fluid.

Introduction

CGP 15720A (1-[2-[2-(4-pyridyl)-1-imidazoline-1-yl]-ethyl]-3-(4-carboxyphenyl) urea) (Fig. 1), a new antineoplastic agent synthesized by Ciba-Geigy, (Pharmaceutical Research Dept., Ciba-Geigy Ltd., Basel, Switzerland) has just finished its Phase I clinical trial at our Institute (1). In preclinical testing it showed activity against diethyl nitroamine induced papillary, epidermoid, and adeno-carcinomatous tumors of the respiratory system in Syrian hamsters and was active against human epidermoid and anaplastic carcinomas transplanted into nude mice (2). However, no information is available on its pharmacokinetics in animals and no method was available for its detection in biological fluids. In this paper we report the development of such a method and the results of a study of the human pharmacokinetics of this drug carried out during its phase I clinical trial.

Materials and methods

Pharmacokinetics were studied over the first 24h after a short (2–4h) intravenous infusion of 0.5, 1, 2, or 3 g/m$^2$/day. The plasma decay was studied in 17 patients, urinary excretion in 16 patients and CSF levels in 2 patients. One patient was studied for 48h after the fifth daily dose of 3 g/m$^2$/day. Five patients receiving continuous infusion of CGP 15720A at 6 g/m$^2$/day for 5–7 days were studied for steady state plasma levels of the drug. Four pa-
Patients received $^{14}$C CGP 15720A (250 μCi) in a single dose (2–3 g/m$^2$) in a 3–4 h I.V. infusion. Plasma decay and urinary excretion of radioactivity and unchanged drug were studied in these patients.

Blood (approximately 5 ml) was collected before the start of the infusion, at mid-infusion and at 0.016, 0.033, 0.08, 0.166, 0.5, 1.0, 2.0, 4.0, 6.0, 12.0, 18.0 and 24 h after the end of drug infusion. Urine was collected every 4 h on the first day and in 24 h pools on subsequent days. In 2 patients who consented to the additional procedures a spinal tap was performed, at 0.5 h in one and 2 h in the other, after the end of infusion of the drug and CSF collected.

Sample preparation

Blood: The blood samples from patients were centrifuged immediately to obtain plasma, which was ultrafiltered immediately at 4°C using Amicon CF25 centrifugal ultrafilters to obtain protein-free plasma. A 5–10 μl sample of plasma ultrafiltrate (PUF) containing CGP 15720A was analyzed by high performance liquid chromatography (HPLC). If the PUF was not assayed immediately for CGP 15720A it was kept frozen until the time of analysis.

Urine: Urine samples were kept frozen until the time of analysis. Urine was processed as follows: 0.5 ml of urine was passed through a Seppak C18 cartridge (Waters Associates), the cartridge washed with 8 ml of 10% methanol in 2.5 mM potassium phosphate buffer (pH 7.0), the void volume and the Seppak eluate pooled and a 5–10 μl volume of this processed urine injected into HPLC.

CSF: No preprocessing was done for CSF.

Analytical methodology

CGP 15720A was separated by HPLC and quantitated by UV detection at 254 nm. The HPLC system consisted of two M6000A pumps, 440 UV detector, an automatic sample injector (WISP) and a Model 720 system controller (Waters Associates). For PUF containing CGP 15720A, and the CSF, the separation was carried out isocratically, with 20% methanol in 2.5 mM potassium phosphate buffer as the mobile phase, on a Waters Associates

Fig. 2. HPLC of plasma from a patient before (A) and after (B) administration of CGP 15720A. Arrow indicates the drug.

μ Bondapak phenyl column (30 cm, 10 μm particle size). Plasma standards were prepared by adding known amounts of CGP 15720A to plasma and subjecting them to ultrafiltration. At a mobile phase flow rate of 1 to 1.5 ml/min CGP 15720A has a retention of approximately 4.5 to 6 min and is well resolved from the other components in plasma (Fig. 2). Separation of CGP 15720A in CSF is shown in Fig. 3. The separation of CGP 15720A in urine was carried out either by the isocratic procedure described above or a gradient elution procedure. For gradient elution, the initial solvent was 10–15% methanol in 2.5 mM phosphate buffer (pH 7.0), the final solvent was 50% methanol in 2.5 mM potassium phosphate buffer, the run time was