Plasma Concentrations of Carminomycin and Carminomycinol in Man, Measured by High Pressure Liquid Chromatography*

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Abstract—In 9 patients with advanced malignant disease who received carminomycin (CMM) in an i.v. bolus injection (dose 18 mg/m²), curves of plasma concentrations of CMM and carminomycinol (CMMOH), a metabolite, versus time were constructed. For determination of plasma concentrations, high pressure liquid chromatography was used. For CMM and CMMOH the median areas under the curves (AUC's) were 31 (range 4–57) × 10⁻⁸ mol/l/hr (measured over 24 hr) and 100 (range 30–158) × 10⁻⁸ mol/l/hr (measured over 48 hr) respectively. From the data an accumulation of CMMOH in patients receiving treatments separated by brief intervals can be predicted (half-life time of plasma disappearance for CMMOH was 2 days). Clinical toxicity was lowest in those 3 patients showing the lowest AUC for both CMM and CMMOH.

INTRODUCTION

CARMINOMYCIN (CMM) is one of a group of new anthracyclines. It was developed with a view to minimising cardiac toxicity while maintaining the antitumor potency of adriamycin [1]. A pharmacokinetic study was designed to find out more about the pharmacology and toxicology of the analogue CMM while it was undergoing phase II trial in patients. The first requirement for pharmacokinetics is a drug assay, and so we have used a high-pressure liquid chromatography assay described by Fandrich and Pittman [2] for the determination of CMM and carminomycinol (CMMOH), a metabolite of CMM. They showed plasma concentrations of one patient after receiving CMM. The CMMOH:CMM plasma concentration ratio was 10, measured 24 hr after injection. As CMMOH is reported to show antitumor activity in mice [3], pharmacokinetic studies are necessary in more patients.

Our assay method was modified in several ways, most importantly leading to reduction in the sample clean-up time. Plasma samples were obtained from cancer patients whose sub-

sequent drug-related toxicity and antitumor response were closely documented, thus affording possibilities for clinical pharmacological analysis.

MATERIALS AND METHODS

CMMOH was kindly provided by Bristol Laboratories (Syracuse, NY, U.S.A.) and 4'-epi-adriamycin (4'-epi-ADM) by Farmitalia (Milan, Italy). For injection, CMM (vials from Bristol containing 10 mg CMM + 20 mg mannitol) was dissolved in 20 ml glucose (5%). Heparinized blood (4 ml) was collected for each sample and centrifuged within 10 min. Plasma samples were stored at -20°C.

Sample clean-up and chromatographic conditions

4'-Epi-ADM was added to plasma as an internal standard for the assay (final concentration, 4.3 × 10⁻⁷ M). Plasma samples were kept in ice prior to extraction. Plasma (1 ml) was vortexed carefully with 5 ml of a mixture of isopropanol/chloroform (1:4, v/v). The organic layer was removed and evaporated to dryness within 20 min with air at 35°C. The plasma was extracted with another 5 ml of organic solvent. The residue was dissolved in 150 µl of methanol. The use of eluent in place of methanol resulted in a turbid solution. Of this

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