PHARMACOKINETIC STUDIES WITH THE CANCER CHEMOTHERAPEUTIC AGENT CISPLATIN

T.S.Gill, D.K.Luscombe, K.James*, R.G.Fish*, Welsh School of Pharmacy, UWIST, and *Department of Biochemistry, Velindre Hospital, Cardiff.

Cisplatin (cis-dichlorodiammineplatinum II) is the first member of a new class of cancer chemotherapeutic agents, the metal coordination complexes. It is believed to represent a major advance in the treatment of some solid tumours in man, being used either as a single agent or in combination with other cytotoxic drugs (Prestayko et al 1979). Structurally cisplatin is a square planar coordination complex containing a central platinum atom surrounded by two chloride atoms and two ammonia moieties, the anticancer activity being much greater when the chloride and ammonia moieties are in the cis-position. Despite its wide clinical use, information on its pharmacokinetic properties is limited. For this reason, we have carried out pharmacokinetic studies in patients with advanced malignant disease who were receiving intravenous infusions of cisplatin.

Nine patients, aged 18 - 35 years, with teratoma of the testes entered the study. Treatment consisted of four i.v. infusions of cisplatin administered at three-weekly intervals. The dose on each occasion was 100 mg/m^2 being infused over a 6h period. Vinblastine (7 mg/m^2) was also administered as a bolus at the start of each cisplatin infusion and 18h post-infusion. Bleomycin (30 mg) was given i.m. at 18h post-infusion and on days 7 and 14. Blood was collected during each infusion and at intervals for up to 21 days. Urine was also collected from some patients during the 6h infusion period and for the following 18h. Plasma and urine samples were assayed for platinum using a modification of the atomic absorption spectrophotometry method described by Bannister et al (1978). The method was initially confirmed as being reliable with a between run reproducibility of $\pm$ 5 per cent. The lower limit of sensitivity of platinum in plasma and urine was found to be 0.1 μg/ml.

Following the first exposure to cisplatin, peak plasma concentrations of platinum ranged from 2.01 - 2.78 μg/ml at completion of the infusion. Steady state plasma levels of platinum were not achieved during the infusion period. Following a short lived rapid decline in platinum plasma levels, probably representing distribution of the metal complex, plasma levels diminished in a biphasic manner being still detectable after 14 days. The mean plasma elimination half-lives for two phases were 41h (range 34 - 46h) and 174h (range 132 - 240h). Three weeks later a mean plasma concentration of 2.64 μg/ml was observed immediately after completion of the second cisplatin infusion. This compared with mean levels of 2.46 and 2.20 μg/ml following completion of the third and fourth infusions of cisplatin. Mean plasma half-lives for the two phases of elimination following the second, third and fourth exposures to cisplatin ranged from 27 - 44h and 177 - 228h. Urinary data indicated that 11 - 28 per cent of the administered platinum is excreted by the kidney within a 24h period.

It is concluded that following intravenous infusions of cisplatin, platinum is cleared from the plasma in a biphasic manner, the elimination half-lives being relatively long. It appears that the pharmacokinetic characteristics of platinum are not markedly changed on repeated infusion of cisplatin.

Bannister, S.J. et al (1978) Clin. Chem. 24: 877 - 880
Prestayko, A.W. et al (1979) Cancer Treat. Rev. 6: 17 - 39

TSG is supported by a Pharmaceutical Society Leverhulme Scholarship

0022-3573/81/120044P-01$02.50/0