J. Pharm. Pharmacol. 1982, 34: 826
Communicated June 9, 1982

0022–3573/82/120826–01 $02.50/0

Intact cisplatin in urine following intravenous infusion

C. M. RILEY, L. A. STERNSON, A. J. REPTA*, S. J. BANNISTER, *Department of Pharmaceutical Chemistry, The University of Kansas, Lawrence, KS 66045, U.S.A.*

Although the clinical pharmacokinetics of intact cisplatin in plasma have been investigated (Patton et al 1982), and recently information on total platinum excreted in urine has been reported (Gill et al 1981), there are no data available on the elimination of intact cisplatin in urine. In view of the use and effectiveness of cisplatin in the treatment of bladder cancer, information of this type appeared to be desirable. Consequently, this study was undertaken and preliminary findings are presented here.

Method

The analytical procedure involved separation by high performance liquid chromatography (employing a solvent generated anion exchanger and column switching (Riley et al 1982)) and detection/quantitation by either off-line flameless atomic absorption (FAAS) or on-line polarography. Both methods of detection gave comparable results but the polarographic detector provided minimum detection limits of about 100 ng cisplatin ml^{-1} of urine which was about an order of magnitude better than that obtained by off-line FAAS. The standard deviations of replicate analyses was about ±5%. The total platinum concentration in the urine was determined directly by FAAS after appropriate dilution of the samples.

For two testicular cancer patients, the clinical protocol involved hydration of the patient with 1 litre of 0·45% NaCl-5% dextrose containing 12·5 g of mannitol together with the administration of vinblastine sulphate (5 mg m^{-2}) by i.v. infusion, before the administration of cisplatin. Cisplatin (50 mg m^{-2}) was then administered as an i.v. infusion (ca 1 mg min^{-1}). The urine samples were collected (voluntary voiding) at various times over 24 h following completion of the infusion of the drug. The urine volume was noted and samples were frozen, maintained at ca −60 °C, and analysed within 48 h. Such handling of samples was found necessary to maintain the stability of cisplatin.

Three ovarian cancer patients were treated similarly except that they all received cyclophosphamide (600 mg m^{-2}) in the prehydration fluid instead of vinblastine. Urine was collected (voluntary voiding) at 30 min only after completion of the cisplatin infusion.

Results and discussion

In all five patients studied, it was found that of the total platinum excreted in the first hour after administration of cisplatin, ≥90% was in the form of the intact drug. During this initial period, 14 to 19% of the total administered drug was excreted and the concentrations of intact cisplatin ranged from 16 to 90 μg ml^{-1} which is 5 to 10 times the levels reported in plasma following dosing with cisplatin (Patton et al 1982).

Furthermore, from the data obtained from the testicular cancer patients whose urine was monitored for ca 8 h in one case, and 24 h in the other, it appeared that the ratio of intact drug to total platinum decreased rapidly with values closely resembling those found in human plasma (Himmelstein et al 1981). From these same two patients, it was found that about 30% of the administered dose had been excreted in the urine within 8 h after completion of the infusion. At ≥8 h the ratio of cisplatin/total platinum was nearly zero.

These data indicate that all five patients behaved similarly in their urinary excretion of cisplatin and total platinum. Additionally it appears that very high concentrations of cisplatin are present in the bladder following infusion of the drug and that the preponderant fraction of the administered drug excreted in the first hour or two after administration is intact cisplatin.

In view of the high levels of intact drug in the urine, it seems possible that the chemotherapeutic response of cisplatin in recurrent bladder cancer may be due to locally high concentrations of the drug in contact with the bladder wall rather than its perfusion of bladder tissue by the general circulation to the bladder. If such is the case, for treatment of superficial bladder cancer, intravesicular instillation of cisplatin solutions might achieve therapeutic effects similar or superior to those achieved by systemic administration while avoiding or reducing some of the renal and gastrointestinal toxicities accompanying i.v. dosing. Further investigations of this hypothesis appear to be warranted.

Supported in part by the American Chemical Society Grant No CH 149 and NIH Grant No CA 24834.

* Correspondence.

REFERENCES

Gill, T. S., Luscombe, D. K., James, K., Fish, R. G. (1981) J. Pharm. Pharmacol. Suppl. 33: 44P

Himmelstein, K. J., Patton, T. F., Belt, R. J., Taylor, S., Repta, A. J., Sternson, L. A. (1981) Clin. Pharmacol. Ther. 29: 658–664

Patton, T. F., Repta, A. J., Sternson, L. A., Belt, R. J. (1982) Int. J. Pharm. 10: 77–85

Riley, C. M., Sternson, L. A., Repta, A. J. (1982) J. Chromatogr. Biomed. Appl. 229: 373–391