Dose-dependent pharmacokinetics of prednisone and prednisolone in man

J. C. K. Loo*, I. J. McGilveray, N. Jordan, J. Moffat, R. Brien, *Drug Research Laboratories, Health Protection Branch, Health and Welfare Canada, Ottawa, Ontario, Canada*

Recently, Pickup, Lowe & others (1977) demonstrated that the plasma clearance was elevated with increasing intravenous doses of [^{3}H]prednisolone phosphate. We have observed similar dose-dependent pharmacokinetics of prednisone and its active metabolite prednisolone following oral administration of prednisone in humans.

Eight normal healthy male volunteers participated in the study, during which each subject received oral doses of 10 or 20 mg prednisone in 5% aqueous ethanol according to a cross-over design. Plasma samples, obtained at 0·25, 1, 2, 3, 4, 6, 8 and 12 h post administration, were evaluated for prednisone and prednisolone content by a radio-immunological assay which incorporated a procedure (Loo, Vilim & others, 1976) to remove interfering endogenous cortisol. The specificity of the assays was confirmed by high performance liquid chromatographic procedure. (Loo, Butterfield & others 1977; Loo & Jordan, 1977).

The results presented in Table 1 include the mean areas under the plasma drug concentration *vs* time curve to 12 h normalized to 10 mg dose (AUC) and the mean clearance values (Cl) from the present study together with those reported by Pickup & others (1977). The AUC for prednisolone for the 20 mg dose was 77·8% of that for the 10 mg dose (significant $P = 0·05$) and the corresponding AUC for prednisone for the high dose was 87·6% that of the low dose (significant $P = 0·10$). The mean clearance values of prednisolone for the 20 mg dose (0·134 mg kg^{-1}) and 10 mg dose (0·268 mg kg^{-1}) were 0·10 and 0·13 litres kg^{-1} respectively. These apparent clearance values which are in good agreement with those reported by Pickup & others (1977), indicate that the dose-dependent effect occurs following oral administration of prednisone. As noted by the previous authors, it is probably a binding effect.

June 9, 1978

* Correspondence.

Table 1. *The mean ($n = 8$) normalized area under plasma drug concentration (AUC) vs time curve and mean plasma clearance (Cl).*

	Mean dose	AUC* Prednisone	R**	AUC Prednisolone	R**	Cl prednisolone ***
	mg kg^{-1}	(ng ml^{-1}) ×h	%	(ng ml^{-1}) ×h		(litres kg^{-1}) ×h
This study using prednisone oral dose	0·134	293·4	100	1295	100	0·10 ±0·012
	0·268	257	87·6 (P=0·10)	1008	77·2 (P=0·05)	0·13 ±0·017 (P=0·05)
Study by Pickup, & others (1977)	0·15	—	—	—	—	0·09
	0·30	—	—	—	—	0·12

*AUC = $\int_0^{12}$ drug concn dt × $\frac{\text{Dose}}{10\text{ mg}}$ expressed in (ng ml^{-1}) ×h.
AUC was derived by the use of the trapezoid rule.

**R = $\frac{\text{(AUC) for 10 mg}}{\text{(AUC) for 20 mg}} \times 100\%$

***Cl = mean apparent plasma clearance and for comparative purposes the values from our study were derived from the following equation:

$$Cl = (\text{Dose}/\text{AUC})\ \text{kg}^{-1}$$

Where dose is equal to dose of prednisone it is assumed that prednisone is completely converted to prednisolone.

REFERENCES

Loo, J. C. K., Vilim, A. B., Jordan, N. & Moffatt, J. C. (1976). *J. pharm. Sci.*, **65**, 461.

Loo, J. C. K., Butterfield, A. G., Moffatt, J. & Jordan, N. (1977). *J. Chromat.* (*Biomedical Application*), **143**, 275–280.

Loo, J. C. K. & Jordan, N. (1977). *Ibid.*, **143**, 314–316.

Pickup, M. E., Lowe, J. R., Leatham, P. A., Rhind, V. M., Wright, V. & Downie, W. W. (1977). *Eur. J. clin. Pharmac*, **12**, 213–219.