Relative bioavailability of prednisone and prednisolone in man

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The synthetic corticosteroids prednisone and prednisolone are both used internally for their anti-inflammatory activity in a wide spectrum of diseases. Prednisone is pharmacologically inactive until reduced at the 11-keto position to form prednisolone by the enzyme 11-β-hydroxydehydrogenase (Jenkins & Sampson 1967; 1967; Lewis et al 1971). The most important site for this conversion is the liver (Jenkins 1966; Powell & Axelsen 1972).

Although hepatic conversion of prednisone to prednisolone is extensive and the two compounds are generally considered to be therapeutically equivalent when used systemically, there is little quantitative information on the relative bioavailability of active prednisolone from the two drug forms. One report showed that orally dosed prednisone resulted in lower circulating prednisolone concentrations compared with equivalent oral doses of prednisolone in three normal subjects, although similar concentrations of prednisolone were obtained from the two drug forms in two patients with liver disease (Jenkins & Sampson 1966). A second report describes significantly lower circulating concentrations of prednisolone in 22 patients with liver disease receiving prednisone, than in the same patients receiving prednisolone, but no differences after dosing the two drug forms in normal subjects (Jenkins 1966).

A case of therapeutic inequivalence between prednisone and prednisolone has been reported (Levy et al 1964), although it is uncertain whether the inequivalence was due to poor bioavailability of the prednisone formulation or inability of the patient to metabolize prednisone (Sugita & Niebergall 1975).

This communication describes a pilot study comparing the bioavailability of commercial brands of prednisone and prednisolone in a human subject.

Methods. The subject, a healthy 42 year old male weighing 77 kg with normal liver and kidney function, received single oral doses of 30 mg (6 × 5 mg tablets) of prednisolone (Delta-Cortef, Upjohn) or 30 mg (6 × 5 mg tablets) of prednisone (Prednisone U.S.P., Phillips Roxane). Two single doses of each drug were given, alternating prednisolone and prednisone, at approximately two weeks apart. Tablets were administered at 8 a.m. on an empty stomach (overnight fast) with 200 ml of water. Serial venous blood samples were taken and plasma prednisolone was measured using the gas-chromatographic method of Bacon & Kokenakes (1969), with slight modifications (Tse & Welling 1977).

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Plasma data were fitted to the pharmacokinetic one compartment open model (Welling et al 1975), incorporating a lag time, t_0, representing the time interval between dosing and the appearance of measurable prednisolone in plasma.

Results. Plasma prednisolone concentrations resulting from the two dosage forms are summarized in Fig. 1. Results of pharmacokinetic analysis are given in Table 1.

From Fig. 1, the time course of the plasma prednisolone profiles are similar after dosing prednisolone and prednisone, but plasma values obtained were much higher during the first 4 h after dosing with prednisolone. Peak values from the two prednisolone doses were 0·65 and 0·55 μg ml^{-1} compared with 0·45 and 0·35 μg ml^{-1} from prednisone, although peaks occurred at similar times from all doses.

The similar values of k, $t_{1/2(abs)}$ and t_0 after prednisolone and prednisone doses confirm earlier reports that both compounds tend to be absorbed rapidly and that conversion of prednisone to prednisolone is almost instantaneous (Jenkins 1966; Sugita & Niebergall 1975). The different dosage forms also had no influence on the rate of prednisolone elimination from plasma. However, although statistical comparison is not possible from these limited data, the calculated values for FD/V and AUC^{∞} indicate either that prednisone is not absorbed as efficiently as prednisolone from the gastrointestinal tract, or that conversion of prednisone to prednisolone in the healthy liver does not go to completion, or both of these. The ratio of the averaged FD/V values from prednisone doses to those from prednisolone doses is 0·61.

Comparison between the present study and previous studies on prednisone and prednisolone bioavailability is difficult. Of the two studies cited, one used different

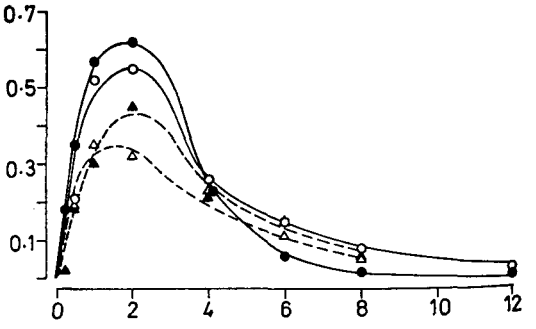

FIG. 1. Plasma concentrations of prednisolone (ordinate: μg ml^{-1}) after oral doses of 30 mg prednisolone. (●, run 1; ○, run 2) or prednisone (▲, run 1; △, run 2). The curves are computer-derived. Abscissa: time (h).

Table 1. Pharmacokinetic parameter values obtained from plasma prednisolone levels after oral doses of 30 mg prednisolone or prednisone.

Parameter	Prednisolone dose		Prednisone dose	
	Run 1	Run 2	Run 1	Run 2
k^a (h^{-1})	1·07	1·90	0·91	2·13
$t_{1/2}$(abs)[b](h)	0·65	0·36	0·76	0·33
K^c(h^{-1})	0·54	0·35	0·42	0·28
$t_{1/2}$(elim)[d](h)	1·28	1·98	1·65	2·48
t_0^e(h)	0·12	0·35	0·22	0·26
FD/V^f(mg litre^{-1})	1·25	0·85	0·79	0·49
$AUC^{\infty g}$(mg h litre^{-1})	2·31	2·43	1·88	1·75
AUC_{trap}[h](mg h litre^{-1})	2·33	2·50	1·90	1·72
r^{2i}	0·994	0·998	0·984	0·996

a: Apparent first-order rate constant for appearance of prednisolone in plasma.
b: Apparent half-time of appearance of prednisolone in plasma (1n2/k).
c: First-order rate constant for prednisolone elimination from plasma.
d: Biological half-life of prednisolone in plasma (1n2/K).
e: Lag time.
f: Fraction F of dose D absorbed expressed as concentration in its distribution volume V.
g: Area under prednisolone plasma concentration versus time curve from zero to infinite time (FD/VK).
h: Area under plasma concentration versus time curve obtained by trapezoidal rule.
i: Coefficient of determination for degree of fit of data to the proposed model $((\Sigma obs^2-\Sigma dev^2)/\Sigma obs^2)$.

commercial sources of drugs from those used by us (Powell & Axelsen 1972), while the other did not disclose the source of the drugs (Jenkins & Sampson 1966, 1967). The different results obtained in the studies could well have been due to formulation factors. However, formulation is not likely to be a significant factor in the present study, with prednisone consistently yielding only 75% of the AUC^{∞} of prednisolone dose. Previous investigators (Sullivan et al 1974; 1975; DiSanto & DeSante 1975) have shown that, whereas formulation differences often result in variations in absorption parameters such as k, $t_{1/2(abs)}$, lag time, peak levels and peak time, their effect on AUC^{∞} values are relatively insignificant.

Despite the small differences in our results, it is becoming evident that oral prednisone will tend to produce lower circulating concentrations of prednisolone than prednisolone by the same route. Thus, considerable variation in plasma concentrations occurred in a single subject, with peak drug values varying almost two-fold.

These preliminary results provide further evidence that oral prednisone products may not be bioequivalent to oral prednisolone products and suggest that substitution of one drug form for another can result in marked changes in circulating concentrations of active steroid. Although the present data are limited to two commercial products, they do indicate that further comparison of the bioavailability characteristics of the various marketed forms of prednisolone and prednisone may be warranted.

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