The *in vitro* metabolism of betamethasone-17-valerate by human skin

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The therapeutic efficacy of topical corticosteroids, particularly the halogenated synthetic analogues, has been well established in a variety of dermatoses. Esterification of the steroid molecule at the 17α position further enhances their biological potency. This has been attributed to the inability of skin to metabolise the steroid ester, which is presumed to confer resistance to oxidation (Whitefield, 1977).

In order to study the fate of one such potent steroid, [^{3}H]-betamethasone-17-valerate was incubated with samples of human skin. Fresh normal human skin samples were obtained from surgical specimens and immediately placed in ice-cold isolation medium (20 mM tris-(hydroxymethyl)-methylamide in 0.3 M mannitol, pH 7.4). After removal of subcutaneous fat whole skin, and separated epidermis and dermis, were incubated with [^{3}H]-betamethasone-17-valerate at a final concentration of 3.37 μmol/l in tris-(hydroxymethyl) methylamide (50 mM) magnesium chloride (3 mM) pH 7.5 at 37°C for 3 h. The reaction was stopped by the addition of ethyl acetate and the radioactivity extracted twice into the solvent, which was then removed under vacuum. The dried extract was then dissolved in chloroform—methanol 1:1, submitted to t.l.c. using silica gel-coated plastic sheets in the solvent system of Anderson, Gennser, Jeremy, Ohrlander, Sayers & Turnbull (1977) and the substrate and metabolite spots located under U.V. light. Radioactivity was located by autoradiography and assayed by liquid scintillation spectrometry.

Betamethasone-17-valerate was metabolised to a compound having the same chromatographic mobility as betamethasone in two solvent systems. Whole skin, epidermis, and dermis were all capable of catalysing the transformation which was linear with time up to 6 h. The amount of betamethasone formed (corrected for non-enzymatic degradation) in whole skin ($n = 9$) was 1.81 ± 0.16 nmol/100 mg tissue/h. In separated epidermis ($n = 4$) and dermis ($n = 3$) the respective amounts of betamethasone formed were 5.94 ± 0.81 and 2.57 ± 0.39 nmol 100 mg tissue^{-1} h^{-1}.

Although topical betamethasone-17-valerate may be resistant to metabolism via oxidation, it appears to be susceptible to hydrolysis in the skin.

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The pharmacokinetics of ethinyloestradiol in women

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There are major discrepancies in previous accounts of the pharmaco-kinetics of ethinyloestradiol (EE) which may reflect inadequate validation in some of the assays used.

A radioimmunoassay for EE has been developed using petroleum ether to free plasma extracts from excess lipid and this method has been exhaustively validated. Five women were given in random order four preparations containing EF (50 μg). EE (50 μg alone), Minovlar (EE 50 μg and Norethisterone acetate (NA) 1 mg) and Gynovlar (EE 50 μg and NA 3 mg) were given orally, and a preparation containing EE (50 μg) and Norethisterone (1 mg) was given intravenously. Blood samples were taken over the succeeding 24 h.

The presence of NA in the 50 μg oral preparations did not alter the pharmacokinetics of EE and data for these three preparations have been pooled. The peak plasma EE concentration following i.v. administration was 636 ± 62 pg/ml (mean ± s.e. mean), and this was followed by a biexponential decline with half-lives of 0.83 ± 0.13 and 6.75 ± 1.03 h. After oral administration the peak plasma EE concentration occurring at 2 h was 128 ± 21 pg/ml, and this declined monoexponentially ($T_{\frac{1}{2}}$ 6.96 ± 0.72 h).

Approximately 12 h after the administration of either the oral or the i.v. preparations there was a second peak in plasma EE concentrations. The oral bioavailability of EE (50 μg), calculated from the areas under the plasma concentration: time curves was 42.4%.

In order to permit determination of the apparent terminal plasma half-life, another group of five women each received EE alone (3 mg) by mouth with subsequent blood sampling over 48 h. A terminal half-life of 12.2 ± 0.83 h was shown following the secondary peak.

The bioavailability of EE is lower than that of the synthetic progestogen, norethisterone (64%) (Back, Breckenridge, Crawford, MacIver, Orme, Rowe & Smith, 1978). The secondary peak of plasma EE concentration is most readily explained as resulting from enterohepatic circulation, since it is already known that EE sulphate is the major metabolite of EE in human bile (Cargill, Steinetz, Gosnell, Beach, Meli, Fujimoto & Reynolds, 1969). The occurrence of enterohepatic circulation may be of clinical significance in drug interactions with antibiotics.

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Pharmacokinetics of disopyramide administered by intramuscular, intravenous and oral routes to normal volunteers

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Disopyramide is an effective agent in the prevention and treatment of cardiac arrhythmias, particularly ventricular arrhythmias. It can be given by mouth or by intravenous injection. The intravenous route should be used with caution as the drug has a hypotensive effect if given too quickly. The intravenous preparation has been given outside hospital to patients with acute myocardial infarction (Ward & Holbrow, unpublished), however, it was considered that the intramuscular route could provide an alternative which would rapidly lead to safe yet effective serum levels. A preliminary pharmacokinetic study was, therefore, performed.

Single doses of disopyramide (100 mg) were administered in random order by the intravenous, intramuscular and oral routes to eight healthy male volunteers and serial blood samples taken. Disopyramide was estimated by gas liquid chromatography (Hayler & Flanagan, 1978).

As the intravenous injection was given over a period of 10 min with the first blood sample being taken on completion of the injection, the highest

Table 1 Means of peak plasma levels, times to peak and elimination half-lives of disopyramide (100 mg) following its intravenous, intramuscular and oral administration to volunteers

Route of Administration	*Mean peak disopyramide plasma level (mg/l) (± s.e. mean)*	*Mean time to peak (min)*	*Mean β half-life (hours)*
Intravenous	3.87 (±0.38)	0*	7.35
Oral	2.08 (±0.15)	90	8.36
Intramuscular	2.31 (±0.15)	15	6.78

* The intravenous injection was made slowly over 10 min and the first blood sample taken on completion of the injection.