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REFERENCES

BODEM, G. & CHIDSEY, C. A. (1972). *Clin. Chem.*, **18**, 363–365.
SCALES, B. & COSGROVE, M. B. (1970). *J. Pharmac. exp. Ther.*, **175**, 338–347.

Elimination biokinetics of some topically-applied steroids

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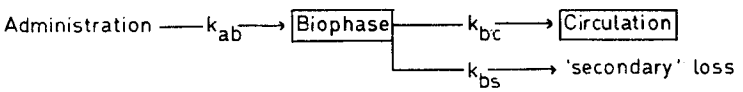
Time variation of a visible, pharmacological response may be expressed mathematically by kinetic theory and a pre-determined relationship between drug level in the receptor compartment (biophase) and observed effect. The vasoconstrictor effects of topical corticosteroids have not yet been described biokinetically.

Ten μl of ethanolic steroid solutions were applied randomly to the forearms of 10 volunteers with Betnovate cream (5 mg) as a control. Application sites were occluded for 6 h with Melinex film, washed with soap and warm water, dried gently and scored in constant lighting conditions using a 0–4 scale with half-point ratings (Barry & Woodford, 1974). Sites were read hourly from 6–13 h and 2 hly from 16–32 h, by separate trials on the same panel.

As peaks occurred in the vascostriction profiles, the biophase and central, systemic compartments were considered kinetically separate. Neglecting any effect of steroid reservoir on transfer rates, the simplest kinetic model postulated had a minimum of two compartments, although curve convexity suggested other compartments were directly communicating with the biophase.



Apparent vasoconstriction half-lives ($t_{\frac{1}{2}}' = 0{\cdot}693/K_{VC}$) were obtained from the descending, linear portion of log % total possible score' against 'time' curves. Although related,

Steroid	% concn	$K_{VC}(h^{-1})$	$t_{\frac{1}{2}}'$ (h)
Betamethasone 17-valerate	0·1 cream)	0·039	18
,,	0·1	0·042	16
,,	0·01	0·036	19
Triamcinolone acetonide	1·0	0·042	17
,,	0·1	0·041	17
,,	0·01	0·037	19
Desonide	0·1	0·037	19
,,	0·01	0·032	22

($K_{VC} = f(k_{bc} + k_{bs})$), vasoconstrictor and biophase drug level half-lives are not necessarily identical.

The 6 h occlusion period was regarded as 'lag' time, corresponding to primary saturation of steroid into membranes before adequate, biophase drug levels produced visible responses. Linearity in the post-absorptive region of the semi-log plots indicated that steroid clearance from the biophase through both systemic absorption and 'secondary' loss (e.g. enzymic bio-transformation) was under the control of apparent first order processes such as passive diffusion.

Conclusions were dependent on several main assumptions. (a) vasoconstriction grading was linear and was always directly related to biophase drug level; (b) all responses were

entirely reversible; (c) vehicles had no effect on elimination rates; (d) all processes could be described by linear compartment modelling, and (e) contribution of the 'reservoir— effect was negligible.

REFERENCE

BARRY, B. W. & WOODFORD, R. (1974). *Br. J. Derm.*, in the press.

Stability of drugs in the presence of pharmaceutical colours

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Colours are used in pharmaceuticals both for aesthetic value and identification purposes. For the colouring of tablet sugar coats, lakes are coming increasingly popular as they offer advantages over water soluble dyes in speed of application and colour uniformity. Although the colour stability of dyes and lakes has been studied (Goodhart, Lieberman & others, 1967), interaction between colours and drugs has received little attention. The following report deals with the degradation of phenylbutazone in the presence of pharmaceutical lakes.

F.D & C Red 2 Lake (Amaranth), F.D & C Red 3 Lake (Erythrosin), F.D & C Yellow 5 Lake (Tartrazine) and F.S & C Yellow 6 Lake (Sunset Yellow) may be used in combination to give a colour suitable for the sugar coating of phenyl-butazone tablets. Suspensions, in Sorensen's phosphate buffer (pH 7·4), of the individual lakes were prepared and stored in subdued light. Solutions of phenylbutazone were similarly prepared. Mixtures of phenylbutazone and the lakes were exposed, in 1 cm quartz cells, to unfiltered light from a 300 W projector bulb, situated 50 cm from the cell. At various time intervals, the cell was removed from the beam, and the phenylbutazone concentration measured spectrophotometrically at 264 nm. Corrections were applied for absorbance due the lake, and interference from the degradation product (Beckstead, Kaistha & Smith, 1968).

Under the conditions used, phenylbutazone alone, and in the presence of amaranth, tartrazine and sunset yellow was stable. In the presence of erythrosin, degradation of the phenylbutazone occurred, the rate constants for the degradation of a 0·001% solution being dependent on the concentration of lake as shown in Table 1.

Table 1.

Concn of lake* (mg litre^{-1})	1·23	2·45	4·90	9·80
Rate Constant (min^{-1})	0·017	0·019	0·091	0·155

* Dye content of lake = 40% w/w.

The reaction did not occur in the dark. In the presence of water soluble erythrosin dye of equivalent concentration, the reaction still occurred, but was slower. Examination of the degradation product of the reaction by t.l.c. (Awang, Vincent & Matsui, 1973), indicated a single breakdown product, which by comparison with standard reference samples was identified as 1,2-diphenyl-4-n-butyl-4-hydroxyprazolidine-3,5-dione (This product is formed from phenylbutazone by oxidation).

It is well recognized that reactions involving dyes as photosensitizers are often mediated by singlet oxygen (Chapelon, Perichet & Pouyet, 1973). Flushing the cells with nitrogen before exposure reduced the rate of degradation. Methylene blue, a known generator of singlet oxygen, also degraded the phenylbutazone to an identical product.

It is suggested that the degradation of phenylbutazone under the experimental conditions described is due to oxidation by singlet oxygen generated by the erythrosin. The effect is enhanced by laking the dye, perhaps due to adsorption of the drug.

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