THE EFFECT OF PARTICLE SIZE AND VEHICLE ON THE PERCUTANEOUS ABSORPTION OF FLUOCINOLONE ACETONIDE.

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WE have shown (Sarkany *et al.*, 1965) that vehicles play a part in the percutaneous absorption of steroids and other topically applied substances. There is, however, no convincing evidence that the particle size of a topically applied steroid is directly related to its penetration of the skin, although there exists a great deal of experimental and clinical information on the effect of particle size on the gastrointestinal absorption of drugs, particularly griseofulvin (Atkinson *et al.*, 1962).

This study provides experimental evidence for the part played by the particle size of fluocinolone acetonide on its percutaneous absorption and shows that the incorporation of propylene glycol in the vehicle further enhances percutaneous penetration of this steroid.

INVESTIGATION.

I. Fluocinolone acetonide in concentrations of 0·025 and 0·01% was incorporated into each of the five vehicles (i) White Soft Paraffin B.P., (ii) White Soft Paraffin B.P. containing 5% Propylene Glycol B.P.C., (iii) Aqueous Cream B.P., (iv) Oily Cream B.P. and (v) Carbowax 1500.

The fluocinolone acetonide, in coarse granular crystalline form, was partially reduced in a mortar before incorporation into the vehicles. Each preparation was carefully milled thrice through a triple roller mill. The preparations containing 0·01% fluocinolone acetonide were made by dilution of those containing 0·025%. The steroid in these concentrations is soluble in propylene glycol and Carbowax 1500.

Standard quantities of each preparation were applied to the flexor aspect of the forearm on squares of polythene film 16 mm. square using the technique previously described (Barrett *et al.*, 1964). The preparations were left occluded for sixteen hours, removed and the area lightly washed with soap and water. The degree of vasoconstriction produced was assessed half an hour later and scored subjectively on a scale of 0–3.

The vasoconstriction produced by the fluocinolone preparations in the five vehicles was measured on two separate occasions and was compared with that produced by Synalar ointment, I.C.I. (0·025%) and Synandone ointment, I.C.I. (0·01%).

II. Micronized fluocinolone acetonide was incorporated into White Soft Paraffin B.P. in concentrations of 0·025 and 0·01%. The size of the majority of the particles in this sample was between 1 and 5 μ but a few were as large as 20 μ.

The preparations containing 0·025 and 0·01% micronized material were compared with crystalline fluocinolone acetonide in White Soft Paraffin B.P. and fluocinolone acetonide dissolved in 5% Propylene Glycol in White Soft Paraffin B.P.

Both groups of fluocinolone preparations were investigated in 10 volunteers.

TABLE I.—*The Percutaneous Penetration of Fluocinolone Acetonide from Five Vehicles.*

Preparation.	Degree of vasoconstriction. Mean (Ten subjects).	Range.
0·025% Fluocinolone acetonide in :		
(i) White Soft Paraffin B.P. . .	1·0	(0–2)
(ii) White Soft Paraffin with 5% propylene glycol .	1·6	(1–3)
(iii) Aqueous Cream B.P. . . .	1·5	(0–3)
(v) Oily Cream B.P. . . .	1·3	(0–2)
(vi) Carbowax 1500	0·1	(0–1)
Synalar ointment, I.C.I. . . .	1·8	(1–3)
0·01% Fluocinolone acetonide in :		
(i) White Soft Paraffin B.P. . .	0·8	(0–2)
(ii) White Soft Paraffin with 5% propylene glycol .	1·5	(1–3)
(iii) Aqueous Cream B.P. . . .	1·2	(0–3)
(iv) Oily Cream B.P. . . .	1·4	(0–3)
(v) Carbowax 1500	0·1	(0–1)
Synandone ointment, I.C.I. . . .	1·3	(1–2)

(Scale of blanching : 0 = none, 1 = slight, 2 = obvious, 3 = pronounced.)

RESULTS.

Table I shows the degrees of vasoconstriction produced by fluocinolone acetonide in concentrations of 0·025 and 0·01 % in the five vehicles. The results indicate the following :

(i) Dissolving fluocinolone acetonide in propylene glycol enhances its penetration from a white soft paraffin vehicle.

(ii) Penetration from a vehicle consisting of white soft paraffin with 5 % propylene glycol is slightly better than from Aqueous Cream B.P. or Oily Cream B.P.

(iii) Using vasoconstriction as a criterion, fluocinolone acetonide is significantly active at a concentration of 0·01 %.

(iv) No consistent penetration takes place from Carbowax 1500. An increase of concentration of fluocinolone acetonide to 0·05 % still fails to produce vasoconstriction.

Table II shows the comparison of micronized fluocinolone acetonide with the coarse-particle form in a white soft paraffin vehicle, with and without propylene glycol. The results show that percutaneous penetration of micronized fluocinolone acetonide is superior to that of the coarse-particle preparation and that it is further enhanced by dissolving the drug in propylene glycol. In a controlled clinical study comparing Synalar ointment and micronized Synalar ointment in the treatment of psoriasis without occlusive dressing, Björnberg and Hellgren (1965) have shown that the fluocinolone acetonide preparation containing propylene glycol was superior to micronized fluocinolone acetonide ointment. This clinical result is consistent with our experimental findings.

TABLE II.—*Comparison of the Percutaneous Penetration of Fluocinolone Acetonide Coarse Particle, Micronized and Solubilized in Propylene Glycol.*

Preparation.	Degree of vasoconstriction. Mean (Ten subjects).	Range.
0·025% Fluocinolone Acetonide in White Soft Paraffin :		
(i) Coarse particle	0·7	(0–2)
(ii) Micronized particle	1·4	(0–2)
(iii) Dissolved in 5% propylene glycol	1·8	(1–2)
0·01 per cent Fluocinolone acetonide in White Soft Paraffin :		
(i) Coarse particle	0·6	(0–1)
(ii) Micronized particle	1·1	(0–2)
(iii) Dissolved in 5% of propylene glycol	1·5	(0–2)

SUMMARY.

The effect of particle size and vehicle on the percutaneous penetration of fluocinolone acetonide was studied experimentally, using a vasoconstrictor method.

It was found that percutaneous penetration was improved when micronized fluocinolone acetonide was used and further improved by the use of a vehicle consisting of white soft paraffin containing 5% propylene glycol. In this preparation a fluocinolone acetonide solution in propylene glycol is dispersed in a paraffin medium.

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