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SHORT COMMUNICATION

The influence of vehicles on skin penetration

C. W. BARRETT, J. W. HADGRAFT AND I. SARKANY

METHODS which have been devised to estimate the rate of release of medicaments from vehicles and their subsequent penetration and absorption have been reviewed by Gemmel & Morrison (1957). Although *in vitro* methods are useful in assessing rates of release of medicaments, they are too far removed from conditions occurring in normal skin to be of real value. We have, therefore, attempted to assess the influence of vehicles on skin penetration by the use of *in vivo* methods in man.

Malkinson & Rothman (1963) and Barr (1962) have drawn attention to the confusion and in some instances, contradictions, that appear in the literature on the influence of vehicles on penetration. Many of the results obtained are difficult to interpret or to compare due to the inherent variability between test subjects and to species differences. There is obviously a need for more methods which are more closely related to conditions occuring in normal human skin.

It has been shown by McKenzie & Stoughton (1962) that when corticosteroids are applied to the skin in alcoholic solution and occluded for 16 hr, a considerable increase in percutaneous penetration over the non-occluded solution is obtained with the production of a noticeable area of vasoconstriction. This method has been used by McKenzie (1962) to compare the percutaneous absorption of some topical steroids.

Cronin & Stoughton (1962) have used the vasodilatation produced by ethyl nicotinate to determine whether regional differences in percutaneous absorption exist and to assess the effect of hydration on the passage of compounds through the skin. In the present investigation, the vasodilatation produced by the local application of methyl nicotinate and the vasoconstriction produced by applying betamethasone-17-valerate under an occlusive dressing have been used in an attempt to assess the degree of their percutaneous penetration from four vehicles. The effect of altering the osmotic properties of an aqueous cream vehicle containing methyl nicotinate was also determined.

METHODS AND RESULTS

Application of a standard quantity of a topical preparation. A circular hole 8·7 mm in diameter was cut in a piece of tin sheet 0·127 mm thick and approximately 7·5 cm square. The sheet was kept flat by placing between two sheets of plate glass. A piece of polythene sheet 2·5 cm square was placed under the circular hole between the tin and the bottom sheet of glass. A quantity of test vehicle was drawn across the tin sheet with a spatula and the polythene square was then carefully removed so that

From the Departments of Pharmacy and Dermatology, Royal Free Hospital, London, W.C.1.

a discreet disc of vehicle equal in volume to the hole in the tin sheet was removed. Ten test weighings of the disc of vehicle thus produced gave a mean weight of 7·8 ± 0·75 mg.

Experiments with methyl nicotinate. Methyl nicotinate was incorporated into aqueous cream, B.P. and oily cream, B.P. by dissolving in the aqueous phase; it was also incorporated into white soft paraffin B.P. and macrogol ointment B.P.C. (Carbowax 1500) by dispersion in the molten vehicle. The concentrations used are shown in Table 1.

TABLE 1. THE PERCUTANEOUS PENETRATION OF METHYL NICOTINATE FROM FOUR VEHICLES

Concentration of methyl nicotinate	Time of onset of noticeable vasodilatation (min)			
	Aqueous cream B.P.	Oily cream B.P.	White soft paraffin B.P.	Macrogol ointment B.P.
1	3·3	4·1	5·3	8·7
0·5	4·0	4·5	6·6	10·8
0·25	—	—	—	17·1
0·1	4·6	5·2	8·0	22·3
0·05	5·9	6·8	13·1	NR
0·01	7·4	10·5	19·7	NR
0·005	10·9	12·5	NR	NR
0·001	NR	NR	NR	NR

NR = No response
Each figure is an average of 20 readings, two from each of 10 subjects.

A polythene square with the standard quantity of ointment was applied to the flexor aspect of the forearm of each of 5 male and 5 female volunteers and covered with a strip of 1 in. wide cellulose tape. The time for the onset of erythema round the edge of the circle of ointment was recorded. Duplicate tests were made simultaneously for each concentration in each vehicle. Where no erythema was noticeable after 1 hr, "no response" was recorded. In this way, the minimal concentration of methyl nicotinate to produce erythema was found for each vehicle. The results obtained for the complete range of concentrations in the four vehicles are shown in Table 1. There is little difference in the rate of penetration from aqueous cream and oily cream, penetration is slightly slower from white soft paraffin and markedly slower from macrogol ointment.

Twenty readings for each of six concentrations of methyl nicotinate in aqueous cream, B.P. were made on one subject to determine the reproducibility of the results of penetration. Concentrations were %: 1, 0·5, 0·1, 0·05, 0·01, 0·005; the means (± s.d.) for the times of onset (min) were respectively: 4·3 (0·37), 4·7 (0·55), 5·3 (0·62), 5·7 (0·78), 10·5 (1·68), 15·0 (0·39).

The osmotic property of an aqueous cream was altered by adding 40 and 60% of glycerin B.P. and the penetration of methyl nicotinate from these preparations was investigated. An increase in the glycerin content produces a decrease in the rate of penetration of methyl nicotinate (Table 2).

A further series of experiments was conducted in 10 subjects to determine the influence of the vehicle on the rate of penetration of betamethasone-17-valerate. With 0·1 and 0·05% concentrations, no significant

difference in the degree of blanching from the four vehicles was noted. The area of vasoconstriction from the macrogol ointment base was consistently larger in all the subjects indicating greater spread of the medicament from this vehicle.

TABLE 2. THE INFLUENCE OF GLYCERIN B.P. ON THE PERCUTANEOUS PENETRATION OF METHYL NICOTINATE FROM AN AQUEOUS CREAM VEHICLE

Concentration of methyl nicotinate %	Time of onset of noticeable vasodilatation (min)		
	Aqueous cream B.P.	Aqueous cream with 40% glycerin	Aqueous cream with 60% glycerin
1	3·6	4·6	6·3
0·5	4·2	5·6	8·5
0·25	—	—	12·1
0·1	4·7	6·7	16·7
0·05	6·3	11·7	NR
0·01	7·9	17·6	NR
0·005	11·6	NR	NR
0·001	NR	NR	NR

NR = No response.
Each figure is an average of 20 readings as in Table 1.

DISCUSSION

It has been suggested that the penetration of a drug depends essentially on its own lipid and water solubility and that the role of the vehicle is of secondary importance (Malkinson & Rothman, 1963). On theoretical grounds, Higuchi (1960) has shown that the thermodynamic activity and the diffusion coefficient of a medicament in the vehicle are significant factors in its penetration whilst Shelmire (1960) has stated that the hydration of the stratum corneum is also an important factor in percutaneous penetration. Greasy vehicles probably promote hydration by restricting moisture loss from the skin surface. Humectants in aqueous creams would tend to produce the reverse effect by preventing evaporation of the aqueous phase and the subsequent deposition of a continuous oil film on the skin surface. Water-soluble vehicles would cause little change in hydration.

The results with methyl nicotinate show little difference in the rate of penetration from aqueous cream and oily cream. Methyl nicotinate is very soluble in water and is therefore probably released quite readily from these vehicles. The fact that penetration from white soft paraffin is slightly slower may suggest that the stratum corneum has to attain a certain degree of hydration before penetration can occur. Macrogol ointment is water miscible and the significantly slower penetration from this vehicle may be due either to its inability to hydrate, or to an osmotic effect which would tend to dehydrate the stratum corneum, or to an adverse diffusion coefficient of methyl nicotinate in this vehicle.

The decreased penetration of methyl nicotinate from aqueous creams containing glycerin is in agreement with Shelmire's view.

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