Effects of Dimethyl Sulfoxide and Trimethylphosphine Oxide on Percutaneous Absorption of Corticosteroids in the Rat

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Abstract □ Dimethyl sulfoxide and trimethylphosphine oxide facilitate absorption of a polar steroid (hydrocortisone sodium succinate) through the rat skin. Neither agent significantly increases the rate at which a highly lipid-soluble steroid (cortisone acetate) can penetrate rat skin.

Keyphrases □ Dimethyl sulfoxide—effects on percutaneous absorption of corticosteroids, rat □ Trimethylphosphine oxide—effects on percutaneous absorption of corticosteroids, rat □ Corticosteroids (hydrocortisone sodium succinate and cortisone acetate), percutaneous absorption—effects of dimethyl sulfoxide and trimethylphosphine oxide, rat □ Absorption, percutaneous—effects of dimethyl sulfoxide and trimethylphosphine oxide on corticosteroid absorption, rat

The percutaneous absorption of steroids is influenced by many factors, including the vehicle in which the steroid is dispersed (1) and the polarity of the steroid (2, 3). The use of dimethyl sulfoxide as a vehicle has been reported to increase percutaneous absorption of many chemicals, including steroids (4–7). Tjan and Gunberg (8) reported that cortisone acetate in dimethyl sulfoxide caused reductions in total body weight, spleen weight, thymus weight, and adrenal gland weight after topical application to immature female rats. These effects paralleled those seen after subcutaneous injections of the same doses of cortisone acetate.

Since phosphine oxides are similar chemically to sulfoxides, it seemed possible that the ability of dimethyl sulfoxide to enhance percutaneous absorption of other chemicals might be shared by trimethylphosphine oxide. Both possess solubilities of the same order in polar solvents, but dimethyl sulfoxide is more soluble in nonpolar solvents. Dimethyl sulfoxide and trimethylphosphine oxide have the high, closely related dipole moment values of 3.96 and 4.39 D, respectively (9, 10).

The purpose of this study was to compare the effects of dimethyl sulfoxide and trimethylphosphine oxide on the biological activity of a lipophilic steroid (cortisone acetate) and a hydrophilic steroid (hydrocortisone sodium succinate) after topical application. This investigation was patterned after two reports of a similar nature involving dimethyl sulfoxide and cortisone acetate (8) and dimethyl sulfoxide and a water-soluble ester salt of prednisolone (11). The former study, however, did not include a control group, leaving the speculation that cortisone acetate might penetrate the skin just as well without incorporation of dimethyl sulfoxide. The latter report indicated that the steroid was applied almost daily for 5.5 weeks, a period that seems excessively long since similar reductions in organ size can be observed within 3–4 days.

Table I—Dosage Schedule for Rats Treated Topically with Cortisone Acetate or Hydrocortisone Sodium Succinate

Group	Treatment	Number of Rats
I	Chloroform (control)	5
	6 *M* Dimethyl sulfoxide in chloroform	5
	6 *M* Trimethylphosphine oxide in chloroform	5
II	Cortisone acetate in chloroform (control)	5
	Cortisone acetate and 6 *M* dimethyl sulfoxide in chloroform	5
	Cortisone acetate and 6 *M* trimethylphosphine oxide in chloroform	5
III	Ethanol (control)	4
	6 *M* Dimethyl sulfoxide in ethanol	5
	6 *M* Trimethylphosphine oxide in ethanol	5
IV	Hydrocortisone sodium succinate in ethanol (control)	5
	Hydrocortisone sodium succinate and 6 *M* dimethyl sulfoxide in ethanol	5
	Hydrocortisone sodium succinate and 6 *M* trimethylphosphine oxide in ethanol	5

EXPERIMENTAL

Male Sprague–Dawley albino rats[1] (mean weight 162 ± 2.1 g) were prepared by shaving, under light ether anesthesia, an area on the back of the neck 72 hr prior to the initiation of drug treatment. Animals were housed individually in wire-bottom cages after shaving and were provided with laboratory chow and water *ad libitum* throughout the experiment.

Preparations of cortisone acetate and hydrocortisone sodium succinate were made such that a 10-mg dose was contained in 100 μl. In preparations containing dimethyl sulfoxide or trimethylphosphine oxide, the steroid was present as a fine suspension. All other preparations were solutions. Details of the dosage schedule are summarized in Table I. One hundred microliters of the appropriate preparations was applied once daily for 4 days to the shaved area with the animal under light ether anesthesia. Twenty-four hours after the fourth dose, the rats were sacrificed by chloroform inhalation. The spleen, thymus, and adrenal glands from each rat were removed, cleaned, and weighed on a tissue balance[2]. Involution of these organs was taken as a measure of the systemic effects of topically applied corticosteroid.

Data from each group were compared by analysis of variance and, where the variance ratio indicated the existence of a statistically significant difference ($p < 0.05$), individual means were compared using the Newman–Keuls test (12).

RESULTS AND DISCUSSION

Results of this study are summarized in Table II. Topical application of either cortisone acetate or hydrocortisone sodium succinate was associated with reductions in total body weight as well as in the relative weights of the spleen, thymus, and adrenal

[1] ARS/Sprague–Dawley, Madison, Wis.
[2] Roller-Smith.

Table II—Effects of Dimethyl Sulfoxide or Trimethylphosphine Oxide on Biological Activities of Topically Applied Cortisone Acetate or Hydrocortisone Sodium Succinate

Group	Treatment[a]	Body Weight Change[b], g	Spleen Weight[b], mg/100 g Body Weight	Thymus Weight[b], mg/100 g Body Weight	Adrenal Weight[b], mg/100 g Body Weight
I	Chloroform (control)	+34 ± 6.0	380.3 ± 28.7	293.1 ± 26.8	32.7 ± 2.0
	Dimethyl sulfoxide in chloroform	+26 ± 2.4	442.0 ± 18.8	326.4 ± 26.1	27.5 ± 1.1
	Trimethylphosphine oxide in chloroform	+22 ± 1.2	396.2 ± 24.4	312.5 ± 13.9	32.3 ± 1.5
II	Cortisone acetate in chloroform (control)	−6 ± 2.4	228.3 ± 11.4	127.6 ± 15.0	20.3 ± 0.9
	Cortisone acetate + dimethyl sulfoxide in chloroform	−15 ± 9.5	258.8 ± 9.2	107.9 ± 10.3	25.7 ± 2.8
	Cortisone acetate + trimethylphosphine oxide in chloroform	+3 ± 1.2	256.4 ± 14.4	113.5 ± 7.8	22.6 ± 1.6
III	Ethanol (control)	+28 ± 3.2	314.7 ± 15.7	296.1 ± 19.9	28.2 ± 2.6
	Dimethyl sulfoxide in ethanol	+28 ± 3.0	292.6 ± 7.9	267.4 ± 17.2	25.5 ± 1.4
	Trimethylphosphine oxide in ethanol	+25 ± 4.5	320.8 ± 10.6	297.7 ± 8.8	24.2 ± 1.7
IV	Hydrocortisone sodium succinate in ethanol (control)	−7 ± 4.9	209.2 ± 11.6	96.9 ± 22.5	27.9 ± 2.0
	Hydrocortisone sodium succinate + dimethyl sulfoxide in ethanol	−3 ± 2.0	209.7 ± 10.6	100.5 ± 13.1	17.6 ± 0.8[c]
	Hydrocortisone sodium succinate + trimethylphosphine oxide in ethanol	−18 ± 2.5[c]	197.0 ± 13.5	87.6 ± 11.0	18.6 ± 0.8[c]

[a] All corresponding treatments and measures between Groups I and II and between Groups III and IV differed significantly, except hydrocortisone sodium succinate in ethanol *versus* ethanol alone for adrenal weight. [b] Mean ± standard error; see Table I for number of animals in each treatment group. [c] Significantly different ($p < 0.05$) from group control.

glands. This was true whether the steroids were applied in solvent only (chloroform for cortisone acetate, ethanol for hydrocortisone sodium succinate) or with the penetrating aid dimethyl sulfoxide or trimethylphosphine oxide.

For cortisone acetate the changes in groups treated with dimethyl sulfoxide or trimethylphosphine oxide were not significantly different from those in groups treated with the steroid in chloroform alone. Thus, cortisone acetate in chloroform readily penetrated the rat skin and the incorporation of dimethyl sulfoxide or trimethylphosphine oxide did not significantly enhance the biological effects of this penetration. It has not been ascertained whether the chloroform serves as a penetrating aid or evaporates too rapidly from the application site to act in any such capacity. In either case, the effect of the nonpolar solvent was no different from those produced by highly water-soluble dimethyl sulfoxide and trimethylphosphine oxide. It appears that cortisone acetate may penetrate as a result of its inherent lipid solubility.

Hydrocortisone sodium succinate also penetrated the skin from each of the three vehicles, as indicated by the decrease in total body weight and relative weights of the spleen and thymus. However, no appreciable decrease in adrenal weight was seen when the drug was applied in ethanol alone. In the presence of dimethyl sulfoxide, adrenal weight was significantly lower than that of controls. In the presence of trimethylphosphine oxide, both total body weight and relative adrenal weight were reduced to a significantly greater extent than in control animals. These data suggest that trimethylphosphine oxide, like dimethyl sulfoxide, may be effective in increasing the rate at which hydrophilic drugs can penetrate the skin.

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