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Tacalcitol Ointment for Psoriasis

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Tacalcitol (1 α, 24 (R)-$(OH)_2$V.D_3), a synthetic analog of active vitamin D_3, is a new antipsoriatic agent (1). Although this compound is applicable topically, transdermal absorption of this vitamin D_3 derivative may cause hypercalcemia. For clinical use, from the standpoints of safety and efficacy, transdermal absorption of this agent from topical preparations should be limited, though the antipsoriatic effect should be satisfactory. To elucidate these points, we studied pharmacokinetics, clinical efficacy and safety of the ointment containing 2 μg/g of tacalcitol.

METHODS

1. Transdermal absorption of tacalcitol from ointment

(1) Serum tacalcitol concentration after topical application

[^{3}H]-tacalcitol ointment was prepared by incorporating the tacalcitol into a white petrolatum-based ointment vehicle to obtain a final concentration of 2 μg/g. 50 mg of the ointment ([^{3}H]-tacalcitol: 100 ng equivalent) was applied on shaved back skin (9 cm^2) of 4 hairless rats. They were immobilized for 24 h and blood was drawn from the orbital sinus periodically to determine radioactivity.

(2) Urinary and fecal excretion of tacalcitol from ointment

The [^{3}H]-tacalcitol ointment was applied to 5 hairless rats in the same way as described above. After 24 h the applied area was washed with KimwipeTR and the rats were placed in metabolism cages for 6 days. Urine and feces were collected to determine cumulative excretion of radioactivities.

(3) Tacalcitol permeability through human skin

The [^{3}H]-tacalcitol ointment was applied on human epidermis mounted on a diffusion cell (Fig. 1). The epidermis had been isolated from surgically excised abdominal skin by thermal treatment at 60°C for 30 min. The cell was equipped with a water jacket and kept at 37°C. Permeation through the epidermis to receptor fluid, whose composition was Hanks' balanced salt solution mixed with 30% of fetal bovine serum, was measured by determining radioactivity in the fluid. The permeation rate through human epidermis was compared with that of hairless rat epidermis.

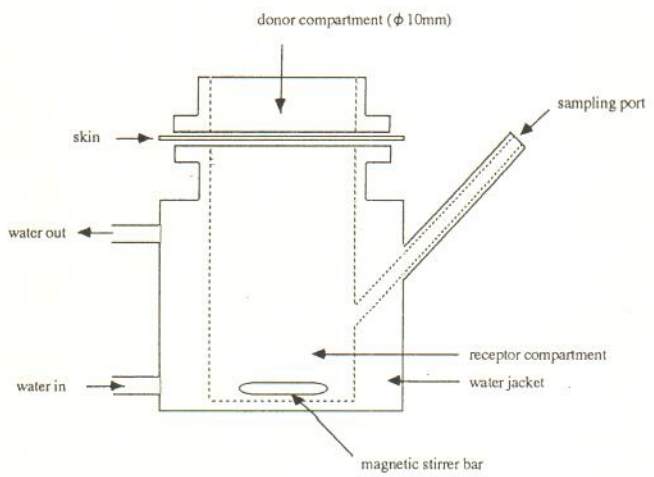

Fig. 1. The diffusion cell.

2. Clinical efficacy and safety

Psoriatic lesions of two symmetrical skin sites in 12 patients each were selected and a placebo-controlled double-blind right/left comparison was performed. One side was treated with ointment containing 2 μg/g of tacalcitol and the other with blank vehicle twice daily for 4 weeks. During the course of the study, weekly scoring for scaling, erythema and thickness of the psoriatic lesions was done using the following gradings: 0, none; 1, slight; 2, mild; 3, moderate; 4, severe. The investigator's global assessment was based on a comparison with the clinical condition at week 0 and used the following gradings: 1, marked improvement; 2, fair improvement; 3, slight improvement; 4, no change; 5, worse. A check was made for local side effects every day. Cumulative doses of tacalcitol were recorded and serum Ca levels were determined before and after the study.

RESULTS AND DISCUSSION

1. Transdermal absorption of tacalcitol from ointment

In *in vivo* studies in hairless rats, serum concentration profile suggested non-negligible transdermal absorption (Fig. 2) and recovery in urine and feces accounted for about 25% of the dose (Fig. 3). Ohta et al. also reported that about 30% of the radioactivity was recovered in urine and feces after a single topical application of a tacalcitol ointment in Wistar rats (2). Thus it was evident that tacalcitol in ointment was rather permeable through rat skin. However, in vitro study showed that the per-

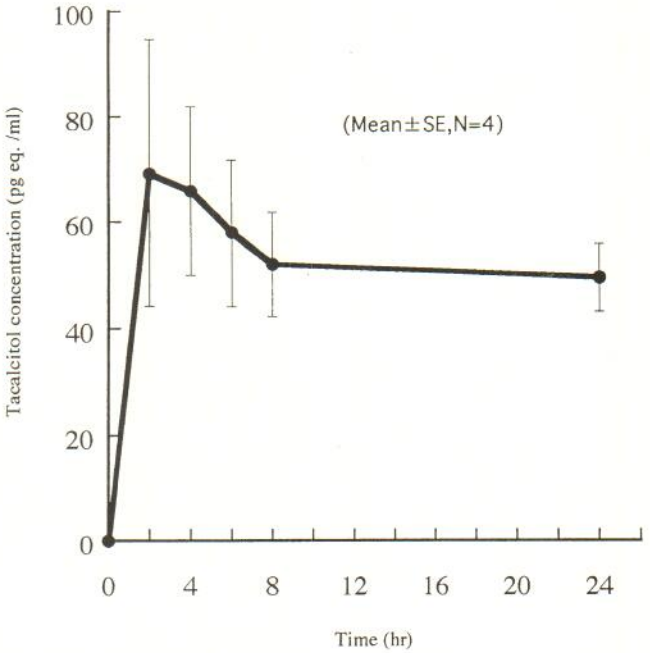

Fig. 2. Serum tacalcitol concentration after topical application of [^{3}H]-tacalcitol ointment on back of hairless rat.

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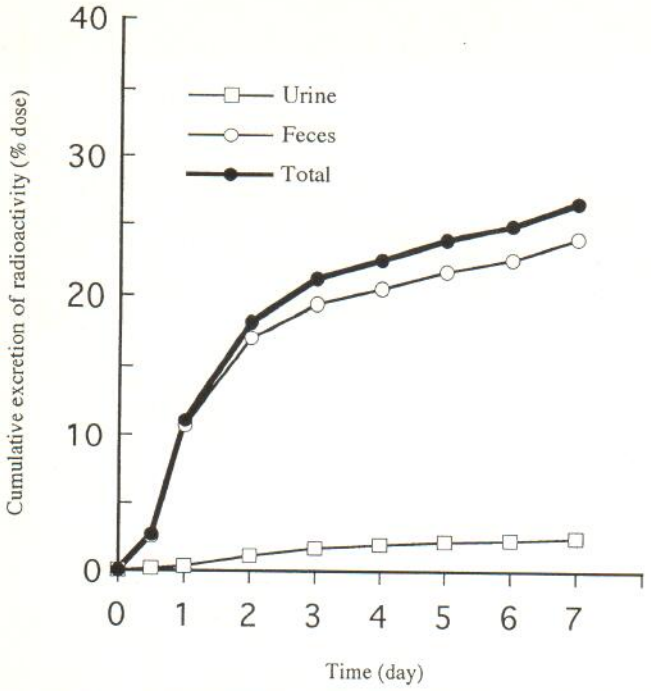

Fig. 3. Cumulative urinary and fecal excretion of radioactivity after topical application of [^{3}H]-tacalcitol ointment on back of hairless rat. The ointment was applied for 24 h.

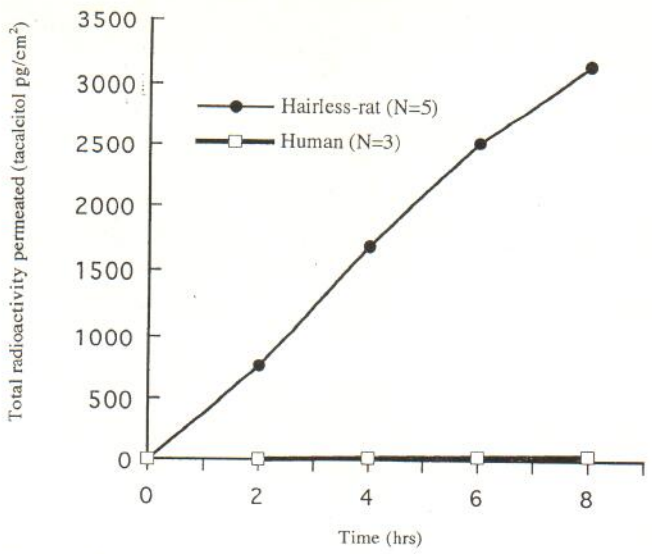

Fig. 4. In vitro permeability of [^{3}H]-tacalcitol in ointment through epidermis of different species. 3.9 mg of the ointment was applied.

meation rate through human epidermis was about one-fiftieth of that through hairless rat epidermis (Fig. 4). Therefore it was expected that tacalcitol might not be practically absorbed transdermally and pharmacological effects would be limited to the local skin site, when the ointment was applied to human skin.

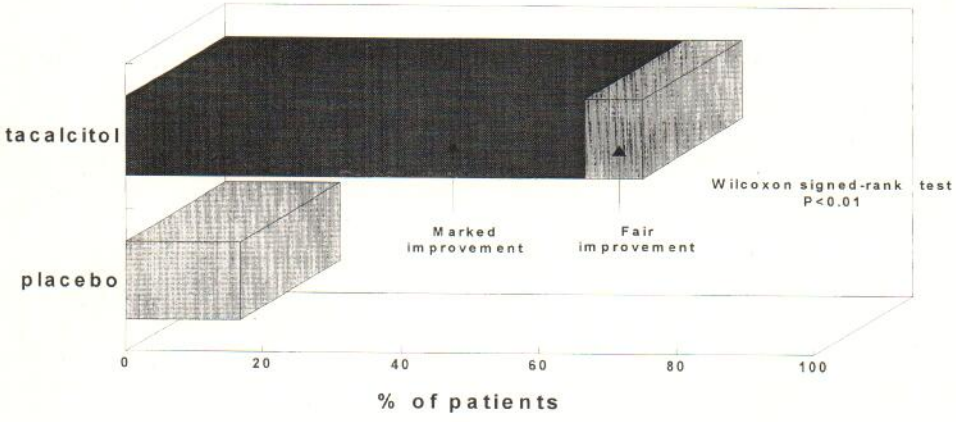

Fig. 5. Overall assessment of clinical efficacy.

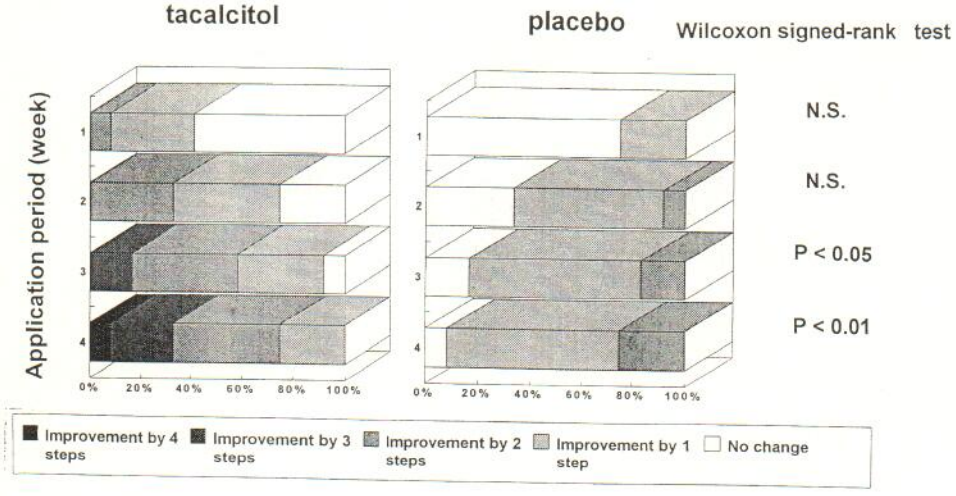

Fig. 6. Weekly improvement of erythema.

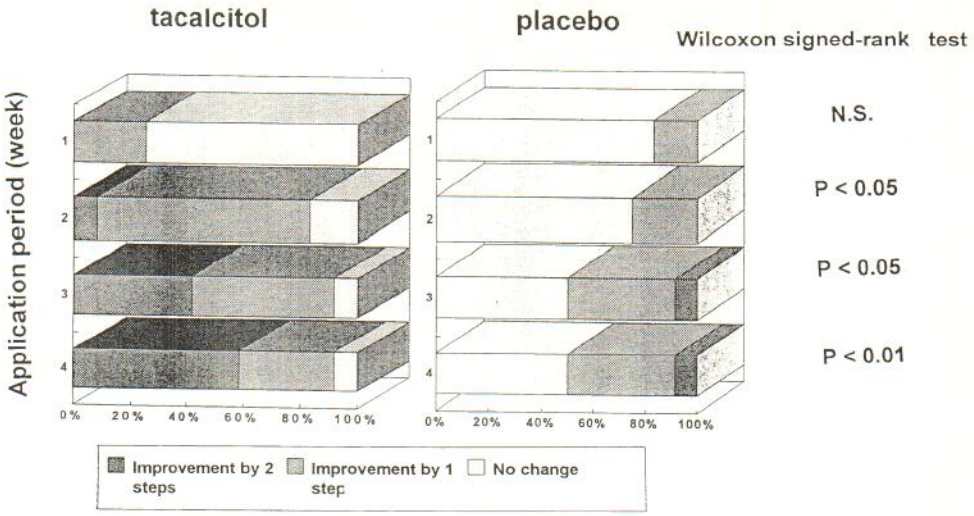

Fig. 7. Weekly improvement of scaling.

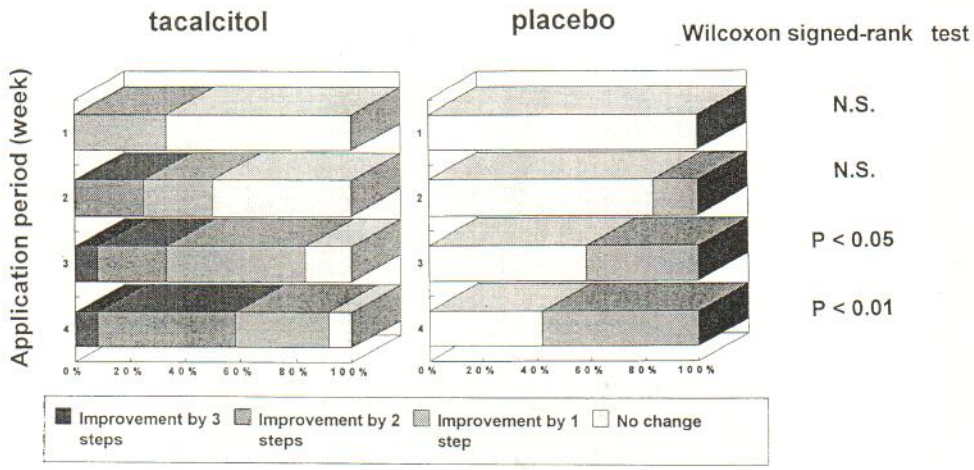

Fig. 8. Weekly improvement of thickness.

2. Clinical efficacy and safety

After 4 weeks of the treatment, the rate of improvement (better than fair) with tacalcitol ointment (75.0%) was significantly higher than that with placebo ointment (16.7%) (Fig. 5). The rate of marked improvement with tacalcitol ointment was 66.7%, while no case showed this rank of improvement with placebo ointment. The superiority of tacalcitol vis-à-vis placebo ointment was evident for scaling even at 2 weeks after starting the treatment and 3 weeks after for erythema and thickness (Figs. 6, 7 and 8).Cumulative doses of tacalcitol were 220 to 640 μg (average 340 μg). None showed any local adverse effects or elevation of serum Ca level in the clinical study.

From the viewpoint of safety and efficacy, we consider that tacalcitol ointment is a sophisticated antipsoriatic agent. However, its tolerability in long-term treatment should be further studied to define the safety of tacalcitol ointment in the treatment of psoriasis.

SUMMARY

Transdermal absorption of tacalcitol from the ointment containing 2 μg/g was studied using hairless rat and human skin. In the animal experiments, a non-negligible amount of tacalcitol was absorbed transdermally, whereas in the case of human skin, this compound was hardly absorbed at all. A placebo-controlled double-blind right/left comparison confirmed that this ointment is effective and safe for the treatment of psoriasis.

REFERENCES

1. Nishimura M, Hori Y, Nishiyama S and Nakamizo Y. Topical 1 α, 24 (R)-dihydroxy vitamin D_3 for the treatment of psoriasis. Review of the literature. Eur J Dermatol 1993; 3: 255–261.
2. T. Ohta et al. Pharmacokinetic studies of 1 α, 24 (R)-$(OH)_2D_3$ (TV-02) (3): Absorption, distribution and excretion after a single or continuous transcutaneous application to rats. Xenobiotic Metabolism and Disposition 1990; 5: 39–52 [in Japanese].