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Novel transdermal targeting in steroid therapy: Evaluation of PK/PD profiles using an animal model of rheumatoid arthritis

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Rheumatoid arthritis is a disease that causes pain of limb joints and functional disorders. Systemic administration of steroids for this disease is associated with serious adverse events such as infection, osteoporosis, fracture and arteriosclerosis. To avoid systemic side effects, we tried to target inflamed joint cells by dermally administering steroid to articular sites. We selected an oral steroid, prednisolone (PN), as a maternal compound, and prepared its farnesilate ester, prednisolone farnesilate (PNF) to enhance cell affinity. PNF had been developed as gel ointment and is prescribed as a medicine in Japan.

PNF activity was 1/160 compared to PN activity. PNF showed cellular uptake approximately 100-fold that of PN (Fig. 1). The intracellular concentration of PN when cells were incubated with PNF was 3.6-fold that when cells were incubated with PN. When PNFgel or PNgel (containing an equivalent mol) was applied to joint of adjuvant arthritic rats, anti-inflammatory effects on the applied side were similar. On the non-applied side (opposite joint), the anti-inflammatory effects of PNF were significantly less potent than those of PN (Fig. 2). In PNF-treated rats, thymic atrophy was significantly less marked than that in PN-treated rats.

Furthermore, when ^{14}C-PNFgel was administered to adjuvant arthritic rats, the ratio of PN to PNF in granulation of joint of adjuvant arthritic rats was higher than that in dermis. To compare the availability of PNF at the target site, we calculated the ratio (A/B) of the local granulation tissue concentration of radioactivity (A) to urinary and fecal excretion of radioactivity (B), which is an index of total absorption. The ratio after ^{14}C-PNFgel administration was significantly higher than that after ^{14}C-PNgel administration.

These results suggest that the availability of PNF at the target site is higher than that of PN, and that PNF is activated into PN in inflammatory tissues, exhibiting anti-inflammatory effects without systemic side effects. The above results were consistent with the report [1–4] that agents with high fat-solubility and high tissue affinity are not readily removed by blood flow during the absorption process after dermal administration, thereby enhancing penetration to deeper areas.

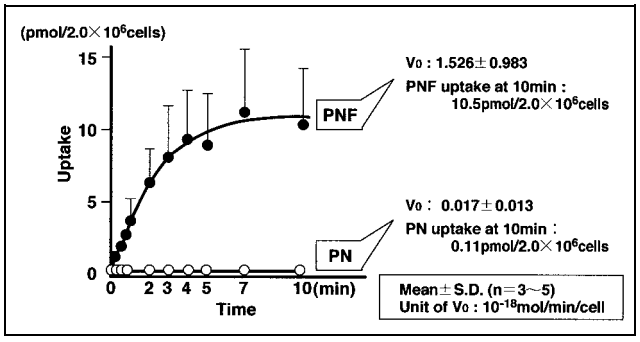

Fig. 1: Time course of uptake of ^{3}H-PNF of ^{3}H-PN by human lymphocytes *in vitro*

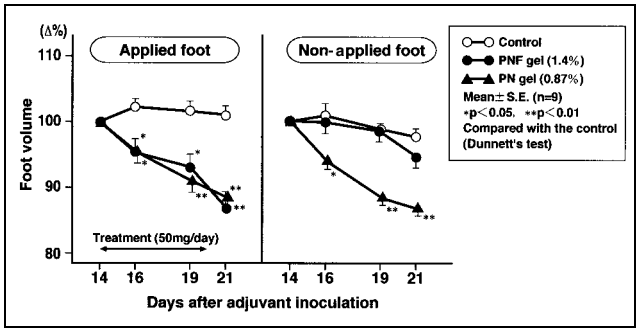

Fig. 2: Therapeutic effects of PNF gel or PN gel on the foot volume in adjuvant arthritic rats

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