

Enhancing Effects of Myristyl Lactate and Lauryl Lactate on Percutaneous Absorption of Indomethacin in Rats

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The enhancing effects of myristyl lactate (ML) and lauryl lactate (LL) on the percutaneous absorption of indomethacin (ID) from test solutions in propylene glycol (PG) were investigated in rats.

ID absorption was observed to be markedly enhanced by the addition of ML or LL to PG as compared with the control (PG alone). The marked enhancing effects were observed at concentrations greater than 3% ML and 3% LL in PG. In particular, the maximal enhancement of percutaneous absorption of ID was achieved at 5% ML and LL.

To elucidate the mode of action of ML as an enhancer, the percutaneous absorption of ID through the skin pretreated with ML alone was investigated. It was suggested that ML acts on the stratum corneum to produce its effect.

Keywords myristyl lactate; lauryl lactate; propylene glycol; indomethacin; percutaneous absorption; enhancer

Since the skin itself presents an effective barrier to topically applied drugs, it is difficult to simply absorb a drug through the skin. Thus, the penetration enhancer is employed to improve the percutaneous absorption of drugs after the topical application. Many substances have been used as enhancers of percutaneous drug absorption. We also observed and reported that cetyl lactate (CL) functioned as an enhancer of percutaneous absorption of indomethacin (ID).¹⁾ In the present study, we investigated the influence of myristyl lactate (ML), and lauryl lactate (LL) on the percutaneous absorption of ID through rat skin. The efficiency of percutaneous absorption of ID was determined by measuring the drug concentration as a function of time in rat plasma.

Experimental

Materials Propylene glycol (PG) was purchased from Tokyo Kasei Kogyo Co., Ltd. ML and LL were kindly supplied by Musashino Chemical Laboratory Ltd. and Ina Trading Co., Ltd., respectively. ID was purchased from Sigma Chemical Company. All the solvents used in this experiment were of reagent grade from Kanto Chemical Co., Ltd.

Preparation of Test Solution The test solutions used for this study were prepared as follows. Lactate esters and ID were dissolved in pure PG with the aid of heat (about 50°C), and the content of ID was controlled so as to give 1% in each test solution. The concentration of lactate esters in the test solutions were 1, 3, 5, 10 and 20%, respectively.

In Vivo Experiment Male Wistar rats weighing 230 and 250 g were used in this study. The hair of the abdominal region was carefully removed with an electric hair clipper and an electric razor without breaking the skin before the experiments. The rat was placed on its back and a glass chamber (27 cm³) was applied to the surface of the treated abdomen (3 × 6 cm²) using a surgical tissue cement (Aron Alpha, Toa Gosei Chemical Co., Ltd.). Then 10 ml of test solution was placed in the chamber. Further, ID was also administered intravenously in 10 mg/kg after dissolving in pH 8.0 phosphate buffer to evaluate the absolute bioavailability of ID after the topical administration of test solution. Blood (0.3 ml) was withdrawn from the jugular vein into a syringe at predetermined intervals, and centrifuged at 3000 rpm for 10 min. The resulting plasma samples were used for analysis of ID by high performance liquid chromatography (HPLC).

Pretreatment Experiment Five grams of ML was put into the glass chamber on the skin and allowed to stand for 4 h. After removing ML thoroughly by using the cotton wool, 10 ml of test solution was applied to the skin and the ID level was determined as described above.

Assay of ID The plasma concentration of ID was determined in the manner described in the previous paper.¹⁾

Results and Discussion

Enhancing Effects of ML and LL The plasma ID concentration–time curves after the topical administration

of test solutions are shown in Fig. 1. In addition, Fig. 2 is a histogram showing the bioavailability of ID absorbed percutaneously within 8 h through the skin as a function of ML and LL concentration in PG.

The percutaneous absorption rates of ID from the test

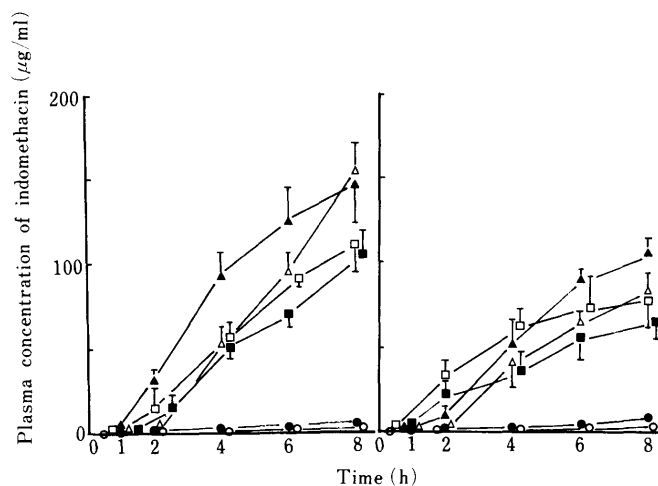


Fig. 1. Effects of the Content of ML (Left) and LL (Right) Added to Test Solutions on Percutaneous Absorption of ID in Rats

○, control (ML free); ●, 1%; △, 3%; ▲, 5%; □, 10%; ■, 20%. Each value represents the mean ± S.D. of four experiments.

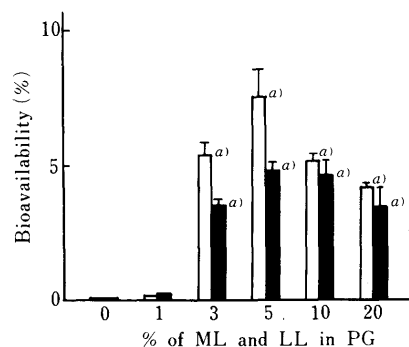


Fig. 2. Relationship between the Content of ML or LL Added to Test Solutions and the Bioavailabilities of ID after Topical Administration in Rats

□, ML (myristyl lactate); ■, LL (lauryl lactate). Vertical bars indicate standard deviations of the mean.

Bioavailability (%) = $(AUC_{p.e.} \times dose_{i.v.} / AUC_{i.v.} \times dose_{p.e.}) \times 100$ where $AUC_{p.e.}$ and $AUC_{i.v.}$ are AUC after percutaneous and intravenous administrations, respectively. a) $p < 0.01$ as compared with 0 and 1%.

solutions containing ML or LL after application were fast as compared with that of the control (PG alone). However, the absorption rate of ID from 1% ML or LL-PG test solution was significantly lower than that of the other test solutions containing ML or LL. Furthermore, the bioavailabilities after the administration of 3, 5, 10 and 20% ML or LL-PG test solutions were also statistically significantly higher than those of the control and 1% ML or LL-PG test solutions ($p < 0.01$). In the case of ML-PG test solution, the bioavailabilities of ID of the solution containing 0 (control), 1, 3, 5, 10 and 20% ML-PG were 0.044, 0.188, 5.45, 7.51, 5.15 and 4.18%, respectively. Further, the bioavailability of ID in solutions containing 1, 3, 5, 10 and 20% LL-PG were 0.302, 3.58, 4.84, 4.78 and 3.48%, respectively. The maximal bioavailability of ID was achieved by the addition of ML or LL to PG at a concentration of 5%. However, the bioavailability decreased as the concentration of ML or LL increased over 5%. From these results, the addition of ML or LL to PG was observed to enhance the percutaneous absorption of ID through the rats skin. The marked enhancing effects were obtained at concentrations greater than 3% in PG. When the bioavailabilities of ID were compared at concentrations of 3 and 5%, the effect of ML was statistically higher than that of LL.

ML has a melting point of 29 to 34 °C. ID was dissolved in ML alone at 34 °C (average skin temperature) at a concentration of above 1%. Thus, ML containing 1% ID (without PG) was usable for topical administration to the skin. However, the bioavailability of ID of this sample was only 0.087%. This value was close to that of the control (PG alone). LL has a freezing point of -11 to -14 °C, and its appearance is liquid at room temperature. The LL solution containing 1% ID (without PG) was similarly able to be administered to the skin. The bioavailability of ID of this solution was 0.092%. This value was almost equal to that of ML.

It was reported in the previous paper that CL had a narrow concentration range of application as a percutaneous absorption enhancer for ID, because the solubility of CL in PG at room temperature was found to be as low as 3%.¹⁾ Further, the marked enhancing effect was observed to be obtained at a concentration greater than 1% CL in PG. When the bioavailabilities of ID absorbed through the skin from PG solutions containing three kinds of esters (CL, ML and LL) were compared at concentrations of 1 and 3%, the effect of CL as an enhancer was highest among the three esters. However, the reason why CL has the effect of maximal enhancement among three esters is still unclear.

The binary systems consisting of a hydrophilic molecule and a lipophilic molecule have shown to be effective enhancers for the percutaneous absorption of drugs.²⁻⁷⁾ Among the binary systems, the combination of PG and oleic acid is seemed to disorganize easily the multilaminate hydrophilic-lipophilic layer within stratum corneum, and consequently its barrier functions are reduced.⁸⁻¹⁰⁾ This percutaneous absorption of drugs resulted from a synergistic rather than a simple additive effect of PG and oleic acid, though PG and oleic acid themselves have been regarded as enhancing the absorption of drugs. The increase of percutaneous absorption of ID by ML or LL is similarly assumed to be due to the synergistic effect of ML or LL

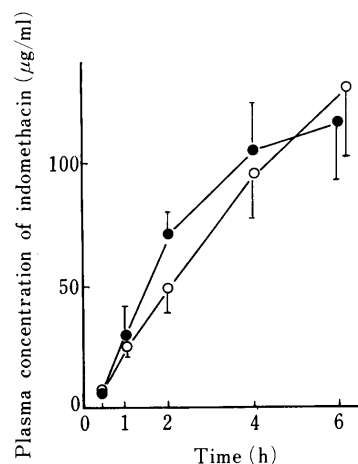


Fig. 3. Percutaneous Absorption of ID from Two Test Solutions through the Pretreated Skin of Rats with ML Alone

●, control (ML free); ○, 5% ML-PG test solution. Each value represents the mean \pm S.D. of four experiments.

and PG, since both ML and LL are lipophilic molecules.

Effect of Pretreated Skin on Percutaneous Absorption of ID In the previous paper, to elucidate the mode of action of CL as an enhancer, we investigated the percutaneous absorption of ID through damaged skin.¹⁾ It was observed that CL acted on, as a result, the stratum corneum to produce its effects. In this study, in order to elucidate the mode of action of ML as an enhancer, the percutaneous absorption of ID from the control and 5% ML-PG solution through the pretreated skin with ML alone were investigated. It has been proved that PG itself functioned as an enhancer for the absorption of drugs through the skin, by decreasing the barrier function of stratum corneum.¹¹⁾ Thus, in this study, ML alone was used to prepare the pretreatment skin.

The plasma ID concentration-time curves after the topical administration of the control and 5% ML-PG solution to the skin pretreated with ML without ID for 4 h are shown in Fig. 3. There was no significant difference in the absorption patterns of ID between the control and 5% ML-PG treatment for 6 h, in spite of containing ML in the latter test solution. Further, as shown in Fig. 1, the mean ID plasma levels at 1 and 8 h after application of the control to non-pretreated skin were 0 and 1.67 µg/ml, respectively. On the other hand, the mean ID plasma levels absorbed through the pretreated skin at 0.5, 1 and 6 h after application were 5.60, 28.0 and 116.9 µg/ml, respectively. These results indicate that the barrier function of stratum corneum was decreased and then the lag time for percutaneous absorption of ID was reduced by the pretreatment of skin with ML. Therefore, ML can be assumed to act on the stratum corneum as the barrier-altering agent. It was observed from the pretreatment method that LL also acted on the stratum corneum to produce its effect, though the results were not indicated in this paper.

The investigations on applicabilities of lactic esters as the enhancers are in progress and the details will be reported in the future.

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