Soft Drugs 18. Oral and Rectal Delivery of Loteprednol Etabonate, a Novel Soft Corticosteroid, in Rats—for Safer Treatment of Gastrointestinal Inflammation

Nicholas Bodor,[1,3] Teruo Murakami,[1,2] and Whei-Mei Wu[1]

Received December 15, 1994; accepted January 9, 1995

Purpose. As a safe anti-inflammatory corticosteroid, the utility of loteprednol etabonate (LE) for the treatment of gastrointestinal inflammation, via oral and rectal administration, was investigated in rats. ***Methods.*** *In vivo,* LE solution and suspension were orally administered (20 mg/kg), and various LE preparations (solution, suspension & suppository) were applied in rectal loops (0.2 mg per loop). *In vitro,* various GI tissues were used to study the stability and partition of LE. ***Results.*** After oral administration of LE solution, LE reached the upper GI tract effectively, but not the colon, due to absorption and/or decomposition. In suspension, LE reached most of the GI tract (except rectum) in 8 hr and showed little absorption. After rectal applications, LE remained intact in the rectal loop for more than five hours with a slow rate of disappearance, however, LE distributed in the rectal membrane to some extent. The concentrations of LE and its inactive metabolites in plasma after both oral and rectal administrations were lower than the detection limit (0.1 μg/ml) at anytime during the experiments. *In vitro,* LE in solution was stable in stomach, but not in cecum, due to the hydrolysis by the cecal resident micro flora. In solution, LE distributed into the mucosal membranes efficiently (about 2.5 ~ 4.0 μg/g tissue). ***Conclusions.*** The results suggest that LE can be orally or rectally delivered in the GI tract for the topical treatment of the inflammatory bowel disease.

KEY WORDS: soft corticosteroid; loteprednol etabonate; oral delivery; rectal delivery; inflammatory bowel disease.

INTRODUCTION

Increasing drug potency by the structural modification frequently leads to a parallel increase in toxicity, especially in drugs that show multiple activities, such as corticosteroid. Drug design must therefore take into account the compound's therapeutic index, the ratio of its efficacy to toxicity. "Soft drug" concept was introduced by means of designing pharmaceutical agents of reduced toxicity with structural modification to achieve a satisfactory therapeutic index (1–7). In this concept, a lead compound is modified so that the active new drug undergoes a predictable and controllable metabolism *in vivo* to non toxic moieties after it achieves its therapeutic role.

Loteprednol etabonate (LE), chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate, one of the most promising soft corticosteroids, was synthesized from an inactive metabolite of prednisolone, Δ^1-cortienic acid (A), based on the "inactive metabolite approach" (3). *In vivo,* LE undergoes a facile, systemic two-step metabolism into first an inactive acid etabonate analog, Δ^1-cortienic acid etabonate (AE), and then into the lead compound, A, in the body. Therefore, LE, although possessing potent topical anti-inflammatory activity, causes much less systemic side effects than other corticosteroids (3). The *in vitro* studies using rat blood have confirmed that LE is mainly hydrolyzed into the inactive metabolite, AE (8). The topical anti-inflammatory activities of LE have been shown to be similar to that of betamethasone, so that the ophthalmic trial in human is currently undergoing (3).

Present studies were carried out to expand the application of LE to the mucosal membranes such as gastrointestinal and colorectal membranes. For this topical therapy in the GI tract, the soft steroid must distribute into targeted mucosal membranes at clinically effective concentrations, then be rapidly detoxicated after entering into the systemic circulation. Therefore, the oral and rectal deliveries of LE were evaluated in rats from the following points of view: *1.* Stability of LE in GI tract, *2.* Distribution of LE into the mucosal membranes along the GI tract, and *3.* Concentration of LE in the systemic circulation. Two different dosage preparations, LE in 20% dimethyl β-cyclodextrin (DMCD) solution and LE in 5% sodium carboxymethylcellulose (CMC Na) suspension, were administered orally for the comparative distribution studies, and various LE preparations, solution, suspension and suppository, were prepared to investigate the the usefulness of LE for rectal application. The blood level of LE was monitored after oral and rectal administration. The *in vitro* studies, such as the stability of LE in the GI membranes, and the partitions of LE into GI membranes were also performed to demonstrate the feasibility of GI application of LE.

MATERIALS AND METHODS

Materials

The soft steroid, Loteprednol etabonate (LE), was kindly supplied by Otsuka Pharmaceutical Co. Ltd. (Tokushima, Japan). Δ^1-cortienic acid etabonate (AE), and Δ^1-cortienic acid (A) were obtained from Xenon Vision Inc. (Alachua, FL). Heptakis(2,6-di-O-methyl)-β-cyclodextrin (DMCD) and Hydroxypropyl-β-cyclodextrin (HPCD) were obtained from Pharmatec Inc. (Alachua, FL). Low density CMC Na, propylene glycol (PG) and polyethylene glycol (PEG, MW = 1450) were obtained from Sigma Chemical Company (St. Louis, MO). Witepsol H-15 was obtained from Dynamit Novel Chemicals (Troisdorf-Oberlat, West Germany). All other chemicals were commercially available products of special reagent grade.

[1] Center for Drug Discovery, J. Hillis Miller Health Center, Box 100497, College of Pharmacy, University of Florida, Gainesville, Florida 32610.

[2] On leave of absence from Institute of Pharmaceutical Sciences, Hiroshima University, School of Medicine, 1-2-3 Kasumi, Minami-Ku, Hiroshima 734, Japan.

[3] To whom correspondence should be addressed.

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Animals

Male Sprague Dawley rats weighing 200 g to 250 g were obtained from Charles Rivers (Wilmington, MA). All the animal studies were conducted according to the guidelines set forth in the declaration of Helsinki and the Guiding principals in the Care and Use of Animals (DHEW Publication, NIH-80-23).

Oral Administration of LE in Rats

Dosage preparations of LE: LE solution was prepared by dissolving the compound (4 mg/ml) in a 50 mM phosphate buffer (pH 7.4) containing 20% DMCD. For the suspension, micronized LE (5–6 μ) was suspended in the previously mentioned buffer containing 5% CMC Na at a concentration of 20 mg/ml. The suspension was further sonicated in a Branson ultrasonicator (Smithkline Company) for 30 min. The osmolarity of the vehicle for the solution and suspension was adjusted to 280 mOsm/kg (μ OSMETTE micro osmometer, Precision Systems) by adding NaCl, if necessary.

Oral delivery of LE: Animals were fasted overnight (about 16 hr) prior to the experiment, but water was given freely. LE was administered orally in solution or suspension by a stomach intubation at a dose of 20 mg/kg (5 ml/kg of solution or 1 ml/kg of suspension). For LE suspension, 4 ml/kg water was also administered orally immediately after the administration of the suspension. At designated time intervals (1, 3, 5, or 8 hr after the administration of LE), the rats were sacrificed by lethal overdose of pentobarbital and the GI tract including the stomach, small intestine, cecum and colon were removed carefully so as not to disturb the luminal contents. The isolated small intestine was further divided into four regions of the same length from the stomach side (S-1, S-2, S-3 and S-4). The rectum was isolated by cutting at the sigmoid flexure, and the rest of the colon (downward of cecum) was divided into two regions with equal length from the cecum side (L-1 and L-2). For the determination of LE and AE remaining in each divided lumen after oral administration, each segment of the isolated GI tract was prepared as follows: The inner luminal contents were washed out with 10 ml of 50% acetonitrile in aqueous solution and then with 15 ml of 100% acetonitrile. The membrane tissue was homogenized in 100% acetonitrile with a Tekmar Tissumizer, and centrifuged. The washings of luminal contents and the supernatant of the tissue homogenate were combined, and pure acetonitrile was added to the combined mixture so that the total volume was 40 ml. The combined mixture was then vigorously shaken with a vortex mixer and centrifuged at 3000 rpm for 10 min. The supernatant was removed and analyzed by high performance liquid chromatography (HPLC). In separate experiments, the recovery of LE and AE was determined by spiking different concentrations of LE or AE to the intestinal lumen, and the samples were prepared by the same extraction method mentioned before. The results indicated that the recovery of LE and AE was 100 ± 3%.

Rectal Application of LE in Rats

Dosage preparations of LE: Five LE formulations were prepared as follows. *a*. LE suspended in pH 7.4, 50 mM phosphate buffer solution containing 5% CMC Na (isotonic); *b*. LE dissolved in a pH 7.4, 10 mM phosphate buffer containing 20% DMCD (isotonic); *c*. LE dissolved in PG; *d*. LE dissolved in PEG 1450, water soluble suppository base; and *e*. LE suspended in Witepsol H-15, oleaginous suppository base. Micronized LE (5–6 μ) was used for preparing suspensions. The suppository was prepared by dispersing LE into the fused suppository base (PEG or Witepsol H-15) and solidifying the suspension in a glass tube (0.55 cm inner diameter) at room temperature. LE concentration in all preparations was 1 mg/g or ml.

Rectal Application of LE: Animals were fasted for 16 hours before the experiment, but water was given freely. Sodium pentobarbital (Nembutal, Abott Laboratories) was injected intraperitoneally in the animals at a dose of 30 mg/kg. After the anesthesia, body temperature of the rats was kept above 36°C by lamps during the experiments. A midline incision was made to expose the peritoneal cavity. A rectal loop, approximately 3 cm, was made by ligating the rectal tract at the sigmoid flexure and by closing the basement of the anus with a drop of surgical cement (Aron Alpha A "Sankyo," Sankyo Co. Ltd., Tokyo, Japan). LE solution or liquid suspension was administered through polyethylene tubing (PE 50, Clay Adams) cannulated into the rectal lumen. LE suppository (LE in PEG or Witepsol H-15) was administered in the rectum and the basement of the anus was sealed with surgical cement. The LE dose administered was 0.2 mg in 0.2 ml or 0.2 g of vehicle per loop. At designated times (1, 3 or 5 hr) after rectal application of LE, blood was withdrawn from jugular vein, and then rats were sacrificed by lethal overdose of pentobarbital. Subsequently, the rectal loop containing luminal contents was isolated and the inner contents of the rectal lumen were washed with 5 ml of 50% acetonitrile in aqueous solution and then 10 ml of 100% acetonitrile. The rectal membrane was homogenized with a Tekmar Tissumizer in 100% acetonitrile and centrifuged. The washing of luminal contents and the supernatant of the tissue homogenate were combined, and pure acetonitrile was added to the combined mixture so that the total volume was 40 ml. The combined mixture was then vigorously shaken with a vortex mixer and centrifuged at 3000 rpm for 10 min. The supernatant was analyzed for LE concentrations by HPLC to determine the total amount of LE remained in the rectal loop and tissue membrane. For the determination of LE in blood samples, 0.2 ml of 5% dimethylsulfoxide (DMSO) in acetonitrile solution was added to 0.1 ml of blood to halt metabolism and precipitate the blood protein. The samples were shaken in the vortex mixer and cooled for several minutes at 0°C to facilitate protein precipitation. The samples were then centrifuged at 3000 rpm for 10 min and the supernatant was analyzed by HPLC. The recovery of LE and AE from the rectal loop homogenates and blood samples, 100 ± 3%, were determined as described in the previous section.

Stability of LE in Stomach and Cecum *in Vitro*

LE was dissolved in an isotonic, pH 7.4 phosphate buffer solution containing 20% DMCD at a concentration of 0.1 mg/ml. The stomach and cecum of overnight fasted rats were freshly isolated. After the insertion of a polyethylene

tubing (PE 50, Clay Adams) into the lumen, the tract was ligated on both sides and kept at 37°C for 5 min. A 0.5 ml of LE solution prewarmed to 37°C was introduced into the lumen via the polyethylene tubing and sealed. The inner luminal contents were mixed by pressing the outside of the sac. The sacs containing LE were incubated at 37°C for 30 min and/or 60 min. Determination of LE and AE remaining in the luminal contents of incubated stomach and cecum was carried out as described before.

Partition of LE into the GI membranes *in Vitro*

Approximately 0.3 g segments of freshly isolated rat GI membranes (stomach, small intestine and colorectum) were incubated in 1.5 ml of various LE solutions at 37°C for 1 hr under slow shaking. Then, the membranes were removed and the concentrations of LE and blue dextran in the incubating media were determined. The stomach membrane and small intestinal membranes were collected as previously described. The colorectal membrane was the region of 5 cm downward of the cecum. LE solutions used for incubation were: *a.* saturated solution of LE (0.5 μg/ml) in an isotonic, pH 7.4 phosphate buffer solution containing 0.1% blue dextran; and *b.* LE 1 or 10 μg/ml in an isotonic, pH 7.4 phosphate buffer solution containing 5% dimethyl β-cyclodextrin and 0.1% blue dextran. The partition coefficient, tissue-to-medium concentration ratio (T/M), of LE was calculated by the following equation, $T/M = (C_0V_0 - C_tV_t)/W/C_t$, where C_0, C_t, V_0, V_t indicate the initial concentration of LE in the medium, the final concentration of LE in the medium after the incubation, the initial volume of the medium (1.5 ml), and the final volume of the medium after the incubation, respectively. W is the weight of the tissue incubated. Blue dextran was used as a volume indicator, and V_t was obtained by the equation, $V_t = B_0V_0/B_t$, where B_0 and B_t indicate the initial and the final concentrations of blue dextran in the medium. The concentrations of LE and blue dextran were analyzed by HPLC and spectrophotometer, respectively.

Analytical Methods

An HPLC system operating at ambient temperature was used for quantitative determination of LE and AE in the samples. A Waters NOVA-PAK phenyl column (4 mm, 3.9 mm × 7.5 cm) was connected to a component system from Spectra-Physics, which consisted of SP 8810 precision isocratic pump, Rheodyne 7125 injector (injection volume 20 μl), SP 8450 UV/VIS variable wavelength detector operated at 254 nm, and an SP 4290 integrator. The mobile phase was consisted of acetonitrile, acetic acid and water in a volume ratio of 45:1:54. With a flow rate of 1 ml/min, the retention time for LE and AE were 5.12 and 1.67 min, respectively, and the detection limit was less than 0.1 μg/ml for both compounds. The concentration of the compound in each sample was determined by comparison of the peak area with that of the corresponding standard curves (0–1 μg/ml, 0–10 μg/ml & 0–100 μg/ml, $r > 0.990$). The standard curves were developed by adding various known concentrations of LE or AE in the blank samples, and then prepared as described in previous sections. In the tissue partition studies, the concentration of blue dextran was determined by a spectrophotometer at wavelength of 620 nm.

RESULTS AND DISCUSSION

For the treatment of inflammatory bowel diseases such as ulcerative colitis and Crohn's disease, corticosteroids are still the mainstay of treatment (9). Corticosteroids are effective particularly on mild and moderate attacks of bowel inflammation, or for maintenance therapy (10). However, the use of corticosteroids has been severely limited because of its widespread systemic side effects and numerous toxic complications (11).

LE, a soft steroid, is designed to undergo a predictable metabolism *in vivo* to non toxic moieties after it achieves its therapeutic role at the local sites of action. It has been shown that LE possesses good anti-inflammatory activity but causes fewer side effects (3). However, in the case of GI application of LE, because of the presence of the ester moiety on the LE structure, a possible degradation of LE in the GI tract has to be considered. Ester moieties, such as chloramphenicol mono- and di- succinate, erythromycin propionate, and penicillin acetoxy methyl ester are easily degraded enzymatically by intestinal micro flora and/or esterase located on the gastrointestinal mucosal membrane (12–13). For the topical GI therapy, soft steroid must distribute into targeted mucosal membranes at clinically effective concentrations. This study was therefore designed to assess whether LE is stable before it distributes into the mucosal membranes, and whether LE distributes to the membranes effectively along the whole gastrointestinal tract.

Distribution of LE in the Alimentary Tract Following Oral Administration

Two different oral dosage preparations of LE, LE in 20% DMCD solution and LE in 5% CMC Na suspension, were examined. DMCD (20%) was used because the solubility of LE could be increased from 0.5 μg/ml to 5.3 mg/ml by the complex formation between DMCD and LE (14–16). When LE was administered orally in either solution or suspension at a dose of 20 mg/kg, the concentration of LE in the plasma was less than its detection limit (<0.1 μg/ml) at any time, which is in good accordance with the soft drug concept. Therefore, the remaining amounts of LE in various segments of the gastrointestinal tract (including the luminal contents and the tissues) were determined. Figure 1 shows the distribution of LE and AE (*a* and *b*, respectively) in the gastrointestinal tract after oral administration of LE solution. Following the administration, LE in the stomach decreased with the time progressing, and distributed to the whole small intestine. The intact form, LE, could be observed staying in the stomach and small intestine for more than 5 hr. However, no LE was detected in the large intestine, except the cecum (e.g., 5 hr), at any time irrespective of the transit of LE to the cecum. In the cecum, about 10% of AE was detected at 1 hr after the oral administration. From the disappearance of AE, it can be considered that further step of degradation happened consequently.

In Figure 2, the total recovery of LE and AE from the whole alimentary tract as a function of time is expressed by the percentage of dose. The loss of total amount (including LE and AE) from the alimentary tract may result mainly from the intestinal absorption of LE into the systemic circulation and the further degradation of AE.

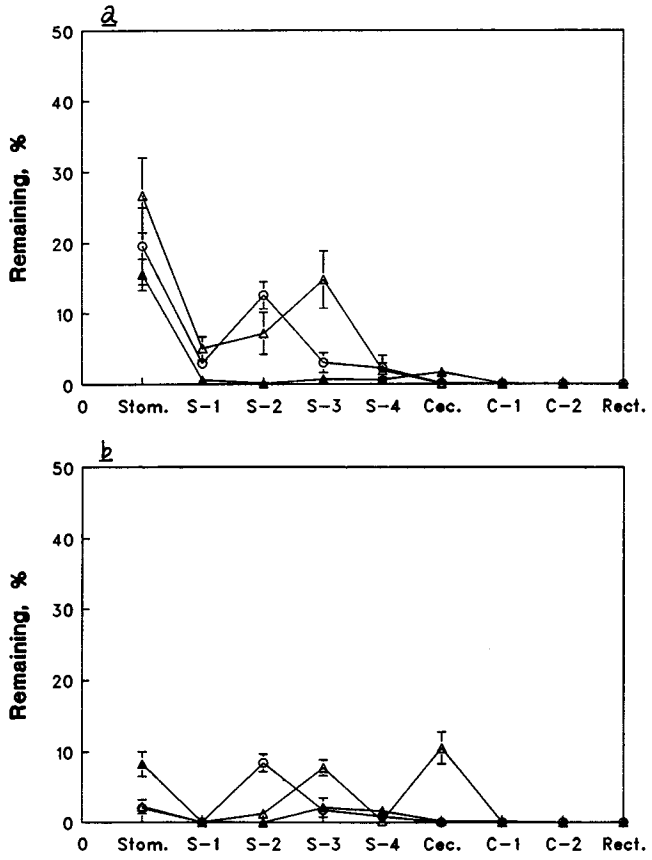

Fig. 1. Remaining amount of LE, *a*, and AE, *b*, in each region of the GI tract at various time points following oral administration of LE solution (LE in 20% DMCD) at a dose of 20 mg/kg. (△), 1 hr; (○), 3 hr; (▲), 5 hr. Each value represents the mean ± S.E. of three trials. Stom, stomach; S-1, 2, 3 & 4, small intestine (between the stomach and the cecum) divided into four equi-length regions; Cec, cecum; C-1 & 2, colon (between the cecum and the rectum) divided into two equi-length regions; Rect, rectum.

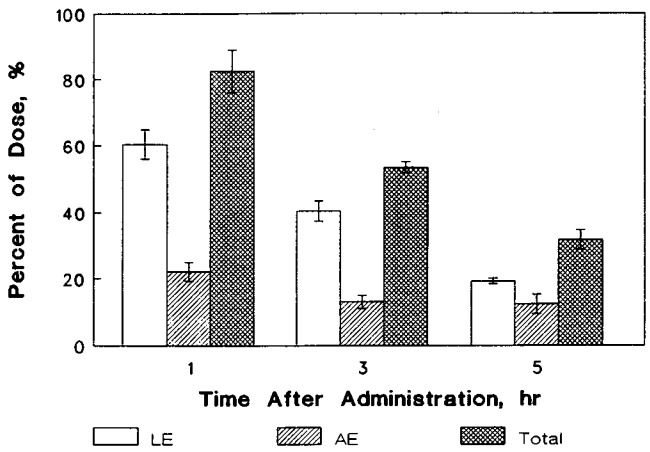

Fig. 2. LE, AE and the total amount of LE and AE remained in the whole GI tract at various time points after oral administration of LE solution (LE in 20% DMCD) at a dose of 20 mg/kg. Each value represents the mean ± S.E. of three trials.

In the case of oral delivery of LE suspension, the distribution of LE in each GI segment varied among animals. Since the time-dependent GI distribution of a drug is mainly dependent on the gastric emptying time as well as the intestinal transit time, a highly viscous dosage preparation, such as LE in 5% CMC Na, may result in highly variable gastric emptying times of LE among animals, and the distribution of LE would be therefore varied. After the oral delivery of LE suspension, no AE was detected (or less than the detection limit) in any part of the gastrointestinal tract, even in the cecum. The overall gastrointestinal distribution of LE after the administration of LE suspension is shown in figure 3. The results indicate that distribution of LE was correlated to the time progressing. During 8 hr of the experiment, LE was found in almost whole GI tract, except rectum where the drug has not reached yet. The total recovery of LE was investigated at various time periods, and the results indicate that about 90% of LE remained in the alimentary tract, even at 8 hr after the administration. Since no AE was found in the alimentary tract, the disappearance of LE is considered mainly resulted from the intestinal absorption.

These results indicate that oral delivery of LE suspension might be effective for the treatment of the whole GI tract inflammations. On the other hand, oral delivery of LE solution will be effective only on the upper GI inflammations, since LE administered by a solution will be almost completely degraded in the cecum, probably by the resident gastrointestinal micro flora.

The Fate of LE Following Rectal Administration

After the application of LE, either in solution (DMCD or PG), suspension (CMC Na) or suppository (PEG or Witepsol H-15), to rectal loop at a dose of 0.2 mg per loop, the remaining amount of LE in the rectal tract and rectal membrane was evaluated. As shown in figure 4, in all kind of preparations, LE retained in the rectum for more than 5 hours. Compared to LE in suspension or suppository, LE in solution disappeared faster from the rectum, and the disappearance of LE displayed a mono-exponential manner. In the case of LE suspension or suppository, the compound disappeared rapidly from the rectum during the first hour, but the rate of disappearance slowed down thereafter. Blood samples were analyzed for LE in all cases, but no LE could be detected in the blood at any time during the experiment. It has been described previously that LE administered orally in DMCD solution, but not in suspension, was degraded almost completely in the cecum, probably by the microorganisms exist in the intestine. In the rectum, however, the degradation of LE may be negligible, since no metabolite of LE was detected in the washings of the rectal luminal contents.

Stability of LE in Stomach and Cecum

When LE was administered orally in a solution, the metabolite, AE, was detected in the whole gastrointestinal tract as indicated in figure 1. However, in the preliminary experiments, LE was proved very stable in 10% homogenate of various GI membranes (no degradation of LE was detected during the 2 hr experiment), so that degradation of LE in the GI tract is considered to be occurred in the luminal contents. Accordingly, the stability of LE in the stomach or cecal contents was determined. The experiments were carried out under anaerobic condition to mimic the *in vivo* environment by

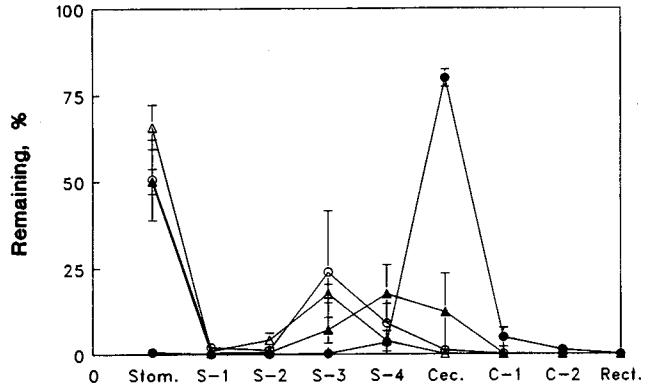

Fig. 3. Remaining amount of LE in each region of GI tract at various time points following oral administration of LE suspension (LE in 5% CMC Na) at a dose of 20 mg/kg. (△), 1 hr; (○), 3 hr; (▲), 5 hr; (●), 8 hr. Each value represents the mean ± S.E. of three trials. Abbreviations of GI regions are the same as in Fig. 2.

tying up both ends of the tract. The results indicate that LE is fairly stable in the stomach (no change in HPLC peak height could be detected during 4 hr experiment), but relatively unstable in the cecum with a degradation half-life of 16.26 ± 2.16 min (n = 3). Since LE is fairly stable in pH 7.4 phosphate buffer solution at 37°C, half-life > 200 hr, the degradation of LE in the cecum can be considered mainly due to the enzymatic hydrolysis by cecal resident micro flora.

Partition of LE into the GI membranes *in Vitro*

To achieve the therapeutic role of LE at the GI mucosal membranes, efficient distribution of LE into the membrane tissues is required. For tissue partition studies, three different concentrations of LE in various media were employed; and three different tissues, gastric, small intestinal and colorectal membranes, were used. Since the solubility of LE in the isotonic, pH 7.4 phosphate buffer is relatively low (0.5 mg/ml), DMCD (5%) was used to obtain higher concentrations of LE in the testing medium (1 mg/ml and 10 mg/ml), as in the case of *in vivo* studies. In Table 1, the partition of LE into the GI membranes is indicated by the T/M ratio of LE.

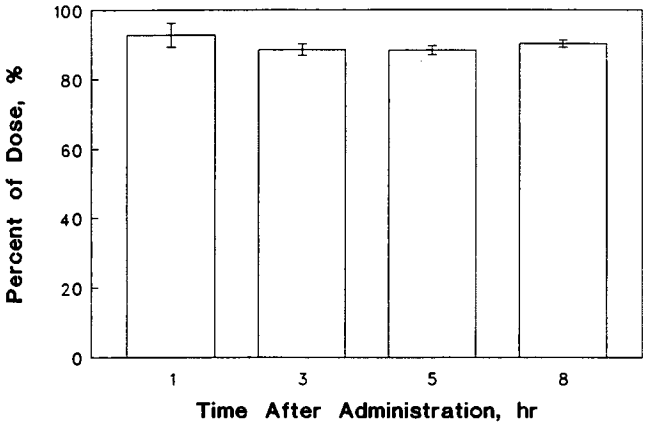

Fig. 4. LE remained in the whole GI tract following oral administration of LE suspension (20 mg/kg in 5% CMC Na). Each value represents the mean ± S.E. of three trials.

In buffer solution, LE concentrations in tissues were four to ten times bigger than in the media, which indicates that LE possesses good tissue affinity. Compared to the case of buffer solution, the T/M ratio of LE was reasonably reduced by cyclodextrin, probably due to the complexation between LE and DMCD. The T/M ratio of LE obtained from three different gastrointestinal regions were comparable in all cases. The concentration of LE in the membrane, when calculated by multiplying the LE concentration in the saturated solution and the T/M ratio, 5–8, could be estimated to be about 2.5–4.0 μg/g tissue. To date, no information regarding to the effective concentration of corticosteroids in the tissue for the treatment of inflammation is available. However, it has been proved that corticosteroids are effective by topical application to the skin or eye (11); and LE suspension (0.1%) was as effective as dexamethason solution (0.1%) for ophthalmic treatment (17). In the case of eye delivery of LE suspension, the absolute amount of LE distributed into the eye tissue from a suspension could be very small compared to that of the GI membranes after oral administration, since most of the drug could be drained away through tear duct. So, it can be considered that concentration of LE in GI membrane after oral administration of a suspension might be sufficiently high for the topical treatment of the GI inflammatory diseases. In the case of lower bowel inflammations, the efficacy of the treatment is markedly influenced by the resident time of the drug within the colon. Because of the "streaming phenomenon" (18), small particles pass through the colon more slowly than big particles, micronized LE suspension can stay in the colon longer than other preparations. It is also known that transit time for most healthy human subjects is 12 hr or longer depending on food takes, bowel habits and the size of the dosage form (19), and that acute ulcerative colitis does not lead to an accelerated transit in the colonic regions in human (20). Therefore, LE might achieve and maintain concentrations in the colon after administration of suspension, which may be beneficial in the treatment of lower bowel inflammatory disease in human.

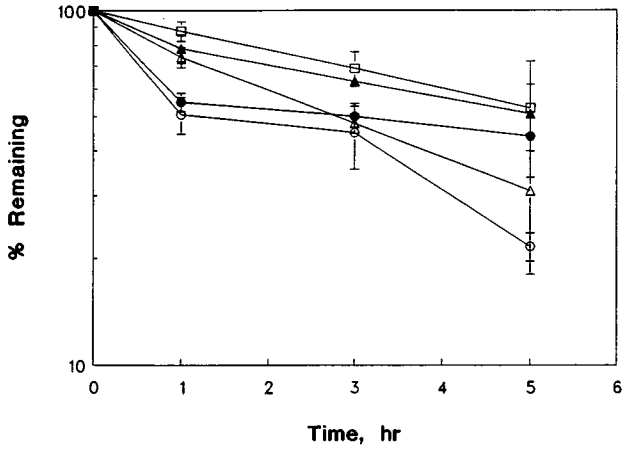

Fig. 5. Remaining amount of LE in rectal loop following rectal application of LE at a dose of 0.2 mg/loop in various vehicles (0.2 g or ml). (△), 20% DMCD solution; (○), propylene glycol solution; (▲), 5% CMC Na suspension; (●), PEG 1450 suppository; (□), Witepsol H-15 suppository. Each value represents the mean ± S.E. of three trials.

Table 1. Partition, T/M Ratio, of LE into Rat GI Membranes

Concentration of LE, μg/ml	0.5[a]	1[b]	10[b]
Stomach	4.71 ± 0.83[c]	0.46 ± 0.20	0.41 ± 0.21
Small intestine	6.94 ± 0.58	0.53 ± 0.14	0.46 ± 0.14
Colorectum	8.24 ± 2.21	0.42 ± 0.13	0.46 ± 0.12

[a] Saturated solution of LE in pH 7.4 isotonic phosphate buffer solution containing 0.1% blue dextran as volume indicator.
[b] LE was dissolved in previous solution containing 5% of DMCD.
[c] Data are the Mean ± SE of three trials.

In this study, although the apparent T/M ratio of LE was largely reduced by DMCD, the solubility and stability of LE were significantly increased (14–16). Therefore, cyclodextrin should be useful as a carrier *in vivo* to transport more drug to the desired sites of the mucosal membrane to contribute the topical treatment of GI inflammation.

In conclusion, this study demonstrates that LE can be delivered to the whole GI tract by a proper formulation design. LE shows relatively high tissue partition, and stability in GI membrane. LE, when administered orally in a suspension, remains as an intact form and distributes to the whole GI membranes effectively. LE can be used as suppository for rectal applications. Also, LE acts in accordance with the soft drug concept, that is, rapid deactivation *in vivo* after entering the systemic circulation, so the unwanted side effects can be avoided. The results obtained from this study suggest that soft steroid, LE, can be successfully delivered to the GI tract for the treatment of the inflammatory bowel diseases.

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