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Effect of non-ionic surfactants in a polyacrylic acid gel base on the rectal absorption of [Asu^{1,7}]-eel calcitonin in rats

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The effect of non-ionic surfactants in a polyacrylic acid gel base on the rectal absorption of [Asu^{1,7}]-eel calcitonin, a calcitonin analogue, was studied in rats. Absorption was enhanced by a microenema which used a polyacrylic acid gel base, but it was reduced by the incorporation of polysorbate 80 (0·1–5% v/v). The incorporation of polyoxyethylene 9 lauryl ether (0·1–5% v/v) in the polyacrylic acid gel base enhanced the absorption. Rectal administration in the base containing 0·5% v/v polyoxyethylene 9 lauryl ether required a dose of the calcitonin 2–3 times greater than an intramuscularly administered dose to achieve an equivalent hypocalcaemic effect.

Rectal administration is considered advantageous for several classes of drugs because the first pass elimination for high-clearance drugs may be partly avoided. However, for rectal administration of poorly absorbable drugs such as those that are water-soluble and macromolecular polypeptides, their bioavailabilities need to be enhanced by pharmaceutical modification. An aqueous gel base of polyacrylic acid, a group of carboxyvinyl polymers cross-linked with allyl sucrose, improved the absorption of insulin from the rectum (Morimoto et al 1980, 1983), vagina (Morimoto et al 1982) and nose (Morimoto et al 1985), and that of calcitonin from the rectum (Morimoto et al 1984) and nose (Morimoto et al 1985). Moreover, it has been recently reported that the absorption of poorly absorbable drugs can be enhanced by coadministration with enamine (Kamada et al 1981), and carboxylic acid (Okada et al 1982) as well as with surfactants.

The present study has been designed to evaluate the effect of non-ionic surfactants, polyoxyethylene sorbitan monooleate (polysorbate 80) and polyoxyethane 9 lauryl ether (POE 9 lauryl), on the enhancement of polyacrylic acid gel base on the rectal absorption of [Asu^{1,7}]-eel calcitonin as evaluated in terms of the hypocalcaemic effect in young rats.

Materials and methods

Materials. The active ingredient used was [Asu^{1,7}]-eel calcitonin (Toyojozo; Japan), a semisynthetic analogue of eel calcitonin in which the S–S bond at the first and seventh amino acid in eel calcitonin molecule is replaced by CH_2–CH_2 bond (Morikawa et al 1976). Polyacrylic acid (Carbopol 941) was obtained from B. F. Goodrich (Ohio, USA). The non-ionic surfactants used were polyoxyethylene sorbitan monooleate (polysorbate 80) from Wako Pure Chemicals, Japan and polyoxyethylene 9 lauryl ether (POE 9 lauryl) from Nikko Chemicals, Japan.

Preparations. Polyacrylic acid aqueous gel base was prepared by presoaking Carbopol 941 in distilled water for 15 h at room temperture (20 °C) and adding 10% NaOH solution to adjust to pH 6·5, the final concentration of gel being adjusted by the addition of water (Morimoto et al 1980). When either of the non-ionic surfactants, polysorbate 80 or POE 9 lauryl was to be incorporated, it was dissolved in the gel base at the concentration of 0·1–5% v/v. [Asu^{1,7}]-eel calcitonin was dissolved in each gel base.

Rectal administration. Wistar strain, male rats (four weeks old), 80–100 g, were fasted for 20 h before experiments but had free access to water. For the experiment, rats were anaesthetized with pentobarbitone (50 mg kg^{-1}) and a portion of the gel preparation warmed to 30 °C was administered into the rectal loop which had been previously isolated by ligation with thread at 2·5 cm from anus. The dose of gel base was fixed at 0·25 ml/100 g weight. Blood samples (0·3 ml) were taken from the femoral vein 10 min before and at 30 min, 1, 2 and 3 h after administration using a heparinized syringe. The plasma calcium concentration was determined by the *o*-cresolphthalein complexane method as described by Morin (1974).

Results and discussion

In a preliminary experiment on the rectal administration of [Asu^{1,7}]-eel calcitonin, preparations in saline solution and an oily suppository (Witepsol H-15) at a dose of 5 U kg^{-1}, failed to reduce the plasma calcium level in rats (Morimoto et al 1984). But the absorption of [Asu^{1,7}]-eel calcitonin from the rectum was promoted by the use of aqueous polyacrylic acid gel base.

Fig. 1 shows the effect of polysorbate 80 in a polyacrylic acid gel base (pH 6·5) on plasma calcium levels after rectal administration of [Asu^{1,7}]-eel calcitonin (1 U kg^{-1}) in rats. With the polyacrylic acid gel without surfactant, the plasma calcium level decreased rapidly and a significant hypocalcaemic effect was obtained 30 min after administration (from 0·972 ±

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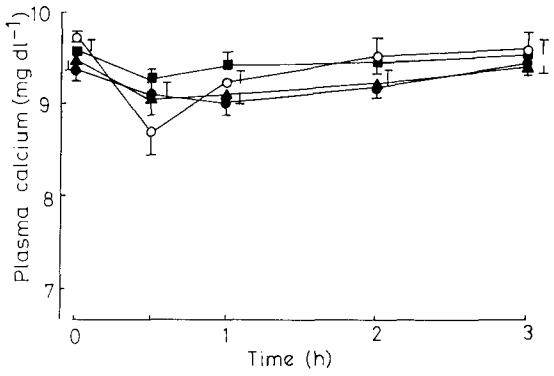

FIG. 1. Change in plasma calcium levels following rectal administration of 1 U kg^{-1} [Asu^{1,7}]-eel calcitonin in polyacrylic acid gel base (0·1% w/v, pH 6·5) containing polysorbate 80, to rats. Concentration of polysorbate 80: (○) 0%, (▲) 0·1%, (■) 1%, (●) 5% v/v. Each point is the mean ± s.e.m. of 5 animals.

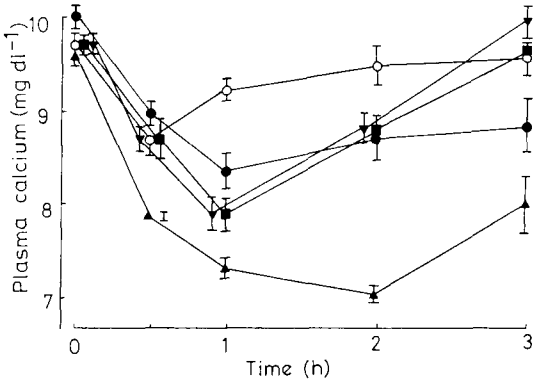

FIG. 2. Change in plasma calcium levels following rectal administration of 1 U kg^{-1} [Asu^{1,7}]-eel calcitonin in polyacrylic acid gel base (0·1% w/v, pH 6·5) containing POE 9 lauryl to rats. Concentration of POE 9 lauryl: (○) 0%, (▼) 0·1%, (▲) 0·5%, (■) 1%, (●) 5% v/v. Each point is the mean ± s.e.m. of 5 animals.

0·018 mg ml^{-1}, to 0·854 ± 0·023 mg ml^{-1}; $P < 0·005$). However, polyacrylic acid gel base containing polysorbate 80 at the concentration range of 0·1–5% v/v produced no hypocalcaemic effect. The effect of polyacrylic acid gel base as absorption promotor may thus be inhibited by polysorbate 80.

Fig. 2 shows the effect of POE 9 lauryl in polyacrylic acid gel base (0·1% w/v, pH 6·5) on plasma calcium levels after rectal administration of [Asu^{1,7}]-eel calcitonin in rats. The hypocalcaemic effects at any concentration of POE 9 lauryl were larger than that with the gel base alone and were in the following order of strength: 0·5% > 0·1% = 1% > 5% > 0% v/v of concentration of POE 9 lauryl. With the gel base containing 0·5% v/v of POE 9 lauryl, the minimum plasma calcium level observed 2 h after administration was 74% of the initial level. The minimum plasma calcium level was obtained at 1 h for 0·1%, 1% and 5% v/v of POE 9 lauryl.

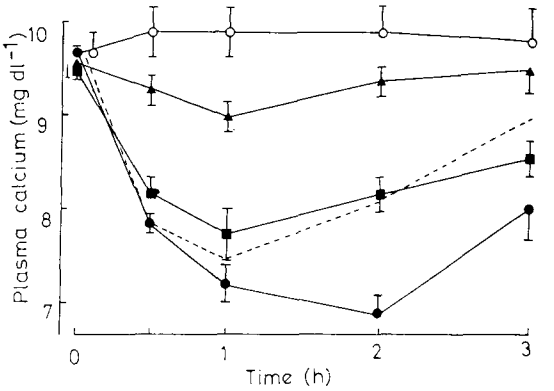

FIG. 3. Dose-dependency of [Asu^{1,7}]-eel calcitonin on plasma calcium levels following rectal administration in polyacrylic acid gel base (0·1% w/v, pH 6·5) containing POE 9 lauryl (0·5% v/v) and intramuscular administration (0·2 U kg^{-1}) to rats. Rectal doses; (○) 0, (▲) 0·1, (■) 0·5, (●) 1 U kg^{-1}. Intramuscular administration: - - - -. Each point is the mean ± s.e.m. of 5 animals.

However, the plasma calcium level after rectal administration of 1 U kg^{-1} [Asu^{1,7}]-eel calcitonin in 0·9% v/v NaCl solution containing 0·5% v/v POE 9 lauryl was 62% and was lower than that of polyacrylic acid gel containing 0·5% v/v POE 9 lauryl.

Fig. 3 shows the dose-response profiles of plasma calcium level following rectal administration of [Asu^{1,7}]-eel calcitonin with gel base containing 0·5% v/v POE 9 lauryl in rats. The hypocalcaemic effect was dose-dependent, and when the plasma calcium levels were compared with those after intramuscular injection of [Asu^{1,7}]-eel calcitonin, 0·2 U kg^{-1}, the rectal route required 2–3 times more than the intramuscular administered dose to achieve an equivalent hypocalcaemic effect.

In conclusion, rectal administration of [Asu^{1,7}]-eel calcitonin resulted in a hypocalcaemic effect that was enhanced by the addition of POE 9 lauryl in polyacrylic acid gel.

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