

Effective vaginal absorption of insulin in diabetic rats and rabbits using polyacrylic acid aqueous gel bases

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Summary

The effect of the gel preparation on the rate of absorption of a vaginally administered insulin which was suspended in a polyacrylic acid aqueous gel base was investigated in the alloxan diabetic rats and rabbits. When insulin (dose 1 IU/kg) was given into the vagina in the gel preparation (0.1%, pH 6.5) to rats and rabbits, the plasma insulin reached a peak, and prominent hypoglycemic effects were observed during the first 30 min, which is indicative of a facilitated rate of vaginal absorption of insulin by the polyacrylic acid aqueous gel base.

However, the plasma insulin quickly diminished after 1 h and plasma levels returned to the initial level after 3 h.

Introduction

In recent years, much interest has arisen in applying some compounds of synthelin and semisynthelin as a biomedical polymer. Studies from our laboratory have focused on whether polyacrylic acid aqueous gel can be used as a suppository base. We have previously reported the use of polyacrylic acid aqueous gel bases for the rectal administration of insulin (Morimoto et al., 1980). Our results were confirmed by others that high bioavailability was obtained by rectal administration of ibuprofen in gel preparation (Hirano et al., 1980). The gel base has the advantage of adjusting the pH and viscosity over a wide range according to type of drugs to be used, because its viscosity remains constant over a wide range, pH 4.5–12. There

have been some reports concerning application as ointment vehicles (Shima et al., 1981) and ophthalmic vehicles (Testard et al., 1978). However, there have been no reports concerning application of them as a suppository excepting our reports.

In this study, we investigated whether insulin could be absorbed through the vaginal mucosa with polyacrylic acid aqueous gel bases in the diabetic rats and rabbits.

Materials and methods

Materials and preparations

The gel was prepared by adding 10% NaOH solution to adjust each pH into various concentrations of polyacrylic acid (Hiviswako 105; Wako Pure Chemical Industries, Japan) presoaked in distilled water for 15 h. The concentrations of the gel bases were 0.1 and 1% (w/v). Bovine insulin (24.9 IU/mg; Sigma) was suspended in each gel base. The viscosity of the gel base was determined with a cone plate viscometer (E type; Tokyo Keiki) at 37°C and 10 rpm.

Animal experiments

Wistar strain female rats, weighing 200–250 g, and female albino rabbits, weighing 2–3 kg, were used. Diabetic rats and rabbits were prepared by intraperitoneal injection and intravenous injection of alloxan solution. Blood glucose levels in diabetic animals were greater than 300 mg/dl within 7–10 days of the alloxan administration. Animals were fasted for 20 h prior to experiment. In rats under pentobarbital anesthesia, the insulin gel preparations were administered into the vagina at a gel volume of 0.2 ml/200 g body weight except in the varying gel volume experiments. In rabbits, insulin in gel preparations were administered into the vagina at the volume of 0.5 ml/kg weight. Blood specimens were obtained from the femoral veins of the rats and ear veins of the rabbits at the designated time intervals.

Analytical methods

Blood glucose was determined by the glucose oxidase/peroxidase method (Kiang, 1975) and plasma insulin was measured by the radioimmunoassay (Nakagawa, 1972).

Results and discussion

The plasma glucose levels change as shown in Fig. 1 following a vaginal administration of the insulin in gel preparation (pH 6.5) of various viscosity levels to diabetic rats and rabbits. The prominent hypoglycemic effect was observed in the first 30 min with a 0.1% gel base, where the viscosity is low. However, when a high viscosity gel (1%) was administered, the hypoglycemic effect was not any more marked than that by the 0.1% gel preparation at 30 min. These effects were obtained by a smaller dose of insulin than that used with the rectal administration of insulin

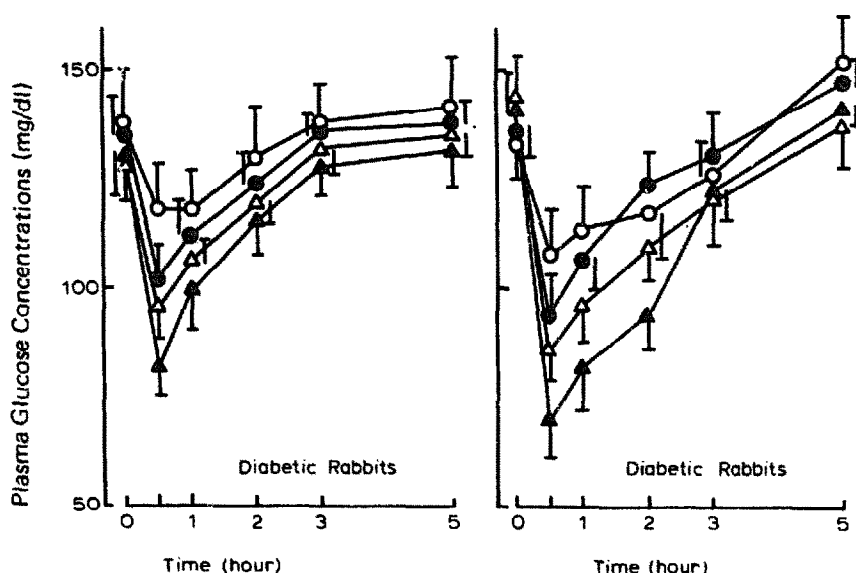


Fig. 1. Plasma glucose levels following vaginal administration of insulin gel (pH .5) at two viscosity levels in alloxan diabetic rats and rabbits. Each point is a mean \pm S.E.M. of 5 animals. 0.1% gel: ●, 1 IU/kg insulin; ▲, 3 IU/kg insulin; 1% gel: ○, 1 IU/kg insulin; △, 3 IU/kg insulin.

in gel preparation in our preceding paper (Morimoto et al., 1980).

The dose-dependency of plasma insulin levels and plasma glucose levels following a vaginal administration of insulin in gel preparation (0.1%; pH 6.5) to diabetic rats is shown in Fig. 2. Plasma insulin levels (IRI) reach a peak within the first 30 min of every dose and was dose-dependent. And then the maximum hypoglycemic effects were recorded at 30 min and the plasma glucose levels rapidly recovered after the first hour. The plasma insulin levels corresponded well with the blood glucose levels.

When the same amount of insulin contained in a different volume of gel base was administered to the diabetic rats, the hypoglycemic effect was not significantly different although the concentrations of insulin were different (Fig. 3). It is very important in the case of clinical application to consider the volume of vehicle on administration.

It has been generally considered that insulin is hardly absorbed through mucosa. Vaginal administration of insulin with the cetomacrogol 1000 vehicle containing a surfactant needing a large dose of insulin for hypoglycemic effect (27 IU/rat) has been reported by Touitou et al. (1978). However, the high hypoglycemic effects were produced by vaginal administration of the insulin in polyacrylic acid aqueous gel base at a low dose (1 IU/kg). The gel preparation, like a film on the surface of the mucosa, was found to be adsorbed into the mucosa; however, the mechanism of accelerating absorption of insulin is not clear.

The results indicate that the vaginal administration of the insulin gel preparation may be useful as a simple and painless dosage form in the long-term treatment of diabetes.

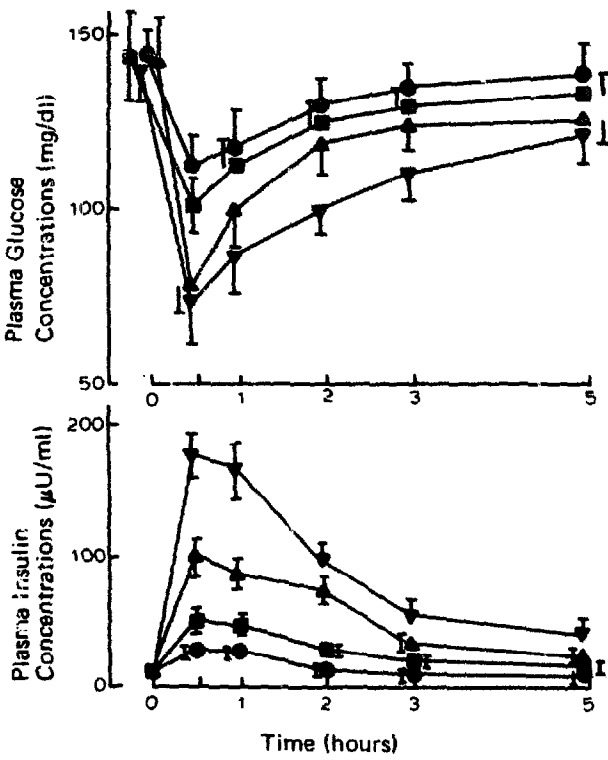


Fig. 2. Dose-dependency of plasma insulin levels and plasma glucose levels following vaginal administration of insulin gel preparation (0.1%; pH 6.5) in alloxan diabetic rats. Each point is a mean \pm S.E.M. of 5 animals. Insulin dose: \bullet , 0.5 IU/kg; \blacksquare , 1 IU/kg; \blacktriangle , 3 IU/kg; \blacktriangledown , 5 IU/kg.

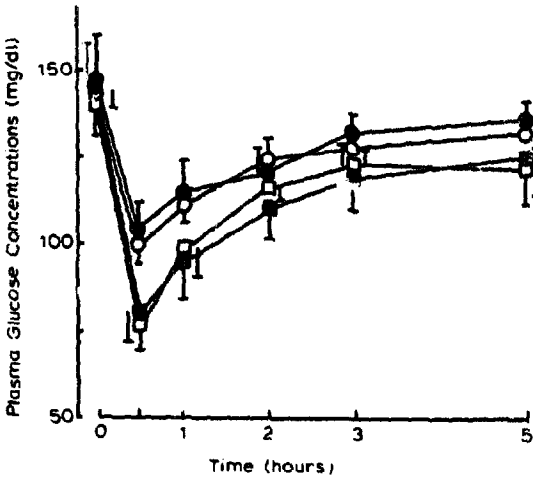


Fig. 3. Plasma glucose levels following vaginal administration of 0.1% insulin gel preparation (pH 6.5) at various volumes in alloxan diabetic rats. Each point is a mean \pm S.E.M. of 5 animals. Gel volume 0.2 ml/200 g rat: \bullet , 1 IU/kg; \blacksquare , 3 IU/kg; gel volume 0.05 ml/200 g rat: \circ , 1 IU/kg; \square , 3 IU/kg.

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References

- Hirano, E., Morimoto, K., Takeeda, T., Nakamoto, Y. and Morisaka, K., Pharmaceutical studies of polyacrylic acid aqueous gel bases. II. Absorption of ibuprofen from gel preparation following rectal administration in rats. *Chem. Pharm. Bull.*, 28 (1980) 3521–3526.
- Kiang, S.W., Kuan, J.W., Kuan, S.S. and Guilbault, G.G., Measurement of glucose in plasma with use of immobilized glucose oxidase and peroxidase. *Clin. chem.*, 22 (1976) 1378–1382.
- Morimoto, K., Hana, I., Nakamoto, Y., Takeeda, T., Hirano, E. and Morisaka, K., Pharmaceutical studies of polyacrylic acid aqueous gel bases: absorption of insulin from polyacrylic acid aqueous gel bases following rectal administration in alloxan diabetic rats and rabbits. *J. Pharm. Dyn.*, 3 (1980) 24–32.
- Nakagawa, S., Sasaki, T. and Horiuchi, H., A study on the insulin radioimmunoassay with sephadex bound antibody. *Radioisotopes*, 21 (1972) 98–101.
- Shima, K., Matsusaka, C., Hirose, M., Noguchi, T., Noguchi, T. and Yamahira, Y., Biopharmaceutical characteristic of indomethacin gel ointment. *Chem. Pharm. Bull.*, 22 (1981) 2338–2344.
- Testard, B. and Etter, J.C., Etude de l'hydrolyse de la pilocarpine dans des hydrogels de Carbopol. *Can. J. Pharm. Sci.*, 10 (1978) 16–20.
- Touitou, E., Donbrow, M. and Azaz, A., New hydrophilic vehicle enabling rectal and vaginal absorption of insulin, heparin, phenol red and gentamicin. *J. Pharm. Pharmacol.*, 30 (1978) 662–663.