basic solution. One of the major degradation products of triamcinolone in basic media is the D-homosteroid III (Timmins & Gray, unpublished observations) and this reaction is therefore not dependent on an enolization step. D-homosteroids were not observed as major degradation products of triamcinolone acetonide.

In summary, it may be seen that in neutral and basic media the presence of the acetonide function stabilizes the steroid ketal in comparison with the parent 16α-hydroxysteroid, preventing hydroxide ion-catalysed decomposition to the D-homosteroid. Below pH 7 the shape of the pH-rate profile for the steroid ketal is almost identical to that for the parent 16α-hydroxy steroid. The shape of the pH-rate profile for the steroid ketal can be explained in terms of enol formation ionization of the enol whereas this has little influence on the decomposition of the parent 16α-hydroxysteroid. The decomposition of the steroid ketal thus parallels that of steroids possessing no C16 hydroxyl such as hydrocortisone.

REFERENCES

Amin, M. I., Bryan, J. T. (1973) J. Pharm. Sci. 62: 1768–1771

Chulski, T., Forist, A. A. (1958) J. Am. Pharm. Assoc. Sci. Ed. 47: 553–555

Dekker, D., Beijnen, J. H. (1980) Pharm. Weekblad, Sci. Ed. 2: 112–116

Dekker, D., Beijnen, J. H. (1981) Acta Pharm. Suec. 18: 185–192

Dekker, D., Beijnen, J. H. (1982) Pharm. Acta Helv. 57: 4–7

Hansen, J., Bundgaard, H. (1979) Arch. Pharm. Chem. Sci. Ed. 7: 135–146

Johnson, D. (1982) J. Org. Chem. 47: 198–201

Oesterling, T. O., Guttman, D. E. (1964) J. Pharm. Sci. 53: 1189–1192

J. Pharm. Pharmacol. 1983, 35: 177–178
Communicated October 11, 1982

0022–3573/83/030177–02 $02.50/0

Insulin suppository: enhanced rectal absorption of insulin using an enamine derivative as a new promoter

TOSHIHITO YAGI†, NOBUYOSHI HAKUI, YOSHIMITSU YAMASAKI, RYUZO KAWAMORI, MOTOAKI SHICHIRI, HIROSHI ABE, SOONIH KIM*, MASATOSHI MIYAKE*, KUNIHISA KAMIKAWA*, TOSHIAKI NISHIHATA*, AKIRA KAMADA*, *First Department of Medicine, Osaka University Medical 1-1-50, Fukushima, Fukushima-ku, Osaka, 553, Japan * Faculty of Pharmaceutical Sciences, Osaka University, 133-1, Yamada-Kami, Suita, Osaka, Japan*

The rectal administration of insulin suppositories containing the surfactant, polyoxyethylene-9-laurylether (BL-9-EX, final concentration of 3% w/w), to diabetic dogs and diabetic patients has been reported to be effective in lowering the plasma glucose concentration with a dose as low as 2 u kg^{-1} without impairment to the rectal mucosae (Shichiri et al 1979; Yamasaki et al 1981a; Yamasaki et al 1981b). However, the use of non-ionic ether type surfactants at a concentration of 0·1% resulted in transient damage to nasal mucosae (Hirai et al 1981). Rectal absorption of antibiotics was found to be enhanced by enamine derivatives (Murakami et al 1981). One such derivative DL-phenylalanine-ethylacetoacetate, synthesized by reacting sodium phenylalaninate and ethylacetoacetate (β-diketone), is hydrolysed to phenylalanine and ethylacetoacetate during absorption. Ethylacetoacetate is widely used as a food flavouring additive in many countries. Thus, it is considered to be one of the most suitable materials in view of its low toxicity. We report the effectiveness of DL-phenylalanine-ethylacetoacetate, as a promoter for rectal absorption of insulin.

Insulin suppositories were prepared by mixing crystalline pork insulin, 5% DL-phenylalanine-ethylacetoacetate, and Witepsol H-15 as a base.

Insulin (12 u g^{-1}) suppositories so prepared were given at a dose of 1 or 2 u kg^{-1} to 5 normal dogs (10·0 ± 1·0 kg) which were fasted for 18 h previously. The results were compared with those from insulin suppositories containing BL-9-EX (3% w/w) as described by Shichiri et al (1979). The suppositories at 1 or 2 u kg^{-1} were administered also to five depancreatized dogs (10·0 ± 1·1 kg) made hyperglycaemic by with-

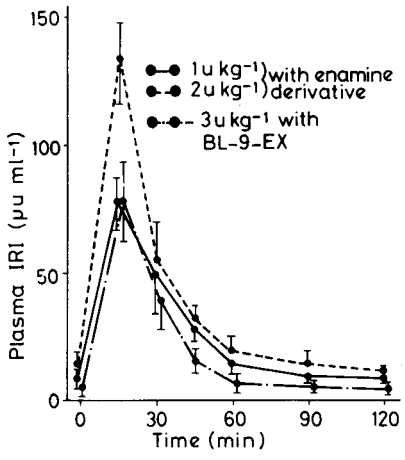

FIG. 1. Plasma insulin concentrations after rectal administration of insulin suppositories (1 u kg^{-1} and 2 u kg^{-1}) containing DL-phenylalanine-ethylacetoacetate, and that (3 u kg^{-1}) with polyoxyethylene-9-laurylether in normal dogs. Data are expressed as mean ± s.e.m. (n = 5).

† Correspondence.

drawal of insulin treatment (Insulin Semilente Novo) for 48 h.

Blood samples were taken from antecubital vein at designated times. Plasma concentrations of glucose were measured by a glucose oxidase method and plasma insulin concentrations were measured by radioimmunoassay.

Blood glucose response curves were almost identical when either 1 or 2 u kg^{-1} of insulin was given with DL-phenylalanine-ethylacetoacetate to normal dogs (the lowest levels were around 59% of the initial levels). As shown in Fig. 1, the mean (± s.e.m.) plasma insulin concentrations at 15 min increased significantly to a peak of 76·4 ± 11·4 μu ml^{-1} with the 1 u kg^{-1} dose, and 132·0 ± 18·0 μu ml^{-1} with the 2 u kg^{-1} dose respectively, and returned to baseline at 60 min. Plasma insulin concentration after the 1 u kg^{-1} dose was similar to that after 3 u kg^{-1} of insulin in the suppository with BL-9-EX.

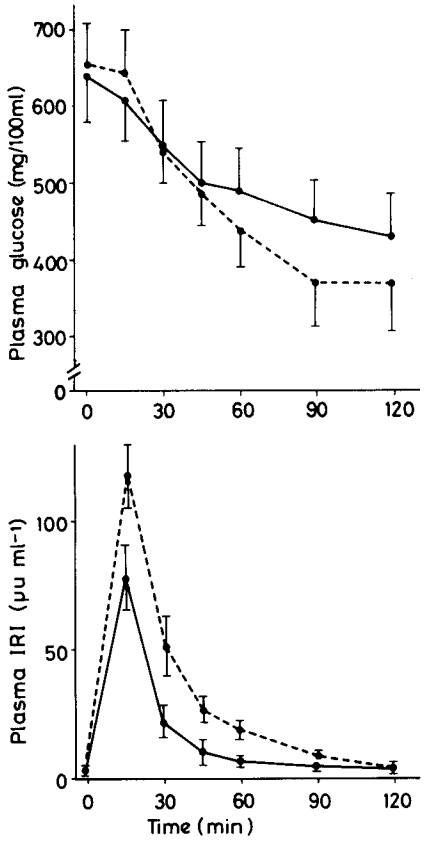

FIG. 2. Plasma glucose and insulin concentrations after rectal administration of insulin suppositories (1 u kg^{-1} and 2 u kg^{-1}) containing DL-phenylalanine-ethylacetoacetate to depancreatized dogs. Data are expressed as mean ± s.e.m. (n = 5).

Fig. 2 slows the plasma glucose and insulin responses after the enamine suppositories containing 1 and 2 u kg^{-1} doses were given to depancreatized dogs. A significant increase occurred in plasma insulin concentrations at 15 min with a maximum of 75·8 ± 12·0 μu ml^{-1} with the 1 u kg^{-1} and 119·0 ± 12·1 μu ml^{-1} with the 2 u kg^{-1} dose at 15 min, respectively. Plasma glucose was significantly decreased from 630 ± 71 mg/100 ml to 450 ± 57 mg/100 ml with the 1 u kg^{-1} dose and 653 ± 53 mg/100 ml to 367 ± 61 mg/100 ml with the 2 u kg^{-1} dose in 120 min. Insulin suppositories that contained neither DL-phenylalanine-ethylacetoacetate nor BL-9-EX caused no changes in plasma insulin or glucose in these dogs.

To estimate the fraction of insulin absorbed, the plasma insulin responses after rectal administration (as reflected by the area under the plasma insulin concentrations) was compared with that after intramuscular injection of 0·1 u kg^{-1} of regular insulin. Approximately 18·6–43·7% (mean value 27·5%) of insulin in the suppository was absorbed from the rectum in normal dogs, an amount some three times more than from suppositories containing BL-9-EX.

Histological examinations of specimens from the rectal tissues of rats administered the enamine insulin suppositories daily for a week, showed no pathological changes.

These results indicate that the enamine derivative is a more effective promoter for rectal insulin absorption than the surfactant, BL-9-EX, and is a candidate for an adjuvant to suppositories for the long-term control of diabetes mellitus.

REFERENCES

Hirai, S., Yashiki, Y., Mima, H. (1981) Int. J. Pharmaceut. 9: 173–177

Murakami, T., Tamauchi, H., Yamazaki, M., Kubo, K., Kamada, A., Yata, A. (1981) Chem. Pharm. Bull. 29: 1986–1997

Shichiri, M., Yamasaki, Y., Kawamori, R., Kikuchi, M., Hakui, N., Abe, H. (1979) J. Pharm. Pharmacol. 30: 806–808

Yamasaki, Y., Shichiri, M., Kawamori, R., Morishima, T., Hakui, N., Yagi, T., Abe, H. (1981a) Can. J. Physiol. Pharmacol. 59: 1–6

Yamasaki, Y., Shichiri, M., Kawamori, R., Kikuchi, M., Yagi, T., Arai, S., Tohdo, R., Hakui, N., Oji, N., Abe, H. (1981b) Diabetes Care 4: 454–458