ELSEVIER

International Journal of Pharmaceutics 128 (1996) 287–289

international journal of pharmaceutics

Intranasal administration of insulin to rabbits using glycofurol as an absorption promoter

Erik Bechgaard[a,*], Sveinbjörn Gizurarson[b], Rolf K. Hjortkjær[c], Anders R. Sørensen[d]

[a]*Department of Pharmacy, The Royal Danish School of Pharmacy, Universitetsparken 2, DK-2100 Copenhagen Ø, Denmark*
[b]*Department of Pharmacy, University of Iceland, IS-107 Reykjavik, Iceland*
[c]*Dansk Toksikologi Center, ATV, Agern allé 15, DK-2970 Hørsholm, Denmark*
[d]*Novo Nordisk AS, Novo allé, DK-2880 Bagsværd, Denmark*

Received 14 October 1994; revised 8 August 1995; accepted 9 August 1995

Abstract

The bioavailability of insulin from a nasal formulation with 5% glycofurol (GF) was studied in vivo in rabbits. A pronounced decrease in the plasma glucose level, comparable to the response for Novolin® Nasal, was observed. A nadir after 30 min was observed where the plasma glucose was 59% of the initial value. The potential for local side effect from 5% GF was found to be very low in the frog-palate model, where the mucociliary clearance rate was only reduced 9%.

Keywords: Nasal administration; Bioavailability; Insulin; Glycofurol 75; Rabbit

Nasal application of insulin, using various absorption enhancers, has been extensively studied e.g. in rat (Hirai et al., 1981a; Hirai et al., 1981b), sheep (Longenecker et al., 1987) and rabbit (Sørensen et al., 1988) and reviews on clinical trials have been published (Gizurarson and Bechgaard, 1991). A pre-requisite for a nasal insulin formulation is that the vehicle facilitate the absorption of insulin, without causing any irritation, unpleasantness or histopathological changes to the mucosa. Pilot in vitro studies, with isolated rabbit nasal mucosal tissue in the Ussing chamber system, has indicated that 1–5% glycofurol (GF) might facilitate the absorption of insulin without local side effects. Glycofurol 75 (ω-(tetrahydrofuranyl)-ω-hydroxypoly(oxy-1,2-ethanediyl)) is a slightly viscous (8–18 mNs/m^2) and biocompatible liquid (Fig. 1). It is known to be an excellent solubilizer, and it is used in parenteral products for intravenous or intramuscular injection, in concentrations up to 50% v/v. The objective of the present study is to confirm in vivo, the absorption promotion effect of 5% GF, which was observed for insulin in vitro.

* Corresponding author, Tel.: + 45 3537 0850; Fax: +45 3537 1277.

SSDI 0378-5173(95)04315-2

Zinc-free human insulin and Novolin® Nasal was kindly provided by Novo Nordisk A/S (Bagsværd, Denmark) and glycofurol 75 (GF) was purchased from Hoffman La-Roche (Basel, Switzerland). All other materials were of analytical grade. For the preparation of the intranasal formulations, 6.6 mg insulin was dissolved in 1.0 ml phosphate buffer (12.5 mM, pH 7.4) containing 5% GF. This formulation was prepared freshly on the morning of the study. New Zealand White rabbits weighing about 3 kg (Novo Nordisk A/S, Bagsværd, Denmark) were used in the experiment. The rabbits were dosed intranasally with 50 μl into each nostril (total dose 0.66 mg insulin equals 15.8 IU), using an Eppendorph pipette. The animals were non-anaesthetized and fixed in a sitting position during the dosing. Blood samples (about 1.5 ml) were collected by venepuncture of a marginal ear vein prior to dosing and at 0, 15, 30, 60 and 120 min after dosing. Blood glucose determination was performed as described (Sørensen et al., 1988). Local toxicity of 5% GF in phosphate buffer (12.5 mM, pH 7.4) was tested on mucociliary clearance in the frog-palate model as described (Gizurarson et al., 1990).

Fig. 2 shows the relative decrease in plasma glucose level after nasal administration of insulin to rabbits. The profile is comparable to results obtained by Sørensen et al. (1988) with the same dose of a known formulation, Novolin® Nasal, which is composed of 200 U/ml human insulin, 2% didecanoyl-L-α-phosphatidylcholine, 1,6% glycerol, 0,4% fractionated coconut oil, 0,2% cholesterol in 5 mM sodium phosphate buffer (pH 7.4). Relative to the control, the results show pronounced decrease in the plasma glucose level after 15 min (90% of initial), with nadir after 30 min (59%), indicating that a rapid absorption of insulin had occurred. After 2 h the plasma glucose level was still depressed (85% of initial). One out of the six rabbits was rejected, due to a possible unsuccessful dosing. The observed absorption may be of clinical relevance, as the bioavailability in humans for Novolin® Nasal has been found to be 8.3 and 23.9% relative to intravenous and subcutaneous administration, respectively (Drejer et al., 1992). The absorption enhancing mechanism for GF is not known.

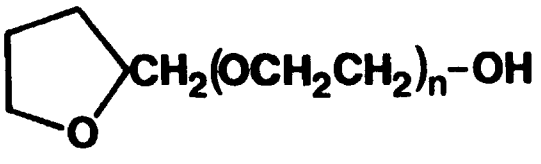

Fig. 1. Glycofurol 75 (ω-(tetrahydrofuranyl)-ω-hydroxypoly (oxy-1,2-ethanediyl)).

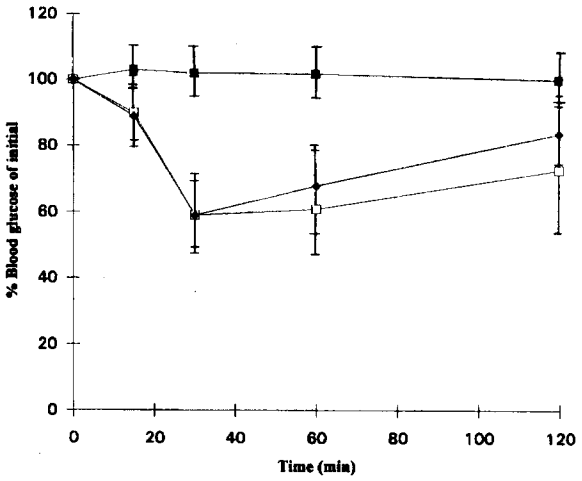

Fig. 2. Mean (± S.D.) blood glucose profile, in rabbits, after intranasal administration of insulin (-◆-) with 5% glycofurol (n = 5). Results for (-□-) Novolin® Nasal (n = 32) and (-■-) no enhancer (n = 234) are also given.

Table 1 shows that the potential for local side effects from 5% GF is very low relative to several other enhancers, which has previously been tested by Gizurarson et al. (1990) in the frog-palate model. The mucociliary clearance rate was only reduced 9% with 5% GF.

These preliminary results show that GF is able to enhance the uptake of insulin in rabbits, resulting in rapid and significant decrement of the blood glucose level.

Table 1
The influence of glycofurol on the mucociliary transport rate, measured in the frog palate model as the average change in speed (mm/s) of applied graphite particles passing from the palate towards the oesophagus. The results are related to some previous results obtained from several enhancers and insulin by Gizurarson et al., 1990

Compound	Change in speed (% of initial)	Comments
0.9% Insulin in saline	−2	
5% Glycofurol	−9	
1% L-α-lysophosphatidylcholine	−100	Irreversible[a]
1% L-α-phosphatidylcholine, didecanoate	−12	
1% Polyoxyethylene-9-lauryl ether	−100	Irreversible[a]
1% Sodium deoxycholate	−100	Irreversible[a]
1% Sodium dihydrotaurofusidate	−100	Irreversible[a]
1% Sodium glycocholate	−2	
Novolin® Nasal	−29	

[a]Irreversible in the test period of 30 min.

References

Drejer, K., Vaag, A., Bech, K., Hansen, P., Sørensen, A.R. and Mygind, N., Intranasal administration of insulin with phospholipid as absorption enhancer: pharmacokinetics in normal subjects. *Diabetic Medicin*, 9 (1992) 335–340.

Gizurarson, S., Marriott, C., Martin, G.P. and Bechgaard, E., The influence of insulin and some excipients used in nasal insulin preparations on the mucociliary clearance. *Int. J. Pharm.*, 65 (1990) 243–247.

Gizurarson, S. and Bechgaard, E., Intranasal administration of insulin to humans. *Diab. Res. Clin. Pract.*, 12 (1991) 71 84.

Hirai, S., Yashiki, T. and Mima, H., Effect of surfactants on the nasal absorption of insulin in rats. *Int. J. Pharm.*, 9 (1981a) 165–172.

Hirai, S., Yashiki, T. and Mima, H., Mechanism for enhancement of the nasal absorption of insulin by surfactants. *Int. J. Pharm.*, 9 (1981b) 173–184.

Longenecker, J.P., Moses, A.C., Flier, J.S., Silver, R.D., Carey, M.C. and Dubovi, E.J., Effects of sodium taurodihydrofusidate on nasal absorption of insulin in sheep. *J. Pharm. Sci.*, 76 (1987) 351–355.

Sørensen, A.R., Drejer, K., Engesgaard, A., Guldhammer, B., Hansen, P.E., Hjortkjær, R.K. and Mygind, N., Rabbit model for studies of nasal administration of insulin and glucagon. *Diab. Res. Clin. Pract.* Suppl. 1, 5 (1988) S165.