Increased intestinal absorption of insulin: an insulin suppository

MOTOAKI SHICHIRI*, YOSHIMITSU YAMASAKI, RYUZO KAWAMORI, MIKIO KIKUCHI, NOBUYOSHI HAKUI, HIROSHI ABE
First Department of Medicine, Osaka University, Medical School, Fukushima 1-1-50, *Fukushima-ku, Osaka*, 553, *Japan*

In recent years, studies from our laboratory have focused attention on the possibility that diabetes could be controlled by orally administered insulin preparations in which the insulin molecules were protected from digestive destruction (Shigeta, Shichiri & others, 1972; Shichiri, Shimizu & others, 1974). We reported the successful short-term treatment of alloxan-diabetic rats with water-in-oil-in-water insulin emulsions (Shichiri, Kawamori & others, 1975). However, because of digestive destruction and low absorption, to control the diabetic state insulin was required in large doses (250 U kg^{-1} three times daily).

We therefore turned to the rectal administration of insulin by means of a suppository prepared by mixing insulin with an oil base and surfactant and this has been examined in normal and depancreatized dogs.

Porcine crystalline insulin (Shimizu Seiyaku Kabushikikaisha, Japan) was ground by pestle and mortar to a suspension in corn oil (Japan Maize Products Co., Ltd., Japan). The non-ionic surfactant, polyoxyethylene-9-laurylether (BL-9-EX, Nikko Chemicals Co., Ltd., Japan), dissolved in corn oil at 60°, was added to the suspension. This resulted in the insulin suspension suitable for rectal administration (insulin suppository). Final concentrations of insulin were 10, 20, 30 and 50 U g^{-1} with BL-9-EX concentrations of 2, 3 and 4% w/w.

Adult dogs, mixed breeds, 8–12 kg, were divided into a normal group and a group made diabetic by removing the pancreas. These were given an injection of Insulin Actrapid 8–12 U subcutaneously twice a day. Insulin injection was withheld 48 h before experiments.

After 36 h fasting, the dogs were given sodium pentobarbitone intravenously and the insulin suppository 0·1 g kg^{-1} body weight, was administered through a pediatric balloon catheter (10 French size, Folatex, Eschmann, England) inserted into the rectum. Blood samples were taken via a catheter in the jugular vein

* Correspondence.

Table 1. *Plasma glucose and insulin responses following rectal administration of insulin suppository with various insulin doses and surfactant concentrations to normal dogs.*

	Surfactant concn						
	2%			3%			4%
	Insulin dose						
Time after administration (min)	1 U kg^{-1} (n = 5)	2 U kg^{-1} (n = 5)	3 U kg^{-1} (n = 5)	2 U kg^{-1} (n = 5)	3 U kg^{-1} (n = 5)	5 U kg^{-1} (n = 5)	5 U kg^{-1} (n = 4)
	Plasma glucose mg/100 ml						
0	74 ± 1·7	81 ± 3·4	85 ± 3·6	72 ± 2·9	79 ± 4·0	85 ± 4·3	80 ± 6·9
15	68 ± 5·3	62 ± 4·7*	68 ± 8·6	57 ± 10·4	63 ● 5·1*	65 ± 3·4*	67 ± 7·3
30	76 ± 3·6	52 ± 5·4*	55 ± 8·6*	56 ± 10·6	49 ± 6·4*	47 ± 8·8*	53 ± 6·9*
45	78 ± 2·4	54 ± 6·2*	48 ± 7·2*	60 ± 4·6	50 ± 8·4*	37 ± 6·2*	58 ± 8·3
60	80 ± 0·3*	63 ± 6·0*	53 ± 5·0*	64 ± 3·1	52 ± 8·4*	41 ± 5·4*	59 ± 8·4
90	77 ± 1·4	72 ± 7·8	66 ± 5·6*	67 ± 5·6	58 ± 10·4	50 ± 6·4*	69 ± 6·9
120	77 ± 3·9	80 ± 3·9	75 ± 4·2	72 ± 6·4	66 ± 6·4	64 ± 4·7*	77 ± 6·4
150	77 ± 2·4	82 ± 4·0	82 ± 3·6	74 ± 4·6	71 ± 3·4	73 ± 5·5*	78 ± 5·4
180	77 ± 3·2	80 ± 3·6	83 ± 2·6	74 ± 3·6	78 ± 4·9	77 ± 6·5	76 ± 6·6
	Plasma insulin μU ml^{-1}						
0	5 ± 1·0	4 ± 1·3	5 ± 1·2	4 ± 1·4	6 ± 2·6	5 ± 1·5	4 ± 1·0
15	24 ± 5·2*	64 ± 13·3*	78 ± 15·2*	41 ± 10·8*	88 ± 16·6*	115 ± 24·9*	61 ± 13·0*
30	6 ± 0·4	24 ± 7·9*	39 ± 10·6*	13 ± 4·2	41 ± 8·6*	49 ± 19·6*	39 ± 8·0*
45	7 ± 0·6	19 ± 4·7*	15 ± 4·6	10 ± 3·4	22 ± 6·7	36 ± 14·2	29 ± 9·2
60	7 ± 2·5	7 ± 2·7	6 ± 3·2	7 ± 2·8	16 ± 4·2	27 ± 7·1*	11 ± 2·8
90	8 ± 1·8	4 ± 1·4	6 ± 1·6	5 ± 2·6	9 ± 3·6	19 ± 6·6	8 ± 1·8
120	7 ± 2·3	4 ± 1·6	5 ± 1·2	7 ± 2·0	6 ± 2·6	14 ± 4·5	8 ± 2·6
150	7 ± 3·1	3 ± 1·2	6 ± 2·4	7 ± 1·6	5 ± 2·6	13 ± 2·2	6 ± 2·4
180	7 ± 2·4	4 ± 1·4	5 ± 1·6	5 ± 2·4	5 ± 2·0	9 ± 2·3	9 ± 2·8

Values are expressed as mean ± s.e.m. * $P<0·05$, compared with a baseline level in each groups.

at 0, 15, 30, 45, 60, 90, 120, 150 and 180 min. Insulin Actrapid (0·2 and 0·5 U kg^{-1}) was injected intramuscularly and blood sampling was as described above. The rate of disappearance of immunoreactive insulin (IRI) from plasma after intravenous injection of Insulin Actrapid (0·1 U kg^{-1}) was measured by the modified method of Stimmler (1967). Plasma glucose was measured by Hoffman's method (1937) using a Technicon Autoanalyzer. Plasma IRI was measured by the method of Hales & Randle (1963). Statistical analyses were carried out using the unpaired *t*-test.

The results from normal dogs given the insulin suppository containing varying insulin doses and BL-9-EX concentrations are in Table 1. In all groups, the mean IRI significantly ($P<0·05$) increased to its highest concentration at 15 min, reverting gradually to the initial value. Plasma glucose reached the lowest concentrations in the 15 to 45 min after administration of the suppository.

When the BL-9-EX concentration was 2% w/w, the peak IRI concentrations were 24, 64 and 78 μU ml^{-1}, and the maximal decreases in plasma glucose were 8, 36 and 44% of the initial values at the insulin doses of 1, 2 and 3 U kg^{-1}, respectively. After a suppository with 3% w/w surfactant and insulin doses of 2, 3 and 5 U kg^{-1}, the peak IRI concentrations were 41, 88 and 115 μU ml^{-1}, and the maximal decreases in plasma glucose were 22, 38 and 55%, respectively. When the BL-9-EX concentration was 4% w/w, the peak IRI concentration was 61 μU ml^{-1} and the maximal decrease in plasma glucose was 21% at the insulin dose of 5 U kg^{-1}. Thus, a dose response relation between amounts of insulin administered and peak IRI concentrations or maximal decreases in plasma glucose was observed in normal dogs. However, to exert maximal effect it appears that the concentration of surfactant should be matched with the dose of insulin.

Table. 2. *Plasma glucose and insulin concentrations following rectal administration of insulin suppository with 3% surfactant to depancreatized dogs.*

Time after Admin (min)	Insulin dose 3 U kg^{-1} (n = 4)	5 U kg^{-1} (n = 5)
	Plasma glucose mg/100 ml	
0	361 ± 24·2	324 ± 13·3
15	361 ± 20·4	307 ± 8·8
30	327 ± 22·0	310 ± 31·5
45	321 ± 22·4	289 ± 9·5
60	315 ± 24·6	273 ± 14·0*
90	295 ± 23·5	246 ± 16·6*
120	309 ± 30·6	229 ± 17·8*
150	297 ± 34·7	214 ± 18·0*
180	329 ± 40·3	200 ± 15·7*
	Plasma insulin μU ml^{-1}	
0	3 ± 0·6	2 ± 0·8
15	84 ± 23·4*	141 ± 30·2*
30	61 ± 10·6*	167 ± 25·8*†
45	24 ± 5·6*	102 ± 31·5*
60	23 ± 2·0*	70 ± 18·5*
90	10 ± 2·2*	38 ± 6·2*
120	11 ± 2·2*	15 ± 3·2*
150	9 ± 2·0*	11 ± 3·2*
180	10 ± 3·0*	9 ± 2·5*

Values are expressed as mean ± s.e.m.
*: $P<0·05$ compared with a baseline level in each groups.
†: $P<0·05$ compared with normal dogs (Table 1).

Table 2 shows the mean plasma glucose and IRI concentrations after rectal administration of the suppository with 3% BL-9-EX and doses of 3 and 5 U kg^{-1} insulin to depancreatized dogs. A dose of 5 U kg^{-1} caused the mean IRI value to rise significantly at 15 min from the mean baseline ($P<0·05$), and to remain higher than the values in normal dogs for up to 90 min but the only value at 30 min was significantly ($P<0·05$) higher. The mean plasma glucose gradually decreased to 62% of the initial value at 180 min. At 3 U kg^{-1}, the mean IRI appeared higher than that in normal dogs at 30 min, but the difference was not statistically significant, and the plasma glucose decreased to its lowest value (82% of the initial) followed by slight rise to the sub-basal value.

The mean (± s.e.m.) peak IRI concentrations after intramuscular injection of Insulin Actrapid at the doses of 0·2 and 0·5 U kg^{-1} were 42 (±4·6, n = 5) and 85 (±5·1, n = 5) μU ml^{-1} in normal dogs, and 40 (±5·0, n = 5) and 95 (±5·8, n = 5) μU ml^{-1} in depancreatized dogs, respectively. These values were obtained at 45 min in both groups of animals. The mean rates of disappearance of immunoreactive insulin from plasma after intravenous injection of insulin were 0·201 (±0·038, n = 5) in normal dogs and 0·162 (±0·031, n = 5) in depancreatized dogs, and the differences were not statistically significant.

There appear to be few reports on the absorption of insulin from the rectum (Inouye & Vars, 1962; Bakth, May & others, 1976) and large doses of insulin were needed to exert a hypoglycaemic effect. We have found with the insulin suppository that doses of 2 U kg^{-1} of insulin or above are effective in lowering plasma glucose significantly in normal dogs and that the absorption was more rapid than after intramuscular injection.

After rectal administration of insulin at a dose of 5 U kg^{-1}, the plasma IRI concentration in depancreatized dogs was higher at 30 min than that in normal dogs, and the plasma glucose was still falling at 180 min. The higher IRI concentration in depancreatized dogs would be because degradation of insulin is decreased in diabetic state. But this would not fully explain this result, as there were no differences in the rates of disappearance of insulin or in peak IRI concentrations and the times reached at the peak of IRI after intramuscular insulin injections between normal and depancreatized dogs.

A second explanation is that the total amount of insulin absorbed was increased in diabetic dogs. In recent years, Olsen & Rosenberg (1970) and Younoszai & Schedl (1972) demonstrated that total absorption of glucose, amino acids, lipid, etc, from the intestine was increased in diabetic animals compared with that in normal animals. The mechanisms of the increased absorption of insulin from the rectum in dabetic state require clarification.

Eighty U kg^{-1} (Patel & Ryman, 1975) and 25 U kg^{-1} (Shichiri & others, 1974) of oral insulin preparations were required to lower the blood glucose concentrations of alloxan rats and of normal rabbits, respectively. These results indicate the insulin suppository to be more effective than oral insulin preparations.

We gratefully indebted to Mr Isao Ohata and Mr Kunihide Ichikawa (Central Research Laboratory, Yamanouchi Pharmaceutical Co., Ltd., Japan) for their cooperation with this study. The technical assistance of Miss Maki Ueno is gratefully acknowledged.

July 31, 1978

REFERENCES

BAKTH, S., MAY, P., AKGUN, S. & ERTEL, N. (1976). *Clin. Res.*, **24**, 636A.

INOUYE, W. Y. & VARS, H. M. (1962). *Surg. Forum.*, **13**, 316–317.

HALES, C. N. & RANDLE, P. J. (1963). *Biochem. J.*, **88**, 137–146.

HOFFMAN, W. S. (1937). *J. biol. Chem.*, **120**, 51–55.

OLSEN, W. A. & ROSENBERG, I. H. (1970). *J. clin. Invest.*, **49**, 96–105.

PATEL, H. M. & RYMAN, B. E. (1975). *FEBS Letters*, **62**, 60–63.

SHICHIRI, M., SHIMIZU, Y., YOSHIDA, M., KAWAMORI, R., FUKUCHI, M., SHIGETA, Y. & ABE, H. (1974). *Diabetologia*, **10**, 317–321.

SHICHIRI, M., KAWAMORI, R., YOSHIDA, M., ETANI, N., HOSHI, M., IZUMI, K., SHIGETA, Y. & ABE, H. (1975) *Diabetes*, **24**, 971–976.

SHIGETA, Y., SHICHIRI, M., OKADA, A. & KARASAKI, K. (1972). *Endocrinology*, **91**, 320–322.

STIMMLER, L. (1967). *Diabetes*, **16**, 652–655.

YOUNOSZAI, M. K. & SCHEDL, H. P. (1972). *Am. J. Physiol.*, **223**, 828–831.

Solubility studies on ethyl cellulose used in film coating

D. J. KENT, R. C. ROWE*, *ICI Pharmaceuticals Division, Alderley Park, Cheshire, SK10 2TG, U.K.*

It has long been recognized that the properties of films are dependent on the solvent used for coating and as a general rule it can be said that maximum coating solvation and polymer chain extension will produce the most superior films showing the greatest cohesion (Banker, 1966). A knowledge of the solubility of polymers is of great importance, therefore, and in this respect polymer chemists have tended to use the solubility parameter approach. This is based on the regular solution theory of Hildebrand & Scott (1950) who proposed that the heat of mixing (ΔH in the Gibb's free energy equation) is given by:

$$\Delta H = Vm\left[\left(\frac{\Delta E_1}{V_1}\right)^{\frac{1}{2}} - \left(\frac{\Delta E_2}{V_2}\right)^{\frac{1}{2}}\right]^2 \phi_1 \phi_2$$

where Vm is the total volume of the mixture, ΔE is the energy of vaporization of component 1 or 2, V is the molar volume of component 1 or 2 and ϕ is the volume fraction of component 1 or 2. The expression $\Delta E/V$ is usually described as the cohesive energy density and the square root of this has been given the symbol δ-the solubility parameter. It can be seen that the heat of mixing of two substances is thus dependent on $(\delta_1 - \delta_2)^2$ and that if $\delta_1 = \delta_2$ complete solubility and miscibility is assured.

This means that each polymer or solvent can be characterized by its solubility parameter which should define its compatibility with every other solvent. For solvents, the solubility parameter can be readily calculated from heat of vaporization and extensive lists are now available (Burrell, 1975). For polymers the solubility parameter is often determined from studies of polymer/solvent interactions (as measured by swelling or intrinsic viscosity) which are assumed to be at a maximum when the solubility parameter of the polymer is equal to the solubility parameter of the solvent. However, it has been argued by several authors (Crowley & others, 1966; Hansen, 1967) that a single parameter is not enough for solvents possessing a significant dipole moment (e.g. alcohols, esters, ketones, aldehydes, etc.) and they have suggested the use of three component parameters. These are difficult to apply practically, and for most purposes the technique described by Burrell (1975) is more commonly used. This involves determining the solubility parameter range of a polymer in three classes of solvents (capable of poor, moderate or strong hydrogen bonding) by mixing a known weight of the polymer in a selected

* Correspondence.