

Rectal Delivery of Insulin: The Promising Route

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Abstract

Diabetes mellitus is a common and progressive disease with potentially serious complications, including blindness and kidney, cardiovascular and cerebrovascular disease. It is caused by a lack of insulin with a decrease in its action and results in chronically elevated blood glucose concentration.

Insulin is the most useful drug in the treatment of diabetes mellitus. Being a peptide is given till now only by parenteral administration. Injections are associated with many risks, reactions at site of administration, psychological stress, cost, inconvenience, lack of patient compliance and inability of some patients to self administer their insulin injection. Many attempts were made to find an effective non-parenteral routes for insulin administration e.g. oral, nasal, inhalation, transdermal and other routes. This has been faced with great difficulty due to the large molecular weight of insulin which hinders its passage across absorbing membranes, degradation of insulin by proteolytic enzymes and the rapid clearance of the administered dose from the site of deposition.

Ideally, insulin therapy mimics the normal physiologic secretion of insulin. However, it can be difficult to achieve this goal without undue inconvenience and adverse effects. New insulin formulations and routes of administration have been tried to improve convenience and therapeutic success.

Rectal administration of insulin showed an increase of portal insulin concentration that results in intensifying the magnitude of the net hepatic glucose uptake induced by portal glucose infusion. These facts indicate that portal insulin delivery is important in normalizing both glycaemia and insulinaemia postprandially.

This rectal route of administration of insulin can be a viable alternative or adjunctive to existing therapies and can be suitable for meal time administration with the goal of tight control of post-prandial hyperglycaemia in diabetic population. It will be also suitable for children as well as adults. This rectal formulations can be formulated to include different amounts of insulin and also rapid release and controlled release insulin to suite most of patients requirements.

Keywords: Rectal Delivery; Insulin; Diabetes Mellitus

Insulin

Insulin is a pancreatic hormone secreted by the β -cells of the Islet of Langerhans in the pancreas in response to a number of stimuli, including blood glucose concentration. It has a molecular weight of 5807. Insulin is a three dimensional structure and it consists of two chains of amino acids, A-chain with 21 amino acid residues and B-chain with 30 amino acid residues, which are joined by disulfide linkages. In most tissues, insulin is involved in the metabolism of sugars, lipids, amino acids and ions. Liver, muscles and fat tissues are the major physiological targets of insulin. The action of insulin is initiated by interaction with its receptor on the plasma membrane [1]. Following one or more unknown transmembrane signalling mechanisms, regulation of three major types of metabolic action occurs [1].

enhancement of membrane events such as glucose transport [2] enzyme activation in the cytoplasm and in organelles and [3] regulation of DNA and RNA synthesis in the nucleus [2]. Gavin, *et al.* [3] showed that the interaction of insulin with its receptors led to loss of insulin binding to target cells (down-regulation of receptors). Insulin may down-regulate its receptors by two possible mechanisms: 1) by accelerating receptor degradation following internalization, and 2) by inhibiting the biosynthesis of its receptors [4].

Human insulin has been prepared by several means including extraction from human cadaver pancreas, complete chemical synthesis, enzymatic conversions of porcine insulin (semisynthetic insulin), and use of recombinant DNA technology (biosynthetic insulin) [5]. Porcine insulin differs from human insulin in having alanine instead of threonine at position 30 of the insulin α chain. Bovine insulin has alanine at positions A-8 and B-30 instead of threonine at the same position in human insulin.

The *in-vitro* potency of semisynthetic or biosynthetic insulin is not significantly different from pancreatic human or purified porcine insulin, as indicated by a variety of assays [6-11]. Such assays include receptor binding, extent of glucose oxidation and stimulation of lipogenesis in adipocytes. Similarly, the hypoglycaemic effect of I.V. human insulin in healthy subjects or in diabetic patients [12,13] is not significantly different from that produced by equal doses of purified porcine insulin [14-17].

Pharmacokinetics of insulin

Absorption of insulin from subcutaneous tissue is variable both within and between various insulin preparations. The same dose of insulin may even have quite different effects on different days in the same patient. This makes it necessary not only to individualize therapy, but also to follow trial and error, supported to some extent by clinical judgement based on experience.

Proteins and peptides are ampholytic and exhibit electrical charges in biological fluids. Insulin exhibits an equilibrium between positive and negative charges at the isoelectric point at pH 5.5. In acidic environment, there is a surplus of positive charges, while in alkaline medium a surplus of negative charges is found. The solubility of insulin is at minimum at the isoelectric point and increases with either decreasing or increasing pH [18].

In a study on the effect of pH and temperature on the stability of regular insulin, it was found that after 18 months, the activity of insulin at pH 3 decreases by about 10% at 5°C, by about 25% at 25°C and by 50% at 37°C. At pH 8, the activity decreases by about 5% at 5°C, by about 15% at 25°C and by about 30% at 37°C [19].

Binder [20] found that neutral insulin is more rapidly absorbed than acid insulin when injected and Galloway, *et al.* [21] suggested that the blood glucose and serum insulin responses appeared to be slightly greater to neutral than those to acidic insulin upon S.C. administration.

A prerequisite for absorption is that the compound in question be present at the absorption site in true solution.

Species of origin may play a role in the rate of absorption. It has been claimed that human insulin is absorbed more rapidly than pork insulin which in turn is absorbed more quickly than beef insulin [22].

Depth of the injection is also important, more shallow subcutaneous injections are absorbed more rapidly than deeper subcutaneous injections (provided that the former are not intra-dermal and the later are not intra-muscular).

Tissue blood flow is another important factor influencing rates of absorption of insulin and this is influenced by temperature and by the site of injection [23].

Exercise and massage of the injected part, can also speed absorption to a clinically important degree and may totally account for hypoglycaemia in insulin treated diabetics during exercise [24].

In a more recent study on the combined effect of exercise and ambient temperature on insulin absorption and postprandial glycaemia in type I diabetic patients, Ronnema and Koivisto [24]. found that warm temperature and exercise had an additive effect in stimulating insulin absorption and in lowering blood glucose concentrations.

The influence of circulating epinephrine on absorption of subcutaneously injected insulin was studied in healthy and in type I diabetic patients by Fernquist, *et al* [26]. The results indicated that circulating epinephrine at levels seen during moderate physical stress depresses the absorption of soluble insulin from subcutaneous injection sites to an extent that might be important for glycemic control in type I diabetic. Furthermore, they found dissociation between changes in insulin absorption and subcutaneous blood flow during epinephrine infusion, suggesting that factors other than blood may also influence the absorption of subcutaneously injected insulin. Klemp, *et al.* [27] showed in a study done in 1982, that smoking reduces insulin absorption from subcutaneous sites. On the other hand, local reactions at the injection sites may alter insulin absorption, by either interacting with antibodies or by degradation in subcutaneous tissues through the effect of a proteolytic enzyme, leading by time to apparent extreme insulin resistance [28].

Ideally exogenous insulin should be administered in a way which mimics the physiological pattern, i.e., maintaining a continuous low basal level of serum insulin throughout the 24 hours, delivering an appropriate bolus as blood glucose levels rise after a meal and returning to basal levels when the blood glucose falls in the post-absorptive phase.

In conventional insulin therapy, twice-daily mixtures of fast and intermediate insulins are usually used in an effort to achieve this pattern, keeping a relatively fixed time relationship between injections and meals. This fixed relationship often results in a temporal mismatch between levels of insulin and blood glucose values. Insulin levels are inappropriately high or low at various times of the day. Furthermore, the insulin is delivered to the peripheral circulation in contrast to the normal intraportal secretion, thus resulting in peripheral hyperinsulinaemia.

Stout [29] concluded that this hyperinsulinaemia stimulates smooth muscle cell proliferation and the incorporation of glucose into lipid in arterial walls, thus might be a causative factor in diabetic microangiopathy.

The belief that maintenance of euglycaemia has a beneficial effect on the long-term complication rate, and the realization that systemic hyperinsulinaemia may be harmful, led to the development of new strategies in the management of the insulin-dependent diabetic patients. Intensive control, using better methods of insulin delivery have been thought of, studied and produced.

Rectal insulin

During the past years, considerable interest has arisen in the rectal route for insulin administration. This route is regarded as a more physiologic route for applying insulin. It is known that about 50% of insulin delivered is degraded in the liver, which is also the locus of highest insulin utilization [30]. About 30% of insulin rectally absorbed enters into the portal vein [31]. An open-loop portal insulin delivery study applied to the depancreatized dogs fed regular meals demonstrated a less hyperinsulinaemia [32] than that observed in the peripheral infusion study [33]. On the other hand, the increment of portal insulin concentration is shown to intensify the magnitude of the net hepatic glucose uptake induced by portal glucose infusion [34].

These facts indicate that portal insulin delivery is important in normalizing both glycaemia and insulinaemia postprandially. Yamasaki, *et al.* (1881) [35] concluded from their study that insulin suppositories attenuated the postprandial glycaemic rise in diabetic subjects and that the peripheral insulinaemia was similar to that present in normal subjects after meals. The studies presented a possibility that

insulin suppositories could control the postprandial glycaemia in a more physiological manner than conventional insulin therapy because substantial amounts of insulin absorbed from the rectum enter directly into the portal vein.

At a time, the efficacy and bioavailability of rectal insulin were very low when compared to i.v. or s.c. injection. This situation was modified when surfactants and other absorption promoters were introduced, as they appear to increase significantly the uptake of high molecular weight polar drugs, such as insulin [36].

Bar-On., *et al.* [37] suggested that the transport of insulin across the rectal mucosa of diabetic and nondiabetic rats was facilitated by cetomacrogol 1000. They added that the hypoglycaemic response was dependent on both the concentration of the surfactant and the dose of the insulin administered.

In 1981, Nishihata., *et al.* [38] used non-surfactant sorption promoters, sodium salicylate, 5-methoxysalicylate, sodium-3-methoxy-salicylate and sodium homovarillate. There were added in microenemas buffered with 0.2 M phosphate reaching a pH of 5. In this study, an increase in insulin dose was not accompanied by an increase in response. Ichikawa., *et al.* [39], studied rectal absorption of insulin in diabetic rabbits. They evaluated the effects of surfactants, bile acids and phospholipids on the reduction of glucose levels. The most effective sorption promoter was polyoxyethylene-9-lauryl ether in concentration 1%. Also in this study an increase in insulin dose did not proportionally increase the response.

Kamada., *et al.* [40], used enamine derivatives of phenylglycine as an adjuvant for the rectal absorption of insulin in male white rabbits and male beagle dogs. They prepared four phenylglycine-enamines, three of which resulted in an increase in the insulin radioimmune levels and a decrease in the serum glucose levels in both rabbits and dogs. They explained the promoting ability of phenylglycine-enamines as being due to their ability to interact with Ca⁺⁺. Thus, possessing a chelating ability for metal ions important for the membrane barrier function, in addition to their ability to permeate through the membrane, depending on their water solubility and partitioning properties. Still, they advised for further work to check safety for long-term administration.

Brij 58 as another promoting adjuvant (surfactant) was studied by Mesiha., *et al.* [41]. A highly significant insulin absorption from rabbits' rectum was observed.

Nishihata., *et al.* [42] studied the promoting effect of a number of preparations of glyceryl esters of acetoacetic acid on the rectal absorption of insulin in rabbits. Two out of four preparations produced a decrease in serum glucose level. This promoting effect was suppressed by the addition of calcium and magnesium to the suppositories. This fact coincides with the study of Kamada., *et al.* [40]. It indicates that adjuvant interaction with calcium and magnesium ions located in the rectal membrane is involved in the enhanced absorption of insulin.

Shichiri., *et al.* [36], administered insulin suppositories with varying amounts of insulin (1 - 5 U/Kg) and varying concentrations of polyoxyethylene-9-lauryl ether (2 - 4%) to normal and pancreatectomized dogs. The greatest reduction in glucose concentration was observed with suppositories containing 5U insulin/Kg and 3% of surfactant. The maximum reduction in glucose concentration in % (C max) was 56.5% after 45 min in normal, 61.7% after 180 min in pancreatectomized dogs. They observed that rectal insulin enters the blood circulation more rapidly than intramuscular insulin. This fact was reaffirmed by Ichikawa., *et al.* [39]. Based on the previous observation, Yamasaki., *et al.* [43] introduced his insulin suppositories to six alloxan-diabetic dogs 30 minutes after meals rather than before meals. They used Bovine crystalline insulin in a dose of 20 - 50U, Witepsol H15 as suppository base and polyoxyethylene-9-lauryl ether 3% as surfactant. They compared their results with that of subcutaneous insulin injections.

In dogs with fasting plasma glucose levels below 300 mg/dl, both insulin suppository at a dose of 20U and subcutaneous insulin at a dose of 0.2 U/Kg showed similar effect in reducing fasting glucose levels. In dogs with higher fasting glucose levels, 0.5 U of subcutaneous

insulin/Kg was less effective in reducing fasting glucose levels than 50 U suppositories. These were obtained after rectal administration of the insulin suppositories twice a day for 6 - 9 days.

Nishihata, *et al.* [44] used six male Beagle dogs for studying rectal insulin delivery. Insulin was received in the form of 0.5 ml or 0.25 ml microenema. These insulin microenema were prepared in either 0.9% sodium chloride or 0.9% sodium chloride in addition to 4% gelatin. Insulin 20 IU was used, 150 mg sodium 5-methoxysalicylate or 300 mg sodium salicylate were added. A significant decrease in plasma glucose levels occurred accompanied by a remarkable increase in insulin plasma levels. The greatest absorption occurred from the formulation including 4% gelatin in the microenema.

The effectiveness of rectal administration of insulin was examined in normal and non-insulin-dependent non-obese diabetic subjects [45]. In normals the suppositories used contained 50U insulin, 3% polyoxyethylene-9-lauryl ether and 0.02M HCl. This resulted in the reduction of glucose level by about 10% after 45 minutes, returned to baseline within 90 minutes. When 100U insulin was used, reduction in plasma glucose was 23% after 45 minutes.

In diabetic patients 100-U insulin suppositories resulted in a reduction of glucose level by 31% after 120 minutes. The insulin response after suppository administration demonstrated a significant positive correlation.

In diabetic patients immunoreactive insulin (IRI) was raised significantly at 45 minutes followed by gradual decline to the prestimulated level at 180 minutes. This level at 45 minutes was significantly higher than that in normal subjects receiving the same insulin suppository dose.

In the same study, diabetic patients were given a 100-U insulin suppository, 15 minutes after meal three times daily. This resulted in a significant improvement in postprandial hyperglycaemia, accompanied by restoration of the circadian profile of plasma IRI. Still, it was not effective in reducing fasting hyperglycaemia. They explained the later finding as a result of using a short-acting insulin in the suppository. Apart from few complains of abdominal discomfort or feeling of rectal urgency, they reported no other untoward reactions.

Hilderbrandt, *et al.* [46] studied the effect of rectal insulin suppositories in eight type I diabetic patients. The ingredients of their suppositories were: insulin 75U, surfactant (Brij 58) 100 mg and the basic mass Rosupol U 2g. In all patients they observed a decrease in blood glucose. The onset of such decrease was after 20 minutes, maximum effect after 50 min and end of the effect after 90 min. Plasma IRI level increased, however, the ratio of subcutaneous to rectal doses required to achieve the same effect was between 1:18 and 1: 26.

Banting and Best [47], who first demonstrated in 1921 that a pancreas extract alleviated the symptoms of diabetes, concluded from their studies that the nasal, vaginal and rectal routes are incapable of lowering blood sugar. In 1924, Peskind, *et al.* [48] instilled a solution of insulin into the rectum along with blood serum and water. They found no significant decrease in blood sugar.

The absorption promoting effect of sodium salicylate, 200 mg/100 U insulin suppository, was studied in 4 normal volunteers and 15 insulin dependent diabetic patients [49]. Insulin rectal bioavailability was quantitated through the measurement of its hypoglycaemic effect and of its serum levels. A hypoglycaemic effect and a significant rise in serum insulin concentrations were traced at 15 minutes and maintained for 90 minutes post administration. The investigated suppositories, thus, proved that sodium salicylate is effective in enhancing the rectal absorption of insulin in humans.

In another study [50] 3,5 Diiodosalicylate sodium (DIS), a highly lipophilic salicylate, was evaluated against 5 methoxysalicylate sodium (MS) as a potential adjuvant absorption promoter for rectal insulin delivery. Comparative blood glucose measurements were made using the two adjuvants under identical conditions as promoters of rectal insulin absorption in rats. Concentrations of DIS greater than and including 0.1M produced an unexpected, progressive decrease in adjuvant activity as determined by a decline in observed hypogly-

caemic response. This was not due to formation of an insulin DIS complex. The adjuvant MS produced a classical, sigmoidal log dose response curve. Possible reasons for the occurrence of the DIS optimum phenomenon are discussed as well as are the observed differences in adjuvant potency of these agents in a propylene glycol containing vehicle.

A rectal gels consisted of emulsion systems prepared from pH 8 buffer solution containing insulin, an oleaginous phase, a surface active agent (bile salts, Myrj or Brij), and a viscosity increasing agent was tested in a parallel and a crossover design in nondiabetic and diabetic rabbits [51]. The selected rectal gel in nondiabetic and diabetic rabbits resulted in a pharmacologic availability of about 25%. By addition of Azone the pharmacologic availability was further increased, although not significantly. In nondiabetic man the pharmacologic availability was about 32%, whereas the bioavailability (measured from plasma insulin) was only about 11%.

The absorption of insulin (from porcine pancreas) from the rectum of rabbits after the administration of hollow type suppositories containing insulin and five kinds of cyclodextrins (CyDs) was investigated [52]. Three types of suppositories were employed: suppository I containing insulin (approximately 26 IU/mg) and various amounts of each CyD in citric buffer solution at pH 3.0 or powder in its cavity, suppository II containing CyD without insulin, and suppository III containing insulin without CyD. Without CyD, the insulin and glucose levels in plasma were unchanged, whereas a significant increase in the plasma insulin concentration and a marked decrease in the glucose levels were found following simultaneous administration of insulin and CyDs by suppository I. The enhancing effect of CyD on rectal insulin absorption (absorption enhancing effect) by chemically modified CyDs (heptakis(2,6 di O methyl) beta CyD (DM beta CyD) and 2 hydroxypropyl beta CyD (HP beta CyD)) was higher than those by natural CyDs (alpha, beta, and gamma CyD). The area under the plasma concentration time curve (AUC) and Cmax of insulin significantly decreased with the preadministration (administration of CyD 6, 24 and 48h before rectal insulin administration) of DM beta CyD. The absorption enhancing effect disappeared 24h after preadministration. These results suggest that CyDs enhance insulin absorption from the rectum, and that attenuation of the membrane transport barrier function in the rectum recovers at a maximum of 24h after administration of CyDs.

The absorption of two kinds of insulin (from porcine or bovine pancreas) from the rectum of rabbits after the administration of hollow type suppositories containing insulin and glyceryl 1 monooleate (GMO) as an absorption enhancing agent was investigated [53]. Two types of suppositories were employed: type I containing insulin in an aqueous solution (approx. 25 IU/mg/100 microliters citric buffer solution at pH 3.0) in the cavity of the suppository and GMO mixed with a base material (Witepsol H 15), and type II containing insulin in a crystalline form in the same amount as in type I. Without GMO, the insulin and glucose levels in plasma were unchanged, whereas a marked increase in the plasma levels of insulin and a decrease of glucose concentrations were found following coadministration of insulin and GMO by the type I suppository. Similar enhancement of rectal absorption of insulin was obtained from porcine and bovine sources. In the case of the crystalline insulin, despite the use of the same amount of GMO, porcine insulin was more efficiently absorbed than bovine insulin by the type II suppository. GMO enhances the absorption of insulin in an aqueous solution or a crystalline form, and the dissolution rate of insulin may be an important factor in the rectal absorption of insulin.

The effect of the bile salt derivative sodium tauro 24, 25 dihydrofusidate (STDHF) on rectal insulin absorption was investigated in rats [54]. At concentrations of 1 and 4% (w/v) it enhanced insulin bioavailability from 0.2 f +/- 0.2 (control) to 4.2 +/- 3.2 and 6.7 +/- 2.1%, respectively, as assessed by radioimmunoassay. Insulin preparations with STDHF reduced blood glucose concentrations considerably in a concentration dependent way. Coadministration of STDHF with Na2EDTA (0.25%, w/v) tended to increase further insulin bioavailability and hypoglycemic response. Varying the site of rectal administration did not influence these parameters.

In order to improve the bioavailability of insulin after rectal application to rabbits, the influence of surface active amino acid fatty acid condensate on absorption and, the effects of a protease inhibitor (aprotinine), of a disinfectant (methyl hydroxybenzoate) and of chemotherapeutics (chloramphenicol, ambazone and metronidazole) were investigated [55]. Only the application of methyl-hydroxybenzoate, ambazone and of metronidazole, which inhibit the anaerobic bacterial flora, improved bioavailability significantly. The examinations show that the proteolytic activity of the anaerobic bacterial flora causes the loss of the biological activity of peptides in the rectum.

The effect of insulin (50U) suppositories containing sodium salicylate (50 mg) without and with 50 mg of either polycarbophil, deoxycholic acid or 50 mg of each on plasma glucose levels of hyperglycemic rabbits was studied [56]. The hypoglycemia of these formulations was determined relative to that produced after s.c. injection of 40U of insulin suspension and were 45.6%, 46.7%, 48.2% and 39.5%, respectively. Insulin suppositories containing sodium salicylate were effective in reducing plasma glucose levels which steadily decreased and reached 66% of the initial values by the 3rd h. The addition of polycarbophil to insulin suppositories containing sodium salicylate induced faster and higher rate of insulin absorption as indicated by the shorter T_{max} and higher C_{max}. Addition of deoxycholic acid increased non significantly the T_{max}, MRT, AUC_{0-7h} of that of insulin suppositories containing sodium salicylate. The incorporation of both polycarbophil and deoxycholic acid in insulin suppositories containing sodium salicylate is not recommended as these additives reduced the C_{max} and AUC_{0-7h}.

Insulin suppositories using polyethylene glycol MW 4000 as a base and containing 50U insulin incorporated with 50 mg of deoxycholic acid, sodium taurocholate, or both were placed in the rectum of alloxan-induced hyperglycemic rabbits [57]. A large decrease in plasma glucose concentrations was observed, and the relative hypoglycemia were calculated to be 38.0%, 34.9%, and 44.4% respectively, compared with insulin subcutaneous (s.c.) injection (40 U). Insulin suppositories containing 50 mg polycarbophil alone or mixed with 50 mg deoxycholic acid produced relative hypoglycemia of 43.1% and 42.2%, respectively. The most pronounced effect was observed with the addition of polycarbophil to the suppository formulation containing a combination of deoxycholic acid and sodium taurocholate, which produced a 56% relative hypoglycemia compared with subcutaneous injection.

Conclusion

1. Clinical evaluation of rectal insulin formulations containing absorption enhancers proved to be effective in controlling hyperglycaemia.
2. Insulin suppositories have the ability to abolish the 2-h post-prandial significant rise in plasma glucose levels after meal.
3. The hypoglycemia resulted from clinical studies of the suppositories compared to that produced after subcutaneous injection of marketed soluble insulin preparation shows that it is possible to develop safe, effective, accepted and well tolerated insulin suppositories.
4. This route of administration of insulin will overcome most of the drawbacks associated with parenteral delivery of insulin e.g. peripheral hyperinsulinaemia which may lead to diabetic microangiopathy, burden of daily injections, reactions at site of injection, lack of patient compliance, cost, risks, infections, inconvenience and inability of some patients to self administer their insulin injections.
5. These suppositories, after complete development, will be a viable alternative to existing therapies.
6. These suppositories are believed to be suitable for meal time administration with the goal of tight control of post-prandial hyperglycaemia in diabetic population.
7. These suppositories will also be recommended in critical conditions where repeated doses of short acting insulin are needed as in diabetic ketoacidosis.
8. These suppositories of insulin will be suitable for children as well as adults.

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