NEW INSULINS AND INSULIN DELIVERY DEVICES

A Review.

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Ever since its discovery in 1921, insulin has been a life saving drug for many thousands of diabetics all over the world. Nevertheless, insulin therapy has not been without problems. Since, the observations of Berson and Yallow in 1958 (1) it has been well established that insulin therapy provokes the production of antibodies which circulate in the blood of insulin-treated diabetics. The qualitative and quantitative immunological responses depend on the species, purity and the pharmaceutical form of insulin (such as crystalline or amorphous form or molecular aggregates).

Firstly, the structure of beef and porcine insulin (which are two of the most frequently used forms) differs from that of human insulin. Human insulin, differs from porcine insulin, by only one amino acid, and from bovine insulin by three amino acids. As a result of this, bovine insulin can exert a more potent antigenic effect in humans, than porcine insulin. Apart from the species difference, the contaminants, which are variable quantities of proteins, extracted from the pancreas during the production of insulin, appear to confer antigenicity, to conventional bovine or bovine porcine mixtures of insulins. Thus, the most important clinical disadvantage of long term use of conventional insulin is development of immunological insulin resistance.

Recently, by the use of column chromatography using sephadex., and ion exchange chromatography several highly purified insulins have been made available commercially (2). They are:

1. Single peak or single component insulins (SP or SC; Eli Lilly, U.S.A.).
2. Monocomponent (M.C.) Insulins (NOVO, Denmark).
3. Highly purified rarely immunogenic (HP-RI; Nordisk, Denmark).
4. Chromatographically purified porcine insulin (CS; Hoechst, Germany).

Clinical advantages of purified insulins:

All these insulins, being highly purified, are less immunogenic, and are helpful in obtaining better regulation of hyperglycemia. Purified insulins have also considerably reduced the frequency of local and systemic allergy (3). The use of highly purified insulins often results in substan-

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tial dose reductions in diabetics previously treated with conventional insulins.

In western countries (both in Europe and U.S.A.), mixtures of bovine-porcine insulins have been almost withdrawn in favour of the highly purified monocomponent or single peak insulins. However in India, these insulins are not freely available (except for a limited availability of M.C. Insulin) and their cost may prove to be prohibitive. Under these circumstances, the indications for the use of M.C. Insulins (4) can be specified as follows:

a) in insulin resistance, due to a high titre of IgG insulin antibodies and in patients requiring a high dose of conventional insulins,

b) in allergy (both local and systemic) to conventional insulins,

c) where interrupted insulin therapy is required such as pregnancy, severe infections and after surgery,

d) in emergencies such as impending gangrene or in the treatment of diabetic coma or ketoacidosis,

e) for obtaining optimal control of diabetes in patients with rapidly progressing microangiopathy,

f) in severe insulin-induced lipodystrophy.

Experience with M.C. Insulin:

Several studies have been published from many centres in the world which document the efficacy of M.C. Insulin in the treatment of diabetes mellitus. Currently, at the Diabetes Research Centre, Madras, more than 350 diabetic patients are being treated with M.C. insulins, with excellent results. The dose of M.C. Insulin was 30-40% lower than that of conventional insulins. Treatment with M.C. insulins also resulted in a significant drop in insulin antibody titres in patients treated with conventional insulins (5, 6).

Clinical studies with human insulin:

It has been possible to obtain human insulin on a commercial scale by recombinant DNA technology from the bacterium Escherichia coli (7). This insulin is known as biosynthetic human insulin. Another type of human insulin called semisynthetic human insulin is obtained by enzymatic modification of porcine insulin involving essentially the replacement of the amino acid alanine at position 30 on the insulin B chain with threonine. Semisynthetic human insulin has been shown to be chemically, physically, immunologically and biologically equivalent to human pancreatic insulin (8).

It has been shown that semisynthetic human insulin and purified porcine insulin are comparable with regard to absorption from subcutaneous depots, blood glucose control, plasma insulin concentrations and binding to insulin receptors from both human and porcine sources (9). Thus, semisynthetic human insulin has been shown to be safe and effective and interchangeable with purified porcine insulin in the treatment of diabetic patients (10, 11).

Exogenous administration of semisynthetic human insulin though homologous to native human insulin, is immunogenic (12-14). Both IgG and IgE insuia specific antibodies have been shown to be present in 50% of subjects after six months of treatment which is similar to purified porcine insulin (15). Such immunogenicity is considerably less if newly diagnosed diabetics are treated from the beginning with human insulin. Trials with human insulin conducted as
Diabetes Research Centre, Madras has shown that at present the use of human insulin is limited to patients who are allergic to M.C. insulin also (13).

**Insulin infusion devices**:

A variety of clinical, biochemical and epidemiological studies have accumulated data to suggest that tight regulation of hyperglycemia would help to prevent or delay the occurrence of vascular complications of diabetes (16, 17). It is also universally accepted that conventional methods of insulin therapy in IDDM fail to achieve and maintain near normoglycemia.

It is conceivable that in insulin dependent diabetics, administration of a single dose of insulin cannot produce adequate amount of circulating insulin levels for 24 hours a day. It has been a practice for many years to give insulin therapy without assessing the regulation of hyperglycemia continuously. It is now accepted that a minimum of two doses of insulin or three injections a day have to be given to patients with IDDM in order to achieve satisfactory control of diabetes. These ways of intensive conventional therapy are important especially in India where the use of insulin infusion devices are limited.

The introduction of open-loop devices in clinical practice for continuous subcutaneous pre-programmed insulin administration (CSII) in diabetes mellitus has raised the possibility of optimizing insulin therapy and nearly normalizing blood glucose levels in IDDM.

Essentially two types of mechanical devices are available at present:

1. Closed-loop system (computer-linked) in which there is feed-back controlled insulin delivery. The dose of insulin given depends on the prevailing blood glucose level.

2. Open-loop systems, in which insulin is delivered in a pre-programmed manner arrived at by trials.

**The Closed-loop System**:

A closed-loop system consists of a continuous glucose sensor, and a computer-controlled insulin infusion system which delivers insulin according to an algorithm. Since 1974, Life Science Instruments Division of Miles Laboratories of Elkart, Indiana, has developed a commercial system for closed-loop insulin delivery called the Biostator. The blood glucose concentrations are displayed continuously and insulin, glucose or both are infused intravenously by means of a constantly turning multichannel roller pump. This is an important research tool today and has limited clinical uses such as determination of insulin requirement in diabetics and maintenance of near normoglycemia during surgery, childbirth, etc. The Biostator has many disadvantages. It is expensive, requires trained personnel and the system is elaborate with multiple infusions.

**Open-loop System**:

There are different modes of open-loop continuous insulin infusion namely (a) intravenous, (b) intra peritoneal and (c) subcutaneous.

Continuous intravenous insulin administration with supplementary doses before meals was the first method to be tried as a means for smooth and sustained regulation of blood glucose. The major advantage of this method is the very short time lag between the infusion and the distribution of the insulin to the body tissues. The problems with this route of delivery are venous thrombosis, phlebitis and infection.
Open-loop intra-peritoneal insulin delivery is more physiological than the other routes of infusion (18) since the insulin is essentially absorbed via the portal circulation with rapid absorption from the peritoneal space. The main drawback of this route is the risk of peritonitis.

Continuous Subcutaneous Insulin Infusion: (CSII):

The use of an adjustable portable electric pump for CSII has become very popular in the Western countries. Its transformation from research tool to commercial patient care device has been phenomenal. Almost a dozen different pumps are now commercially available and new models are being introduced every few months. Most of them pump insulin, by slowly pressing the plunger of a disposable plastic syringe; a few use peristaltic pumps. The pump is usually worn on a belt; but it can be concealed in a coat pocket or under clothing. Insulin is delivered from the pump to the patient through a small plastic tube ending in a tiny 27 gauge needle, which is inserted subcutaneously on the abdomen or thigh. The tubing is changed every two or three days.

Pumps use only short acting (regular) insulin which is delivered in two modes, basal and bolus. In the basal mode, the pump delivers insulin continuously at a slow rate (programmed by the patient) 24 hours a day. This provides the constant low level of plasma insulin required during the basal and post absorptive states. Fifteen to 30 minutes before each principal meal, the patient presses a button and the pump delivers a bolus to provide an additional quantity of insulin to cover the meal. On the average, 40-60% of the total daily insulin is delivered in the basal mode with the remaining being given in three roughly equal boluses at meals. The total daily insulin requirement may be calculated using a Biostator (19) or an intravenous insulin infusion system (20). The Mill-Hill infuser (U.K.), the Autosyringe (U.S.A.) and the Siemens' pump (West Germany) are some of the most commonly used open-loop devices for continuous infusion of insulin.

Advantages of Pump Therapy:

1. CSII has been useful to achieve optimal regulation of hyperglycemia in IDDM patients, who fail to respond to multiple injections of insulin (21). Concomitant with the regulation of hyperglycemia elevated levels of serum lipids are also normalized (22).
2. Long term therapy has helped to normalize glycosylated haemoglobin and improve nerve conduction velocity (23).
3. It has been found to be highly effective in achieving glycaemic control in brittle diabetes and pregnant diabetics (24).
4. The growth of diabetic children may be improved by pump therapy (22).

Experience with Insulin Pump in India:

The experience with insulin pump therapy in India is limited. At the Diabetes Research Centre, Madras, we have been using the Mill Hill infuser for insulin infusion as an inpatient treatment. The prohibitive cost and the non-availability of software are the two important drawbacks. We have used the pump to achieve control of diabetes in patients with insulin resistance who were not controlled with high doses of insulin. A short term therapy for a few days with the insulin pump in the hospital helped to break the insulin resistance. Thereafter not only we could achieve
control of diabetes, but also could maintain them on smaller doses of insulin. We also found that by using the pump we could achieve smoother control in many brittle diabetics (25).

Hazards of Pump Therapy:

The most common complication of pump therapy is infection at the site of needle insertion. Mechanical failure such as leakage of tubing or accidental removal of the needle from the skin might cause loss of diabetic control. The high cost of the modern insulin pump is a limiting factor.

Insulin pumps are relatively new and hence they should be installed only by specialists in the care of diabetes in medical centers with the resources to undertake this intensive form of management. Wearing an insulin pump does not simplify a diabetic patient's life; in many ways it may complicate it. In order for the pump therapy to be successful the patient must be motivated, committed and able to monitor blood glucose concentration and take care of the pump. Perhaps more important, he or she must be intelligent enough to undertake self-adjustment of insulin dosage after appropriate education. Hopefully, development of miniature implantable computerized models in the future could obviate many of these problems in the use of pump therapy in the control of diabetes mellitus.

REFERENCES:


ABSTRACT


Halofenate, an investigational drug known to reduce triglyceride, uric acid and platelet aggregation was used in NIDDM along with Chlorpropamide. Fasting blood sugar fell from 227 ± 27 to 107 ± 19 in halofenate group where as in placebo group the drop was from 242 ± 22 to 208 ± 29. Although the blood sugar showed normalization, the insulin response was not different. The important side effect of halofenate is peptic ulcer. It is likely that the halofenate may have action on insulin receptor mechanism.

--- S. D. M.