New Drugs

Diabetes I: Insulins

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Sixty years after the first therapeutic use of insulin treatment of insulin dependent diabetes continues to be with subcutaneous insulin injections. Nevertheless, this does not imply lack of progress. Recent years have seen important developments in insulin purification, the commercial production of human insulin, the development of new techniques of insulin administration, and the growing acceptance that good control reduces diabetic complications. The present change to U100 (100 units/ml) insulin has resulted in important changes in the range of insulins marketed—notably, only highly purified insulins will be available in the new strength.

Insulin preparations

The table summarises the presently available U100 insulin preparations. Soluble insulins consist of insulin in simple solution and are, therefore, rapidly absorbed when injected subcutaneously. They are the only insulins suitable for intravenous administration. The insulin injection *BP* formulation is acidic (pH 3.3), may cause pain and local reaction at injection sites, and has, therefore, been largely superseded by neutral soluble insulins. A highly purified acid soluble insulin is, however, available in U100 strength. The insulin zinc suspensions utilise the relative insolubility of insulin in combination with zinc in acetate buffer to retard absorption from the injection site. Amorphous suspensions (semilente insulins), having small particle size, are rapidly absorbed with a duration of action somewhat longer than that of soluble insulin, whereas crystalline suspensions (ultralente insulins), having larger particle size, are more slowly absorbed with duration of action extending over more than 24 hours. Lente insulins constitute a 30% amorphous, 70% crystalline mixture. Protamine zinc and isophane insulins utilise the relative insolubility of a protamine zinc insulin combination to retard insulin absorption. All soluble insulins may be safely mixed in the syringe with any of the intermediate or long acting insulins with the exception of protamine zinc insulin, with which a varying quantity of soluble insulin becomes bound to protamine.

Clinically it is more useful to classify insulins into short, medium, and long acting (table). The duration of action of the same insulin, may, however, be very different in different patients and may also vary with the total dose, injection site, and the patient's insulin antibody status. The classification in the table

should be interpreted in this light. It is often only by trial and error that the true duration of action for any insulin in a particular patient is established. In general, the larger the dose of insulin the longer the duration of action and insulin absorption is fastest from the abdomen and slowest from the resting thigh.

Characteristics of currently available U100 highly purified beef, pork, and human insulin preparations and approximate activity

	Peak activity (h)	Duration (h)
<i>Short acting insulins</i>		
Acid soluble insulin		
Insulin Injection BP (Wellcome, no brand name) (beef)		
Neutral soluble insulins*	2-5	6-8
Actrapid MC (pork); Human Actrapid (human emp); Human Velosulin [†] (human emp); Humulin S (human crb); Hypurin neutral (beef); Neusulin (beef); Quicksol (beef); Velosulin (pork)		
<i>Intermediate acting insulins</i>		
Isophane insulins*		
Human Insulatard [†] (human emp); Humulin I (human crb); Hypurin Isophane (beef); Insulatard (pork); Monophane (beef); Neuphane (beef)	6-12	12-24
Biphasic insulins (mixtures)		
Human Initar [†] (human emp); Human Mixtard [†] (human emp); Initar (pork); Mixtard (pork); Rapitard MC (beef and pork)	3-8	16-22
Insulin zinc suspension		
(a) Amorphous (Semilente): Semitard MC (pork)	5-10	12-16
(b) Mixed: Human Monotard (human, emp); Monotard MC (pork)	6-14	16-22
<i>Long acting insulins</i>		
Insulin zinc suspension		
(a) Mixed (Lente)*: Hypurin Lente (beef); Lentard MC (beef and pork); Neulente (beef); Tempulin (beef)	6-14	18-30
(b) Crystalline (Ultralente): Ultratard MC (beef)	10-24	24-36
Protamine zinc insulin		
Hypurin Protamine zinc (beef)	10-20	20-36

*Evans preparations had no brand names as of March 1983. [†]Available late 1983. emp = enzymically modified porcine; crb = chain recombinant bacterial.

With the advent in the 1970s of highly purified porcine insulins it became apparent that the duration of effect of some of these newer preparations was shorter than that of their conventional insulin equivalents. Thus Semitard insulin commonly has too short a duration of action to be useful as a medium acting insulin and Monotard insulin has a shorter duration of action than the older lente insulins. These differences may be explained in part by the reduced formation of insulin antibodies in response to these highly purified preparations, but it is likely that other factors such as differing solubility and altered diffusion characteristics of bovine and porcine insulins play a part. With the present introduction of human insulins similar differences in duration of action are being encountered and it seems that human insulins have shorter durations of action than their porcine and bovine equivalents.

The change to U100 insulin will be accompanied by the introduction of further branded insulins and the withdrawal from the United Kingdom market of globin zinc insulin and of bovine semilente. The porcine semilente (Semitard) will

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remain on the market. Present ranges of conventional and purified insulins in 20, 40, and 80 units/ml strength (as listed in the *National Formulary*) will continue to be available while there is a viable demand. Appropriate reusable glass and single use plastic syringes are now available both in 0.5 ml (numbered 0-50 units) and 1.0 ml (0-100 units) capacity. Several studies have shown that disposable plastic insulin syringes may be reused safely (the syringe needle being replaced when it becomes blunt) over seven days without chemical sterilisation between injections.

Insulin purity and species

Insulins prepared from beef or porcine pancreas and purified by repeated crystallisations contain impurities including proinsulin, various insulin derivatives, glucagon, pancreatic polypeptides, vasoactive intestinal polypeptide, and somatostatin. These impurities are important in eliciting an antibody response to insulin in patients. Highly purified insulins, from which most of the impurities have been removed, elicit a much reduced antibody response. Before the present U100 change more than half of the British insulin market was accounted for by highly purified insulins. Completion of the conversion to U100 will result in all patients receiving highly purified insulins.

Change to highly purified insulins is of established value in some instances in which the presence of high titres of circulating insulin antibodies has been shown to be harmful. Thus lipodystrophy at the site of insulin injection and local cutaneous reactions to insulin may be cured by conversion to highly purified insulins. Some cases of insulin resistance are associated with high antibody titres and respond to change to highly purified insulins, although in many cases other factors such as impaired subcutaneous absorption or inactivation may be responsible. In addition, the intermittent use of conventional insulins in non-insulin dependent diabetics—for example, during infections and surgery—is associated with production of insulin antibodies, and highly purified insulins are indicated in this instance.

In new patients starting insulin treatment there are several theoretical reasons for advocating the use of highly purified insulins. Antibodies to exogenous insulin may cross react with endogenous insulin and may reduce endogenous insulin production. Absence of these antibody induced effects may account for the remission phase of diabetes being prolonged in patients treated from the outset with highly purified insulins. Retention of residual endogenous insulin production may favourably influence diabetic control. Insulin antibodies cross the placenta and may contribute to raised fetal insulin concentrations in diabetic patients who are pregnant. Against these factors proponents of the continued use of conventional insulins have argued that equally good metabolic control may be achieved with conventional as with purified insulins and that low immunogenicity does not confer any advantages to patients. These arguments, however valid, have to a large extent been made irrelevant by the U100 change.

Bovine insulin is intrinsically more antigenic than porcine insulin, and where a highly purified insulin is to be used in the belief that low immunogenicity confers advantages it is more logical to choose a pure porcine or human preparation rather than a beef or mixed beef/porcine preparation. The change from conventional bovine to highly purified porcine or bovine insulins commonly results in a reduced insulin requirement of up to 20% (especially in patients receiving over 60 U/day) and this should be borne in mind when patients are changed from treatment with conventional bovine insulins to their U100 highly purified equivalents.

Human insulins

Both bovine and porcine insulins differ from human insulin in having alanine in place of threonine as the C terminal amino

acid of the B chain. Human insulin is now being produced on a commercial scale by two different processes. Novo and Nordisk use an enzymatic conversion to replace the alanine of the B30 portion of porcine insulin by threonine. The resultant insulin is designated by the *British Pharmacopoeia* as human insulin "emp"—enzymically modified porcine. In the process used by the Eli Lilly Company separate A and B chains of human insulin are produced by recombinant DNA (deoxyribonucleic acid) technology using *Escherichia coli* fermentation and the chains are combined chemically to produce biosynthetic human insulin, the resultant insulin being designated as human insulin "crb"—chain recombinant bacterial.

Although recombinant DNA technology should overcome any problems in the supply of insulin, there are at present no indications to change patients already satisfactorily controlled on bovine or porcine insulins to human insulin, and there are no data as yet on whether patients first starting insulin treatment will derive benefit from their use. Preliminary studies have shown human insulin to be safe and effective in controlling diabetes. Initial impressions with human insulin suggest that this is more quickly absorbed and cleared than porcine and bovine insulins, resulting in a slightly more rapid onset of action and a shorter duration of effect. Human insulins may be used in the rare event of a patient who is allergic to highly purified insulin, but further experience is necessary to define a broader role.

Insulin regimens

It is relatively easy to devise insulin regimens that will prevent primary diabetic manifestations of thirst, polyuria, weight loss, and ketosis. The vast amount of interest and research into this topic in recent years, however, derives from the long held belief (for which there is increasing scientific evidence) that normalisation of metabolism in diabetic patients will prevent the development of long term complications. Achieving such normalisation has proved difficult and requires a continuous effort by both patient and doctor.

In normal subjects insulin is secreted at two rates: a basal rate during fasting to exert an inhibitory control on the catabolic processes of glycogenolysis, gluconeogenesis, lipolysis, and protein breakdown and a rapid rate in response to meals to promote the storage of absorbed fuels. The aim of all insulin regimens attempting to achieve good control is to mimic this pattern of insulin secretion.

The commonest approach to this problem is the use of a combination of a short and medium acting insulin injected twice daily, before breakfast and before the evening meal. The morning short acting insulin produces a rise in insulin concentrations after breakfast while the medium acting insulin injected in the morning reaches its peak action in the afternoon. Insulin action after the evening meal and during the night is similarly provided by the evening injection of short and medium acting insulins respectively. The patient is instructed to adjust the dose of the morning short acting insulin to the before lunch blood or urine test; the morning medium acting insulin to the before evening meal test; the evening short acting insulin to the before bedtime test; and the evening medium acting insulin to the before breakfast test. Examples of insulin combinations for this type of regimen are soluble and isophane insulins or Actrapid and Monotard. One suitable starting regimen is to give two thirds of the total daily dose before breakfast and one third before the evening meal with each injection being divided equally between the short and medium acting component. These doses are then modified by the patient in accordance with home blood or urine tests. Home blood glucose monitoring of capillary samples using reflectance meters or simple enzyme impregnated strips has helped considerably in achieving good control.

It has been suggested that adjustments in the ratio of short and medium acting insulins in this type of regimen make little impact on the degree of diabetic control so that fixed ratio

mixtures such as Mixtard, Initard, or Rapitard may be substituted, although these claims require further substantiation in properly designed large trials. In addition, the premixture of insulins deprives patients of flexibility in response to short term changes in diet and exercise patterns. It therefore seems wise to reserve such fixed combinations for patients unable to understand or manage a more flexible regimen.

An alternative approach to mimicking normal insulin secretion patterns is the morning injection of Ultratard insulin combined with injections of a short acting insulin before meals. Such regimens may provide better diabetic control during the early hours of the morning. If insulin antigenicity is considered to be a disadvantage a present drawback of this regimen is that there are no porcine or human preparations of IZS crystalline insulin available and because of the greater solubility of the latter two insulins such preparations are unlikely to be developed.

The use of battery powered portable pumps for continuous subcutaneous insulin infusion has provided a new approach to mimicking normal insulin delivery patterns. With this technique insulin is delivered through an indwelling subcutaneous needle at a basal rate throughout 24 hours and boluses are delivered before meals to match meal time rises in blood glucose concentrations. The use of programmable pumps allows further refinement such as a rise in insulin infusion rate in the early hours of the morning (4-8 am), when increase in insulin resistance may occur. While such pumps are of established value in achieving good diabetic control, their use requires a high degree of patient motivation. Furthermore, they have the particular disadvantage that if the pump fails the onset of ketosis tends to be more rapid than with conventional treatment because of the lack of a subcutaneous depot of insulin. This procedure should be restricted to centres with a special interest in this technique at least until lighter second generation pumps with automatic alarms become generally available.

In elderly patients, those with limited life expectancy, and those unable to understand more complex insulin regimens preventing symptoms of diabetes may be the sole aim of treatment, and in these patients a single daily injection of a long acting insulin may offer the simplest form of treatment. In young diabetics a remission phase often occurs shortly after diagnosis

when a small dose of almost any insulin may control diabetes adequately. The use of single injections of long acting insulins from the outset in such patients is not, however, recommended. Patients usually acquire their life time habits in diabetic care during the first few weeks of their illness, and preferably they should be educated in the use of a suitably rigorous insulin regimen from the outset. Patients should be forewarned then that insulin requirements may temporarily become very low for the first few months after starting treatment.

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Clinical curio: butterfly in the ear

The vogue for piercing the ears of children has led to a spate of consultations about foreign bodies within the earlobe. Though stories

FIG 1—Radiograph showing butterfly clasp embedded in earlobe. FIG 2—Butterfly clasp excised from earlobe.

of such cases are common, only one is mentioned in published work.¹

A 7 year old girl presented to a nurse complaining of a painful left earlobe, which had been pierced two months previously. The nurse found little on examination, and the mother was advised to see her family doctor. Five days later the child was taken to the accident and emergency department at Ilkeston Community Hospital, the whole of the left earlobe having now become painful, swollen, and tender with a purulent discharge through the superimposed sinus. A hard nodule was palpable within the lobe, which was opaque on transillumination. At this stage the mother made known her fear that somehow the butterfly clasp of the child's earring had found its way into the tissue of the lobe since this had been lost and, despite careful searching, not retrieved. An x-ray examination confirmed the mother's fears (fig 1).

The foreign body was excised from the earlobe under local anaesthetic (fig 2). A single suture was inserted, and the wound healed without complications.

Children's earrings have remarkably small clips, and with the fiddling fingers of a young child it is possible that such a clip might be forced through the pierced hole and into the soft tissue of the lobe. This is a potential source of pain and infection and should be brought to the attention of earring manufacturers, who should consider increasing the size of the clips on such earrings for greater safety.—N W LAWRENCE, medical student, Nottingham, and J L SKINNER, general practitioner, Ilkeston.

¹ Smith, RB. Earring clasp as a foreign body in the earlobe. *Plas R Surg* 1978;62:772.