ABC of Diabetes

PETER J WATKINS

INSULIN TREATMENT

The use of insulin has to be tailored to meet individual requirements. The aim is to achieve the best possible control in the circumstances, avoiding at all costs the disabling hypoglycaemia that can occur if too fine a degree of control is attempted. In elderly patients or those who lack motivation it is therefore wise to aim only at alleviating symptoms and not to attempt very strict control.

Types of insulin

Soluble	}	}	Beef
Isophane			Pork
Insulin zinc			Human
Suspension			

There are three main types of insulin.

Soluble insulins were first introduced in 1922 and still play an important part not only in daily maintenance of insulin-dependent diabetics, but also in managing diabetic emergencies, when they can be given intravenously or intramuscularly.

Protamine insulins are long- and medium-acting insulins introduced in Denmark during the 1930s. The most useful insulin containing protamine is isophane (NPH=Neutral Protamine Hagedorn).

Insulin zinc suspensions were first introduced during the 1950s; there are several preparations with widely ranging duration of action.

Insulin types are further divided according to their animal source (pig, beef, or human) and purity. Some preparations of insulin are presented as proprietary mixtures, eliminating the need for patients to mix insulins in the syringe. Details of the twenty-three types of insulin available in the UK are shown in the table.

Insulin preparations available in the United Kingdom

Type	Animal source	Purity	Type	Animal source	Purity
Soluble insulin	Beef		Semitard MC	Pork	Purified
			Lente*	Beef	
<i>Neutral soluble insulins</i>			Hypurin Lente*	Beef	Purified
Actrapid MC	Pork	Purified	Neulente*	Beef	Purified
Velosulin	Pork	Purified	Lentard MC*	Beef and pork	Purified
Neusilin	Beef	Purified	Monotard MC*	Pork	Purified
Hypurin Neutral	Beef	Purified	Ultralente	Beef	
			Ultratard MC	Beef	Purified
<i>Isophane insulins</i>			<i>Mixed insulins</i>		
Isophane NPH	Beef		Rapitard MC*	Beef and pork	Purified
Hypurin Isophane	Beef	Purified	Mixtard* (Neutral 30%, Retard 70%)	Pork	Purified
Neuphane	Beef	Purified	Initard* (Neutral 50%, Retard 50%)	Pork	Purified
Insulatard	Pork	Purified			
<i>Insulin zinc suspensions</i>			<i>Other insulins</i>		
Semilente	Beef		Protamine zinc insulin	Beef	
			Hypurin PZI	Beef	Purified

*Insulin mixtures. MC=Monocomponent (highly purified) insulin.

Selection of insulin

The choice of insulin preparation is based on the duration of action, animal source, purity, and strength.

Duration of action

Although insulins can be broadly classified as having short, medium, or long durations of action, their effect varies considerably from one patient to another: thus soluble insulin, usually considered to be of rather short duration, may have a more sustained effect in one patient than isophane, generally described as a medium-acting insulin, has in another patient. The duration of action of insulin in an individual patient can therefore be discovered only by trial and error.

Animal source and purity

Insulin extracted from pigs is less antigenic than that extracted from beef sources, and highly purified pig insulins are less antigenic than conventional insulins. Human insulin can now be manufactured either by genetic manipulation of *Escherichia coli* (recombinant human insulin) or by chemical manipulation of pig insulin. Different sources of insulin are not known to confer any advantages to patients. In practice the purer insulins have few advantages. Fat atrophy at the injection site does not occur with their use, and if it has already occurred with conventional insulins the use of purified insulin injected around the edge of the hollow, will reverse the atrophy and the hollows will fill out. The localised red itchy patches which are common at injection sites for a few weeks after a patient starts insulin are probably less common when purified insulins are used. Also, in rare cases of insulin resistance when very high doses are needed, patients may respond to the introduction of purified insulin and the dose can be considerably reduced. Thus purified insulins should be used in patients with fat atrophy and those who need very high doses. It is probably also an advantage to use them when insulin is required temporarily—for example, in pregnancy or after surgery—to minimise the development of insulin allergy in later years should insulin ever be needed again. Children, too, should usually be treated with purified insulins.

When purified insulins are substituted for conventional insulins the dose sometimes needs to be reduced, especially when the total dose is greater than 60 units. When making such a change, it is best to reduce the dose immediately by 20-30%, thereafter making appropriate adjustments.

Porcine insulin crystals.

Insulin regimens

Starting insulin—For relatively ill patients with acute-onset diabetes, treatment should be started with short-acting soluble insulin two to four times a day. For those less severely ill treatment should be started with a medium-acting insulin given once or twice daily; 8 units twice daily is a suitable initial dose for most patients. Many patients who present with acute diabetes enter remission soon after diagnosis, when a small dose of almost any insulin is enough to maintain good control. The practice of withdrawing insulin at this stage is not encouraged because after a few months the need for insulin is almost inevitable.

Maintenance regimens—Most insulin-dependent diabetics who want to achieve very good control will need twice-daily injections, taken 15 to 30 minutes before breakfast and the main evening meal. A mixture of short- and medium-acting insulins is usually the best: thus soluble and isophane insulins may be used together, or, if purified insulins are to be used, neutral soluble insulin may be mixed with either purified isophane or Monotard (insulin zinc suspension). Semitard insulin generally has too short an action to be useful. For very fine control, such as that needed in pregnancy, three injections daily can give even better results. A regimen of soluble and medium-acting insulin in the morning, soluble insulin before the evening meal, and medium-acting insulin at night is often very successful, reducing both nocturnal hypoglycaemia and the post-breakfast

peak. For patients who lack either motivation or ability to mix insulins in a syringe, because of old age, poor intelligence, or blindness, fixed mixtures of short- and medium-acting insulins are available (Rapitard MC, Mixtard, or Initard). In these patients, a single daily injection may suffice, and this has the added advantage of preventing the nocturnal hypoglycaemia, which is a hazard especially for elderly patients living alone.

Injection sites

Insulin for routine treatment is given subcutaneously by intermittent injections or by continuous infusion. Insulin can be injected subcutaneously almost anywhere if there is enough flesh. The best site is the front of the thigh. The lower abdominal wall, buttocks, and upper arms may also be used. Women who want to wear short sleeves should normally avoid using the arms in case unsightly marks should appear: some may then prefer to confine injections to the bikini area.

It is important to vary the injection sites from day to day, using, for example, each thigh alternately over as wide an area as possible. Absorption of insulin ranges from one site to another, and if there are any difficulties with "control" it is advisable to use one area consistently—for example, the thigh.

Injection of insulin

Drawing up the insulin

(1) (a) Glass syringe: work the syringe plunger up and down several times to remove all traces of spirit. (b) Plastic syringe: these are used directly and without cleaning.

(2) Clean top of insulin bottle with industrial methylated spirit.

(3) Draw air into syringe to the number of marks of insulin required and inject this into the insulin bottle; then draw the required dose of insulin into the syringe, and before withdrawing the needle from the insulin bottle, expel the air bubble if one has formed.

If clear and cloudy insulins are to be mixed, inject the correct number of marks of air first into the cloudy insulin bottle; withdraw the needle from the cloudy bottle; inject the air into the clear bottle, and withdraw the insulin into the syringe; finally insert the needle into the cloudy bottle and withdraw the insulin.

Injection technique

(1) The skin need not be specially cleaned; repeated application of spirit hardens the skin.

(2) Stretching the skin at the injection site is the best way to obtain a painless injection; in thin people it may be necessary to pinch the skin between thumb and forefinger of the left hand.

(3) The needle should be inserted briskly at almost 90° to the skin to almost its whole length (needles are usually 3/8 inch to 5/8 inch long).

(4) Inject the insulin by depressing the plunger. It is not necessary to pull back the plunger beforehand.

(5) Withdraw the needle and press briefly on the injection site with cotton wool.

(6) (a) Glass syringe: rinse the syringe with industrial methylated spirit and then replace it with needle attached into the same spirit in a suitable container. (b) Plastic syringe: replace the needle cover and return the whole syringe-needle unit to its container. Keep in the refrigerator. Plastic syringes can be used up to 1 month or until the scale becomes indistinct; disposable needles are used until they are blunt. Plastic syringes should not be kept in any form of preservative, but disposable needles can be kept in methylated spirit when used with a glass syringe.

Insulin dose

From 1983 100 U/cc (U/ml) insulin will be introduced: in the interests of safety it is hoped that 40 and 80 U/cc will then be withdrawn as rapidly as possible; otherwise confusion and errors could be serious. New syringes will be marked *directly in units* for 100 U/cc insulin.

Problems associated with insulin injection

Soon after starting insulin injections, small red itchy marks about one inch across may occur at the injection sites. These are temporary and will disappear within a few weeks. On the very rare occasions when they continue to be troublesome the addition of hydrocortisone to the insulin bottle, so that each injection contains about 1 mg hydrocortisone, may eliminate the problem.

Many patients develop some blurring of vision soon after starting insulin, which makes reading difficult. This is due to a change of lens refraction and corrects itself within two to three weeks. Transient oedema of the feet is not uncommon during the first few weeks of insulin treatment.

Fat atrophy used to be common in women taking conventional insulins but is most unusual in those using the newer purified insulins. If fat atrophy has already occurred it can be reversed by injecting purified insulin around the edge of the hollow towards its centre, and during several weeks the hollow will fill out.

Fatty tumours occasionally occur. Their cause is not known but they sometimes develop if injections are repeatedly given over a very limited area of skin. For this reason it is best to vary the site from day to day. They are rarely troublesome, but once present they tend to persist.

Insulin allergy causing urticaria is very rare indeed. If it occurs, desensitisation may be needed. Abscesses at injection sites are also remarkably rare.

Dr Peter J Watkins, MD, FRCP, is consultant physician, Diabetic Department, King's College Hospital, London.

The illustration of porcine insulin crystals was reproduced, by permission, from *Insulin: Islet Pathology, Islet Function, Insulin Treatment*, ed Rolf Luft, published by Nordisk Insulinlaboratorium.