Pharmacology of Antidiabetic Preparations

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Insulins

Indications

(i) Insulin dependent (type I) diabetes mellitus
(ii) During pregnancy — when hyperglycaemia is present.
(iii) During acute insulin deficiency states uncontrolled diabetes with ketosis hyperglycaemia with dehydration and hyperosmolarity.
(iv) Hyperglycaemia complicated by acute infections, major surgery, severe trauma and/or steroid therapy.
(v) Diabetic patients with severe kidney disease or serious liver damage.
(vi) Certain cases of type II diabetes — not controlled by diet and manifesting oral hypoglycaemic agent failure.

Insulins are commonly extracted from beef and pork, produced in conventional purity and highly purified forms and available in different strengths — the common ones stocked being U40/ml and U80/ml — duration of action subdivides the preparation into short-, intermediate- and long-acting insulins. All these insulins are derived from pork, except for 'Lente' and 'Rapitard' which are beef and pork, and 'Ultralente' which is beef.

Storage

Insulins should preferably be stored between 2° and 8°C and not exposed to heat or sunlight. They should never be frozen. The vial in use could be kept at room temperature (max. 25°C) for a few weeks.

Mixing

When longer-acting insulins are mixed with shorter-acting insulins the latter should be drawn into the syringe first, and the mixture injected immediately.

Highly Purified Preparations

The main indications for considering the use of these insulins include:

(a) newly diagnosed juvenile type I (IDDM) diabetics.
(b) cases of genuine allergic reactions to conventional purity insulins.
(c) cases of lipodystrophy at injection sites.
(d) cases of genuine insulin resistance — daily doses in excess of 100U/day.

Table 1.

Type of Insulin	Degree of Impurity		Average time of Action (hours)		
	Conventional	Highly Purified	Onset	Peak Action	Duration
Short-acting and rapid results.	'Neutral' or 'soluble'	'Actrapid' or 'Velasulin'	1/2	1 1/2 — 4	8
Intermediate acting	'Lente' or 'N.P.H.'	'Monotard or 'Insulatard'	2	5—12	23
Long-acting and slow-onset		'Ultralente MC'	6	10—24	30
Biphasic (mixture of short intermediate acting)		'Rapitard'	3/4	4—10	23

A reduction in dose may be necessary when transferring patients from conventional purity to highly purified insulins. The mixing of conventional and highly purified preparations should be avoided.

Strategy of Insulin Therapy

Insulin dependant diabetics usually need intermediate insulin twice daily to cover their basal needs and very often the addition of one or two doses of short acting insulin (mixed with the above) to cover the challenges of meals.

Non-insulin dependant diabetics, especially during periods of 'stress' eg. intercurrent serious illness, may need insulin for a time in order to achieve better metabolic control — in these cases the use of intermediate insulin may often be sufficient.

Satisfactory control — as measured from blood glucose levels fasting and 2 hours after meals (HbA_1 levels) and urine samples checked before meals — would present with blood glucose levels ranging between 80 and 160 mg/dl; (HbA_1 values less than 8.5%), with essentially absent glycosuria in adults. 'Strict control' could mean the need of more intense insulin therapy.

The timing of the insulin injections, especially in relation to food; proper insulin injection technique and suitable meal planning are essential for adequate management.

In cases of uncontrolled hyperglycaemia, stabilization could be attempted with short-acting insulins given 4—8 hrly. according to blood glucose levels and body weight. Cases of diabetic ketoacidosis and hyperglycaemic, hyperosmolar non-ketotic acidosis should be managed with short-acting insulins only.

Complications of Insulin Therapy

These include:
1. Hypoglycaemia
2. Chronic overdosage (average daily dose well above 1.0U/Kg body weight)
3. Lipohypertrophy and/or lipoatrophy.
4. Insulin allergy.
5. Insulin antibodies.
6. Insulin resistance.

Oral Hypoglycaemic Agents

Clinical Use

There are two types of oral hypoglycaemics with different modes of action: sulphonylureas and biguanides. The former are generally preferred to the latter, especially, as first line treatment because they are more potent and have fewer side-effects.

Indications

These preparations are usually only indicated in uncomplicated, type II (non-insulin-dependant) diabetics where dietary compliance, daily exercise and body weight control fail to achieve satisfactory metabolic control. They are contra-indicated in type I (insulin-dependant) diabetics (at least as monotherapy); in uncompensated diabetes with ketosis, and during pregnancy. In certain serious 'stressful situations' like severe infections, major surgery and severe trauma, temporary substitution with insulin may be indicated.

Table 2

Pharmaceutical Preparations

Preparation	Tablet Strength	Mean Daily Dose	Potency	Duration of Action
Tolbutamide	500mg	500—2000mg	mild	short
Chlorpropamide	100mg; 250mg	100— 500mg	Intermediate	long
Glibenclamide	2.5mg; 5mg	2.5— 15mg	strong	intermediate
Metformin	500mg	500—1000mg	mild	intermediate

Special remarks: *In the case of glibenclamide - avoid high doses in the elderly and/or those with renal impairment. Metformin may give rise to lactic acidosis. Hence, avoid in elderly patients, in alcoholics, in states of shock, and in those patients with liver disease, serious cardiac or pulmonary disorders.*

It is often safer to start with low doses of the less potent sulphonyureas, increasing gradually the dose as needed, up to the maximum dose. If control remains poor, substituting for a stronger preparation seems advisable (e.g. tolbutamide then chlorpropamide then glibenclamide), and should the metabolic condition still remain unsatisfactorily stabilized, addition of a biguanide may be considered in selected cases. Both primary and secondary failure of sulphonylurea therapy occur, the causes are often not known — in such cases resorting to insulin might have to be considered especially if hyperglycaemia and symptoms persist in spite of dieting and maximum doses of oral hypoglycaemics. However, one must constantly remember that the commoner causes of 'loss of diabetic control' include: infection, changes in diet, body weight and/or exercise, emotional stress, erratic administration of medicines and drug-induced effects.

Side-Effects

Adverse effects are relatively uncommon, the ones more frequently met including:

(i) variety of skin rashes, often accompanied by pruritis.
(ii) upper gastro intestinal symptoms — anorexia, dyspepsia, nausea, vomiting, abdominal fulness.

and less often:

(iii) severe skin eruptions — including sensitivity reactions.
(iv) bone marrow suppression.
(v) cholestatic jaundice.
(vi) porphyria-like syndrome.
(vii) disulfiram-like reaction in certain cases of alcohol intake whilst on chlorpropamide.

Drug Interactions in Diabetics

Drugs taken by diabetics for reasons other than control of blood glucose may effect the response to insulin or oral antidiabetic drugs. The mechanisms of these drug interactions may involve the alteration in the

(a) absorption,
(b) distribution,
(c) metabolism (biotransformation) or
(d) excretion of the primary agent.

The factors predisposing to clinically significant drug interactions include, two or more drugs taken simultaneously or close together; taken for several days or longer; or if given to patients with underlying hepatic or renal disease; undefined genetic differences; and/or when an agent is added to or deleted from a previously effective therapeutic programme.
Summerizing the principal adverse drug interactions of clinical importance to diabetics consist of:

(a) drug interactions that may make diabetes worse:-
  (i) glucocorticosteroids;
  (ii) oral contraceptives;
  (iii) oral diuretics, especially the salt losing thiazides;
  (iv) diazoxide;
  (v) sympathomimetic agents; and
  (v) nicotinic acid.
(b) drug interactions causing potentially significant hypoglycaemia in diabetic patients:
  (i) alcohol;
  (ii) bishydroxycoumarin;
  (iii) phenylbutazone;
  (iv) salicylates;
  (v) sulphonamides;
  (vi) propranolol.

One must remember that a not insignificant proportion (estimated probably to be circa 30%) of elderly type II diabetics are also often suffering from concomitant diseases like cardiovascular disorders (especially congestive cardiac failure, ischaemic heart disease or hypertension) anxiety states and/or osteoarthritis — for which they are also frequently receiving treatment that could possibly interact with their antidiabetic therapy (be it oral hypoglycaemic agents — of which the commoner are glibenclamide and glymidine with chlorpropamide and metformin less common — and/or insulin preparations). Among the medical drugs probably more often concurrently being prescribed and taken are diuretics (thiazides and frusemide), digitalis, potassium supplements; benzodiazepines (especially diazepam) methyldopa and betablockers (esp. propranolol). Possibly, also not infrequent are preparations like indomethacin, hydralazine, nitrates (short or longer acting), nifedipine, vitamin supplements, bronchodilators and clofibrate.

Other disorders frequently of a temporary nature, also often encountered in diabetics but which rarely require chronic medication include obesity and hyperlipidaemia.

Drugs may also interfere with tests for glucose or ketones in the urine or those estimating glucose in the blood. Regarding the latter, the commoner preparations that can give rise to a false positive or false negative with the estimation of blood glucose include adrenaline, amino-salicylic acid, levadopa, ascorbic acid, dextran, hydralazine, tetracyclines and iron sorbitol. With urine tests, false negatives can occur in glucose oxidose test strips with ascorbic acid (esp. high doses) and levodopa, whilst false positives can occur in copper reduction tests with ascorbic acid, nalidixic acid, cephalosporins, methyldopa, probenecid, and salicylates, streptomycin, isoniazid and para-amino-salicylic acid (with Benedict's test).

References:

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