Drug Treatment of Non–Insulin-Dependent Diabetes Mellitus in the 1990s
Achievements and Future Developments

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Summary

Non–insulin-dependent diabetes mellitus (NIDDM, type 2 diabetes) is a heterogeneous disease resulting from a dynamic interaction between defects in insulin secretion and insulin action. There are various pharmacological approaches to improving glucose homeostasis, but those currently used in clinical practice either do not succeed in restoring normoglycaemia in most patients or fail after a variable period of time.

For glycaemic regulation, 4 classes of drugs are currently available: sulphonylureas, biguanides (metformin), α-glucosidase inhibitors (acarbose) and insulin, each of which has a different mode and site of action. These standard pharmacological treatments may be used individually for certain types of patients, or may be combined in a stepwise fashion to provide more ideal glycaemic control for most patients.

Adjunct treatments comprise a few pharmacological approaches which may help to improve glycaemic control by correcting some abnormalities frequently associated with NIDDM, such as obesity (serotonergic anorectic agents) and hyperlipidaemia (benfluorex).

There is intensive pharmaceutical research to find new drugs able to stimulate insulin secretion (new sulphonylurea or nonsulphonylurea derivatives, glucagon-like peptide-1), improve insulin action (thiazolidinediones, lipid interfering agents, glucagon antagonists, vanadium compounds) or reduce carbohydrate absorption (miglitol, amylin analogues, glucagon-like peptide-1). Further studies should demonstrate the superiority of these new compounds over the standard antidiabetic agents as well as their optimal mode of administration, alone or in combination with currently available drugs.

Non–insulin-dependent diabetes mellitus (NIDDM, type 2 diabetes) is a common disorder which is associated with a markedly increased morbidity and mortality rate. It is a heterogeneous condition caused by both genetic and environmental factors. The development of impaired glucose homeostasis results from a dynamic interaction between defects in insulin secretion and insulin action. It has long been recognised that drugs represent only part of the management of NIDDM and that other interventions, such as patient education, modification of diet and promotion of physical activity play a crucial role. Updated recommendations for the management of NIDDM been have
recently published by the European NIDDM Policy Group[5] and by a consensus panel of the American Diabetes Association.[6]

1. Standard Treatments

Drug treatments of NIDDM patients include sulphonylureas, biguanides (metformin), α-glucosidase inhibitors (acarbose) and insulin.[2-8] These agents may be used as monotherapy or in various combinations. Unfortunately, it is not known which between sulphonylureas, metformin or insulin is the best treatment to retard progression of the disease and to prevent diabetic complications. The ongoing United Kingdom Preventive Diabetes Study (UKPDS) is expected to answer this important question before the end of the millennium.[9,10]

1.1 Sulphonylureas

1.1.1 Pharmacodynamic, Pharmacokinetic and Dosage Considerations

Sulphonylureas stimulate insulin secretion by interacting with specific receptors on the β-cell surface that act to close K+ channels in the membrane; the resulting depolarisation allows Ca++ to enter the β-cell, which triggers the release of insulin-containing secretory granules.[11-13] Extra-pancreatic effects have also been described,[14] but their therapeutic role remains controversial. They may indeed be only the result of the reduction of ‘glucose toxicity’, due to the stimulation of residual insulin secretion which leads to better glycaemic control.

Sulphonylureas are a rational choice to begin pharmacological intervention because almost all patients with NIDDM are relatively insulin deficient.[11] In responsive patients, therapy with a sulphonylurea can lower glycated haemoglobin (HbA1c) levels by 1 to 2%. However, at best 60 to 70% of such patients might achieve ‘good’ glycaemic targets, and those with high fasting blood glucose levels and severe obesity rarely succeed. In addition to the rather high initial failure rate, about 10% of patients per year will fail to respond to therapy.[15]

The description of the pharmacokinetic and pharmacodynamic differences between the various sulphonylurea compounds [tolbutamide, chlorpropamide, glibenclamide (glyburide), glipizide, gliclazide, glibudone] is beyond the scope of this article but these properties have been detailed in recent general reviews.[8,11-13] One interesting topic for discussion is the option of prescribing either a sulphonylurea with a short half-life 3 times daily before each main meal, or one with a more prolonged action once daily. The use of the first-generation compound chlorpropamide has markedly decreased in most countries, essentially because of its longer duration and associated higher risk of hypoglycaemia.

Interestingly enough, however, a new slow release form of the fairly short-acting second-generation sulphonylurea compound glipizide has been recently developed in order to allow once-daily administration.[16,17] Although this new formulation may favour patient compliance, it is not clear whether it can improve blood glucose control without increasing hypoglycaemia. Finally, there is no consensus on the maximal doses of sulphonylureas to be used, and the maximal recommended doses of glibenclamide and glipizide are higher in the US than in Europe.[18] Recent data, however, have indicated that the maximum effect of sulphonylureas is reached at much lower doses than previously assumed.[19]

1.1.2 Adverse Effects

Hypoglycaemia is the main problem of sulphonylurea derivatives, especially in elderly people.[20] Hypoglycaemic episodes are more often associated with chlorpropamide and glibenclamide, although all sulphonylureas have such an adverse effect.[21] The risk is increased in the presence of alcohol consumption, poor food intake, renal impairment and drugs which potentiate the action of sulphonylureas, e.g. fibrates, nonsteroidal anti-inflammatory agents, etc.[22] Weight gain, sometimes of several kilograms, may occur with these agents and is undesirable in already overweight patients.[9,10] The anabolic effects of increased insulin levels, together with reduced uri-