Sulfonylureas
Why, Which, and How?

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Although controversies remain as to the usefulness of sulfonylureas, most evidence is in favor of their use in many if not most patients with non-insulin-dependent diabetes mellitus. When used properly, sulfonylureas improve insulin secretion and action, and these effects may be maintained for years. If combined with hypocaloric dietary regulation, rapid- and short-acting sulfonylureas may help patients reach and maintain euglycemia without provoking chronic hyperinsulinemia or weight increase. There is no evidence that sulfonylurea treatment causes β-cell exhaustion; instead, the antihyperglycemic effect helps improve β-cell function. Sulfonylurea "failures" are often dietary failures or may be due to late introduction of these drugs, i.e., when β-cell function is already attenuated. Desensitization of the insulinotropic effect of sulfonylureas may occur but might be avoided by discontinuous (<24 h/day) sulfonylurea exposure, i.e., once-daily administration of a short-acting sulfonylurea in a moderate dose. The most important adverse effect of sulfonylureas is long-lasting hypoglycemia, which may lead to permanent neurological damage and even death. This is mainly seen in elderly subjects who are exposed to some intercurrent event, e.g., acute energy deprivation or a drug interaction, i.e., aspirin. Long-acting sulfonylureas may be more likely to promote long-lasting hypoglycemia. The dose-response relationships of sulfonylureas have been poorly investigated, and sulfonylurea therapy should always be initiated and maintained at the lowest possible dose.
***Diabetes Care* 13 (Suppl. 3):18–25, 1990**

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WHY SULFONYLUREAS?

Despite 35 yr of practice and thousands of scientific publications, controversy still shrouds the use of sulfonylureas in the treatment of patients with non-insulin-dependent diabetes mellitus (NIDDM). Those who ascribe little therapeutic value to these drugs raise several critical issues: *1*) some NIDDM subjects never achieve a satisfactory response to the drugs (primary failures); *2*) many of those who respond initially become resistant subsequently (secondary failures); *3*) sulfonylurea treatment could be counterproductive, because it may lead to weight increase, chronic hyperinsulinemia, and more severe insulin resistance; *4*) long-term sulfonylurea treatment might cause β-cell exhaustion; *5*) according to the University Group Diabetes Program (UGDP) study, sulfonylurea treatment may increase the risk of cardiovascular mortality; and *6*) sulfonylurea therapy may be associated with severe hypoglycemia that leads to neurological sequelae or even death.

Those who support the therapeutic use of sulfonylureas point out that the above-mentioned arguments are for the most part invalid or based on inappropriate use of these drugs. Primary failure occurs but only exceptionally; when seen, it may be occurring in a subpopulation of NIDDM patients with a different metabolic defect or in an advanced stage of NIDDM that should have been treated many years earlier. Several primary and secondary failures can be attributed to lack of appropriate coordination of dietary and sulfonylurea treatment, misdiagnosis of slowly evolving insulin-dependent diabetes mellitus (IDDM) as NIDDM, or acute intercurrent events that increase the need for insulin. The validity of the conclusions of the UGDP has been debated for almost 20 yr and has not been substantiated in other studies. There is no scientific support

of the concept that sulfonylurea treatment would exhaust β-cell function; instead, the blood glucose reduction may help improve and maintain β-cell function. Indeed, sulfonylurea treatment may delay the development of NIDDM and reduce its cardiovascular complications.

This review addresses the use of sulfonylurea drugs in maximizing benefits and minimizing problems, e.g., weight gain, hyperinsulinemia, long-lasting hypoglycemia, and secondary failure.

Metabolic control and diabetic complications. Apart from amelioration of subjective symptoms, antidiabetic treatment should aim at prevention of diabetic complications. There is increasing support for the view that the microvascular and neuropathic complications of diabetes mellitus are related to the degree and duration of hyperglycemia (1–5), whereas the acceleration of macrovascular disease that occurs in NIDDM patients is thought to result from the combined effect of hyperglycemia, hyperinsulinemia,* hyperlipidemia, and hypertension (6–11). Accordingly, therapeutic intervention should attempt to normalize not only blood glucose but also plasma insulin, plasma lipids, and blood pressure. It is of particular importance that the common coexistence of insulin resistance, hyperglycemia, hyperinsulinemia, hyperlipidemia, and hypertension may be not only coincidental but consequential (12–14), and that sulfonylureas may have a beneficial influence on all of these disturbances (see below).

Acute and chronic effects of sulfonylureas. In most newly detected NIDDM subjects, sulfonylureas reduce blood glucose acutely and chronically, and the effect may be maintained for many years. Because sulfonylureas are unquestionably able to stimulate insulin secretion, and because they are ineffective in IDDM subjects, it is reasonable to ascribe at least part of their antihyperglycemic effect to their insulin-releasing capacity. The sulfonylurea-induced release of insulin from the β-cell might be mediated by specific plasma membrane receptors on the β-cell surface, coupled to ATP-sensitive K^+ channels (Siconolfi-Baez et al., this issue, p. 2). In addition, sulfonylureas may increase the systemic availability of insulin by reducing hepatic insulin clearance (15–18). Furthermore, sulfonylureas improve insulin action in muscle, liver, and adipose tissue (19–25). β-Cell function, insulin availability, and insulin action are also secondarily improved as a result of reduced hyperglycemia (26,27).

It has been extensively debated whether the insulinotropic effect of sulfonylureas is maintained during long-term therapy or the chronic antihyperglycemic effect mainly reflects an extrapancreatic action. Many studies have shown that, after the initial elevation of plasma insulin, insulin concentrations return toward pretreatment levels or even below them. However, this need not signify that the stimulating effect of sulfonylurea on insulin secretion has been attenuated; the reduced insulin levels may be consequent to the reduced blood glucose levels. However, note in this context that chronic sulfonylurea therapy may lead to β-cell desensitization (28). By conjecture, this infers that the insulinotropic action might be maintained during long-term therapy but only if the exposure to sulfonylurea were discontinuous, as would occur with once-daily use of a short-acting sulfonylurea in moderate dosage (27).

Antihyperglycemic efficacy of sulfonylureas. Dietary regulation can be very effective in reducing hyperglycemia, but euglycemia maintained during long-term therapy by dietary regulation alone is the exception (29–31). This may at least be partly due to the difficulty in adhering to strict (particularly hypocaloric) dietary regulation, especially in the long term. However, even when hypocaloric dietary regulation is well adhered to, it seems unable to improve the characteristic delay of insulin release in response to meals and hence seems unable to reduce the net elevation and prolongation of blood glucose after a meal (31). In contrast, sulfonylureas are not only able to lower fasting blood glucose, but they may improve acute insulin release and reduce postprandial hyperglycemia (32). In addition, sulfonylureas may have an extrapancreatic antihyperglycemic effect that is maintained during long-term treatment (Faber et al., this issue, p. 26). There is recent evidence that, if introduced during the early phase of NIDDM, addition of sulfonylurea treatment to dietary regulation may keep blood glucose levels near normal for at least 2–3 yr (33). Moreover, sulfonylurea "secondary failures" often turn out to be dietary rather than true drug failures, and reintroduction of proper dietary restriction may restore the efficacy of sulfonylureas (34).

It follows that dietary regulation and sulfonylurea therapy are complementary treatments, both of which are often needed to attain euglycemia, and there should remain little doubt as to the long-term antihyperglycemic benefit of sulfonylureas. Whether sulfonylureas are able to delay the development of NIDDM and its complications is discussed by Melander et al. (this issue, p. 53).

Sulfonylureas and hyperinsulinemia. Because sulfonylureas enhance the secretion of insulin, and because they may reduce its hepatic clearance, plasma levels of insulin are increased after initiation of sulfonylurea therapy. This may seem to be counterproductive, because it might promote hyperinsulinemia. However, during long-term therapy, plasma insulin concentrations usually return toward pretreatment levels, whereas blood glucose reduction persists. This is due to a combination of factors. First, the initial increase of insulin secretion lowers the levels of blood glucose and thereby reduces glucose stimulation of insulin secretion. Second, sulfonylureas improve insulin action and hence lessen the need for insulin. Third, the reduction of blood glucose improves both β-cell function and insulin action, further lessening the demand for insulin. It follows that the risk

*A recent study by Temple et al. (*Lancet* 1:293–95, 1989) indicated that part of the hyperinsulinemia in NIDDM may be hyperproinsulinemia, particularly elevation of 32–33 split proinsulin.

of chronic hyperinsulinemia as a consequence of sulfonylurea therapy may be minimal, at least in subjects whose insulin resistance is not too advanced. The risk can be further minimized by appropriate dietary regulation combined with a rapid- and short-acting sulfonylurea (33).

Sulfonylureas and hyperlipidemia. Untreated NIDDM is characterized by elevated very-low-density lipoprotein (VLDL; triglycerides), low high-density lipoprotein (HDL), and normal or moderately elevated low-density lipoprotein concentrations (35–38). Several cross-sectional studies associated sulfonylurea therapy with low HDL concentrations, but this and elevated VLDL may be an expression of inadequate blood glucose control rather than a drug effect (27). Prospective studies indicated that glyburide and glipizide therapy may be associated with increased HDL levels (37,39), and tolbutamide treatment of subjects with impaired glucose tolerance (IGT) was associated with reduced levels of total cholesterol and triglycerides (Melander et al., this issue, p. 53).

There is an inverse relationship between plasma triglycerides and plasma HDL, and there is also an inverse correlation between plasma insulin and plasma HDL (47). Lowering of the plasma glucose concentration is usually associated with a reduced triglyceride level. Direct effects of sulfonylureas on plasma lipids are unlikely; in NIDDM subjects whose insulin secretion had been attenuated and who had been maintained on exogenous insulin, glipizide was ineffective not only on blood glucose but also on the levels of triglycerides, total cholesterol, and fractionated cholesterol (40). To summarize, it seems likely that sulfonylureas have no inherent effect on plasma lipids but that they can be indirectly beneficial by improving glucose control.

Sulfonylureas and hypertension. There are few prospective studies assessing the influence of sulfonylureas on blood pressure. In IGT subjects, however, long-term tolbutamide treatment was associated with reduced diastolic blood pressure (Melander et al., this issue, p. 53).

WHICH SULFONYLUREA?

The structures of sulfonylureas are given in Fig. 1.

Differences in potency. The difference in potency among the various sulfonylureas has often been argued as a reason for selecting one over the other. However, it is obvious that, if examined carefully, this thesis is flawed. Although there seems to be a correlation between the binding affinity of a certain sulfonylurea to the putative β-cell receptor and its insulin-releasing activity, the same maximal in vitro insulin release and in vivo blood glucose–lowering activity seem to be achieved by all sulfonylureas, albeit at different concentrations (27; Siconolfi-Baez et al., this issue, p. 2). Maximal clinical effectiveness of sulfonylurea is the important parameter to assess rather than the intrinsic molecular activity. Indeed, there are no adequately controlled prospective studies making comparisons of the long-term efficacy of glycemic control between the newer more-potent sulfonylureas and the older less-potent ones.

Although having little influence on maximal antihyperglycemic effectiveness, variations in potency may result in relevant differences in other effects than antihyperglycemic ones. Tolbutamide and chlorpropamide seem to be active only when their plasma concentrations exceed 50–100 μM, whereas the most potent sulfonylureas, glipizide and glyburide, are active at plasma concentrations of 50–100 nM (27). This 1000-fold difference in effective plasma concentration equals the difference in selective β-cell binding (Siconolfi-Baez et al., this issue, p. 2). Acetohexamide and tolazamide seem to have a potency in the same range as tolbutamide and chlorpropamide, whereas gliquidone, glibornuride, and gliclazide are somewhat less potent than glipizide and glyburide (27). Thus, insofar as drug-drug or drug-enzyme interactions depend on the molecular concentration of the sulfonylurea in question, the less-potent agents, e.g., chlorpropamide and tolbutamide, would be more likely to exert such adverse effects than would more-potent sulfonylureas, e.g., glipizide and glyburide. The seemingly lesser toxicity and almost absent alcohol-induced flushing with glipizide and glyburide might be explained on this basis.

Differences in onset and duration of action. Variations in the pharmacokinetics of sulfonylureas, i.e., their rate and extent of absorption, distribution, metabolism, and excretion, seem to be clinically relevant because of the consequent differences in the rate of onset and the duration of action. The rate of onset is important because it relates to the capacity to reduce the delay in acute insulin release and hence to reduce the elevation and prolongation of postprandial hyperglycemia (27,31,32). The duration of action is important because it relates to the risk of causing chronic hyperinsulinemia,

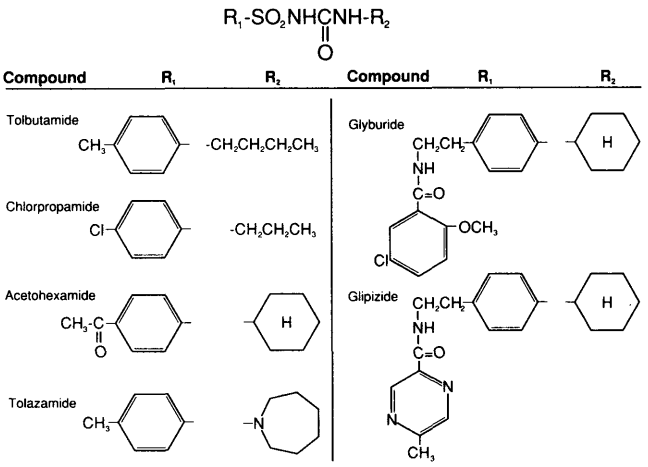

FIG. 1. Structures of some sulfonylureas.

long-lasting hypoglycemia, and, possibly, desensitization to sulfonylurea.

Glipizide is the most rapid- and short-acting sulfonylurea available. This is because it has the most rapid absorption, distribution, and elimination (27) but possibly also due to some inherent molecular property (18). It has been shown that glipizide can improve acute insulin release and postprandial blood glucose control and that this can be attained without evoking chronic hyperinsulinemia (32,33). In addition, the short duration of action may reflect the fact that its metabolites are inactive (27). Tolbutamide is also rapid and short acting, although seemingly less so than glipizide (27).

The most slow- and long-acting sulfonylurea is chlorpropamide, and it is more likely to promote long-lasting hypoglycemia than most other sulfonylureas (27). In addition, its elimination is partially dependent on kidney function; hence, its effect is particularly prolonged in patients with renal insufficiency. Glyburide is also rather slow and long acting, particularly when given in the nonmicronized formulation that is marketed in the United States and many other countries. However, glyburide is more slow acting than glipizide, even when the two drugs are infused at equal rates and to similar plasma levels (18). It is not yet known whether the slower onset of action and the longer effect duration is due to slower distribution, a longer elimination half-life, accumulation of an active metabolite, or the fact that glyburide, in contrast to other sulfonylureas, might accumulate within β-cells (41). In addition, glyburide has an active metabolite that accumulates in subjects with renal insufficiency (42). Reviews of the kinetic-dynamic relationships of sulfonylureas have been published (27,43). Some characteristics of different sulfonylureas are given in Table 1.

Long-lasting hypoglycemia. Because sulfonylureas lower blood glucose, hypoglycemic reactions should be expected to occur. Normally, hypoglycemia promotes release of epinephrine and glucagon, whereby hypoglycemia is counteracted through increased hepatic glucose output. In elderly patients, however, this defense mechanism may be weakened; therefore, hypoglycemia may occasionally become more pronounced and more long lasting, and this may lead to permanent neurological damage and even death (44–46). Long-lasting hypoglycemia can occur only if there is sustained suppression of hepatic glucose output. This is most likely to occur with long-lasting sulfonylureas in combination with some complicating factor (44–46). In addition to being longer acting, glyburide has been shown to cause a 50% greater suppression of hepatic glucose output than glipizide (47). This may help explain why glyburide seems more likely to provoke long-lasting hypoglycemia than does glipizide (27,46).

Note in this context that unless alcohol has been involved, most fatal hypoglycemic cases have involved elderly people (>75 yr old), and usually some complicating factor has also been implicated, e.g., drug interaction, i.e., aspirin or sulfonamides, or acute energy deprivation. This justifies particular caution in the use of sulfonylureas, especially long-acting agents, in older subjects. Another complicating factor is renal insufficiency. This may become particularly important if sulfonylureas are used that are partially eliminated by the kidneys or have active metabolites that are eliminated by this route. At least in younger subjects, alcohol is an important contributor to hypoglycemia (46).

Other adverse effects of sulfonylureas. Apart from hypoglycemic reactions, the overall frequency of adverse effects of sulfonylureas is low, and they are usually mild and reversible. Among these adverse effects are nausea, dizziness, skin reactions, and headache. Rare cases of agranulocytosis, thrombocytopenia, and jaundice have been reported. In addition, water retention, hyponatremia, and alcohol intolerance have been observed, mainly with chlorpropamide (27,44).

Selection of sulfonylurea. When selecting a sulfonylurea for a specific patient, onset of action, duration of action, risk of hypoglycemia, and other side effects must be considered. An otherwise healthy well-nourished 30- to 60-yr-old NIDDM patient can be effectively treated with most sulfonylureas. A rapid-acting sulfonylurea may improve early insulin release and promote better control of postprandial blood glucose, whereas a long-acting sulfonylurea may give better control of overnight glycemia. A short-acting agent may allow a better chance to maintain the insulinotropic effect through discontinuous exposure (see below). An older, less-well-nourished and chronically ill NIDDM patient is at risk for the development of severe hypoglycemia and should be treated (if at all) with a short-acting sulfonylurea that has no active metabolites.

Chlorpropamide, because of its very long duration of action, high incidence of alcohol-induced flushing, significant water retention with ensuing hyponatremia, and somewhat higher frequency of other adverse reactions,

TABLE 1
Characteristics of some sulfonylureas

	Potency	Onset of action	Duration of action	Bioavailability	Active metabolites
Tolbutamide	Low	Rapid	Short	Unknown	Yes
Chlorpropamide	Low	Slow	Very long	Unknown	Yes
Tolazamide	Low	Slow	Short	Unknown	Yes
Glyburide	High	Intermediate	Long	Incomplete	Yes
Glipizide	High	Very rapid	Short	Complete	No

is a less-suitable sulfonylurea than glipizide or glyburide.

NIDDM patients with decreased kidney function (glomerular filtration rate [GFR] 30–100 ml · min^{-1} · 1.73 m^{-2}) are best treated with a sulfonylurea that has a short duration of action and is metabolized by the liver to inactive derivatives. Sulfonylureas that are excreted directly by the kidney or are converted to active metabolites that are excreted by the kidney are contraindicated in patients with severe kidney impairment (GFR <20 ml · min^{-1} · 1.73 m^{-2}) or severe liver disease.

HOW SHOULD SULFONYLUREAS BE USED?

Early intervention. The chronic hyperglycemia of NIDDM evolves slowly, and subjective symptoms of disease appear rather late. However, vascular complications may develop in the early phase of NIDDM; indeed, the risk of cardiovascular complications is increased even in the pre-NIDDM phase of IGT (48). Retinopathy may be present in 25–30% of NIDDM patients when subjective symptoms bring them to medical care (49). Another reason for early detection and early intervention is the fact that chronic hyperglycemia is a self-perpetuating condition; it not only results from but also promotes impaired insulin secretion and action (50). Intervention should start as soon as persistent hyperglycemia is noted, and the initial intervention should be dietary regulation. If euglycemia is not achieved after 2–3 mo of dietary regulation, addition of a sulfonylurea is indicated. However, sulfonylurea must never be used instead of dietary regulation but always as a supplement. If not, secondary failure is likely to ensue, and even primary failure may occur.

Discontinuous exposure? Sulfonylureas appear to release insulin by activation of a receptor-mediated mechanism in the β-cell (Siconolfi-Baez et al., this issue, p. 2). This raises the possibility that chronic, continuous exposure to sulfonylurea may desensitize the β-cell by downregulation of the putative receptors. This hypothesis is supported by the observation that the insulin-releasing effect of a single dose of sulfonylurea (tolbutamide) vanished during chronic treatment with another sulfonylurea (tolazamide) (Fig. 2). Moreover, the acute effect of tolbutamide reappeared after withdrawal of the chronic treatment (28). In vitro, high concentrations of sulfonylureas inhibit proinsulin biosynthesis (51) and attenuate insulin secretion (52). A dose increase of glipizide from 15 to 25 mg/day was associated with impaired instead of improved blood glucose control in NIDDM subjects (53). Conversely, early insulin release and euglycemia could be maintained in screening-detected NIDDM patients during low-dose once-daily glipizide treatment (33).

Sulfonylurea therapy should be initiated with the lowest possible dose, because severe and symptomatic hypoglycemia is most likely to occur in individuals who are very sensitive to these drugs. The dose may be increased until euglycemia is obtained or until the maximal depression of glycemia possible is achieved. However, note that reduction of chronic hyperglycemia improves β-cell function and insulin action. This signifies that dose increase should be very slow and gradual. As mentioned above, continuous exposure to a high concentration of sulfonylurea may be counterproductive. Accordingly, there may exist an optimal dose that may or may not equal the recommended maximal dose.

Drug treatment of several chronic diseases, i.e., bronchial asthma and epilepsy, aims at chronic exposure by reaching and maintaining a steady state, with a minimum of fluctuations of the plasma drug level within the steady state. The appropriate frequency of dosage is based on knowledge of the elimination half-life of the drug in question. For sulfonylureas, the appropriate dosage principles may be different. Insofar as the drug is supposed to enhance the rate of insulin release after meals without provoking chronic hyperinsulinemia, the sulfonylurea should ideally be present in plasma only before meals. If, on the other hand, the aim is to in-

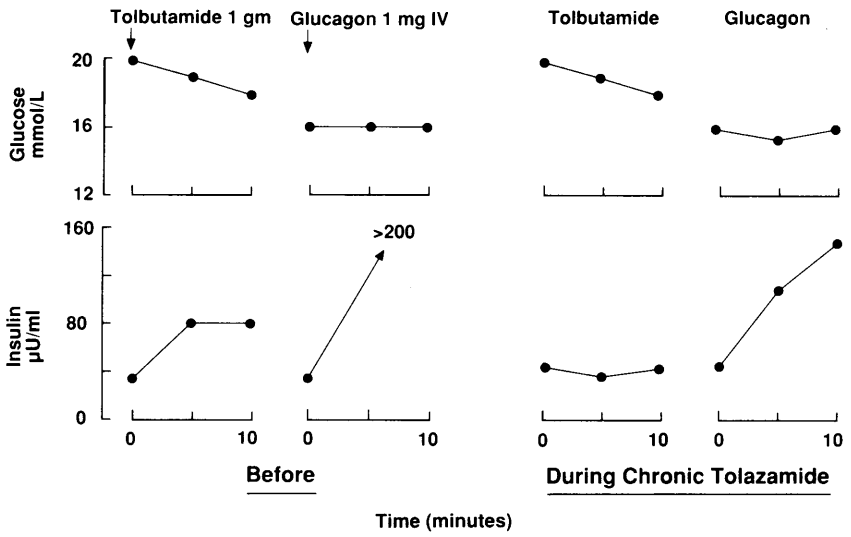

FIG. 2. Selective desensitization of insulinotropic effect of sulfonylurea in 7 subjects with non-insulin-dependent diabetes mellitus. Note that insulinotropic response to tolbutamide is present during acute exposure but is lost during chronic exposure to another sulfonylurea, tolazamide. Also note that insulinotropic effect of another secretagogue, glucagon, is maintained. (Adapted with permission from Karam et al. [28]. © by the American Diabetes Association.)

crease the basal and mean plasma insulin level in relatively hypoinsulinemic patients, it would seem more rational to maintain an effective sulfonylurea plasma concentration continuously, provided that this does not desensitize the β-cell.

Also, note that the elimination half-lives of different sulfonylureas correlate rather poorly with the duration of action; e.g., the elimination half-life of glyburide is allegedly short, although the drug behaves as a long-acting sulfonylurea (27). Finally, the timing of sulfonylurea intake relative to meals might be more important than the dose size; 2.5 mg glyburide 30 min before breakfast was more effective than 7.5 mg with a meal (54). Similarly, the efficacy of glipizide is improved when given 30 min before breakfast (55). On the other hand, when glipizide was given 3 times/day, i.e., attaining continuous exposure, there was no difference in therapeutic efficacy when giving the doses 30 or 2 min before meals (Faber et al., this issue, p. 26). However, this is to be expected during continuous exposure, because the drug would be present in due time before breakfast regardless of the morning dose.

Obviously, more studies are needed to establish the most appropriate dosage schedules for sulfonylureas. Available data suggest that once-daily (morning) administration would be the initial choice of therapy. It is probable that administration 30 min before breakfast may improve the efficacy of sulfonylurea treatment, but only if the exposure to the drug is discontinuous. If postprandial hypoglycemia ensues in the early part of the day, or if inadequate glycemic control occurs in the later part of the day, a divided dosage schedule could be tried.

Drug interactions. Many NIDDM patients are on various medications, e.g., antihypertensive, anti-inflammatory, anticoagulant, and antibiotic drugs. Sulfonylureas may interact with several of these agents, and this must be kept in mind in each case. Note in particular that aspirin can augment sulfonylurea-induced hypoglycemia, especially because aspirin may be taken by the patient without a prescription from the physician. Among the antihypertensive drugs, thiazides presumably are able to impair glucose tolerance (56), and β-blockers have been shown to impair the efficacy of sulfonylureas (57).

CONCLUDING REMARKS

Sulfonylureas may be useful in many if not most patients with NIDDM, provided that the drugs are used in conjunction with hypocaloric dietary regulation and that they are introduced at a time when they are able to improve both insulin secretion and action. If rapid- and short-acting sulfonylureas are introduced early—but not until dietary regulation has been established—euglycemia can be reached and maintained in many cases, without chronic hyperinsulinemia or weight increase. There is no evidence that sulfonylureas cause β-cell exhaustion, and sulfonylurea failures are in fact often dietary failures. Desensitization of the insulinotropic effect of sulfonylureas might occur and might be avoided by discontinuous (<24 h/day) exposure. Long-lasting hypoglycemia is the most serious adverse effect of sulfonylureas. It occurs mainly in elderly subjects due to some intercurrent event and may be more likely to occur if long-lasting sulfonylureas are used. Sulfonylurea therapy should always be initiated and maintained at the lowest possible dose.

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