Glucose Tolerance During Antihypertensive Therapy in Patients with Diabetes Mellitus

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SUMMARY Many antihypertensive drugs have adverse effects on glycemic control when they are used in diabetic patients. This was noted for thiazide diuretics in 1960, and the mechanism of the effects remains uncertain. Indirect evidence suggests that changes in the serum potassium are at least contributory, although the principal mechanism of thiazide-induced hyperglycemia is probably a reduction in the insulin response to glucose. Beta blockers also adversely affect blood sugar control but only by a small margin. The main cause for concern with beta blockers, however, is their effect during hypoglycemia in which nonselective agents delay blood sugar recovery. In diabetic patients, the institution of antihypertensive therapy should be followed by a reassessment to note any changes in sugar, potassium, and lipids, or side effects. (Hypertension 7 [Suppl II]: II-95-II-101, 1985)

KEY WORDS • hypertension • hyperglycemia • hypokalemia • β-adrenergic receptor antagonists

THE prevalence of arterial hypertension in patients with diabetes mellitus is high. Both diseases are major cardiovascular risk factors and it would seem logical to treat both conditions vigorously; however, nearly all antihypertensive drugs have at least theoretical disadvantages or limitations when used in diabetic subjects. In addition, there are very few controlled trials comparing different regimens in this situation. Those that are available are generally short-term studies, and there are no long-term studies of mortality and morbidity to guide us. The choice of antihypertensive therapy must depend, therefore, on an assessment of short-term trials of each drug’s metabolic effects in hypertensive diabetic persons against a background of the information available from large, long-term studies of patients with essential hypertension but without diabetes.

Several large studies have shown that the treatment of essential hypertension reduces the frequency of cerebrovascular disease, renal failure, and cardiac failure. Of major concern, however, is the observation that antihypertensive therapy has had little impact on the prevalence of coronary heart disease. Indeed, in the recent Multiple Risk Factor Intervention Trial,1 hypertensive men with initial electrocardiographic (ECG) abnormalities at entry had higher coronary heart disease mortality and total mortality when their blood pressure was treated vigorously than the control group. In this particular study and in many others, the antihypertensive treatment employed was usually thiazide diuretics, and it has been suggested that one or another of the potentially adverse metabolic effects of these drugs might offset the benefit of reduced blood pressure. The obvious candidates for mediating adverse effects are impaired glucose tolerance, decreased serum potassium, elevated blood lipids, and increased serum uric acid, or even a combination of these. Obviously, if these metabolic sequelae were to be so detrimental in patients with uncomplicated essential hypertension, they might be even more so in hypertensive patients who also had impaired glucose tolerance initially.

Thiazide Diuretics

Chlorothiazide was first introduced in 1957 and since then there have been numerous reports implicating benzothiadiazine diuretics in the production of impaired glucose tolerance and even hyperglycemia.2 In the early days, attention was drawn to this phenomenon by the concomitant use of hydrochlorothiazide and diazoxide, which together had a potent diabetogenic effect.3,4

The deterioration in glucose tolerance after thiazide diuretics appears to be greater in those who already have impaired glucose tolerance. Also, in diabetic patients this deterioration in glucose tolerance occurs early after only a few weeks of therapy. Shapiro et al.5

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performed glucose tolerance tests before and after 2 weeks of therapy with chlorothiazide, 1 g daily, in 15 "potential diabetics" and 15 nondiabetic controls. The former group were defined by having a blood glucose level greater than 11 mmol/L 1 hour after the ingestion of oral glucose. They showed significant deterioration of glucose tolerance after chlorothiazide, while no such changes were seen in the control group. In another study the hyperglycemic effects of 6 weeks of therapy with clopamide, clorexolone, or hydrochlorothiazide were compared in 18 established diabetic patients with mild hypertension. All three diuretics were shown to increase postprandial levels of blood glucose in comparison with placebo, although the changes with hydrochlorothiazide were not significant. Of interest is the observation that during the clopamide and clorexolone study periods, there was significant negative correlation between the absolute values of blood glucose and plasma potassium. Goldner et al. also demonstrated a hyperglycemic effect for various thiazide diuretics in diabetic patients after only 5 days of therapy, but it was only demonstrable in 6 of 20 subjects. Obviously, we cannot be sure that the other 14 patients would not develop hyperglycemia if the diuretic therapy had been continued for a longer period of time. This was the first study, however, to suggest that only some patients might be susceptible to thiazide-induced glucose intolerance rather than this being a generalized effect, although these authors were unable to identify any predisposing factor. In particular, the serum potassium levels in the susceptible and nonsusceptible patients were not different.

Where thiazide-induced hyperglycemia can be readily demonstrated in diabetic patients within only a few weeks, it requires large-scale studies over longer periods of time to demonstrate such an effect in patients with normal glucose tolerance. Murphy et al. followed a cohort of thiazide-treated hypertensive patients since 1966 and measured glucose tolerance before treatment and after 1, 6, and 14 years of therapy. Glucose tolerance showed little change in the first year, but it had deteriorated significantly after 6 years and even further at 14 years (Figure 1). These results do not necessarily implicate thiazide diuretics, since glucose tolerance does deteriorate with advancing age and there was no control group in this study for comparison. In the healthy population, however, the rate of increase in fasting blood glucose is reported as 0.055 mmol/L per decade, which is less than was found in the thiazide-treated group. This figure relates to the healthy population and is not strictly applicable to hypertensive patients, who have increased frequency of abnormal glucose tolerance in comparison. Furthermore, there are no precise data available on the rate of increase in fasting blood glucose per decade of life in untreated hypertensive subjects. Murphy et al. were, however, able to withdraw the thiazide diuretic in 10 of their patients and demonstrate an improvement in glucose tolerance by 7 months, which is strong evidence that at least some of the glucose intolerance was due to thiazide treatment (Figure 2).
zide together with 50 to 100 mg triamterene. Fasting blood sugar did not change significantly in the placebo group even after 3 years, whereas in the diuretic-treated group, it increased 6.0 mg/dl after 1 year, 9.6 mg/dl after 2 years, and 13.8 mg/dl after 3 years. The hyperglycemic effect appeared to be related to potassium loss, since impairment of glucose tolerance was most marked in those in whom serum potassium decreased; this applied to both the treated and control groups. There was no relationship between blood glucose changes and age, sex, body weight, blood pressure, or changes in uric acid or creatinine. Also there was no relationship between blood glucose changes and another marker of thiazide ingestion, uric acid, which suggests that compliance with the diuretic regimen was not the source of the potassium-glucose relationship. Although serum potassium changes may be contributory to blood glucose changes, they are not the whole story; even when serum potassium changes were matched, fasting blood glucose rose more in the treated group than in the placebo group.

Not all studies have confirmed the diabetogenic effect of thiazides in healthy subjects. In particular, Berglund and Andersson randomly allocated hypertensive patients to either propranolol (80–160 mg) or bendroflumethiazide (2.5–5 mg) plus potassium chloride (0.57–1.14 g). In both groups there was no change in either the fasting or 1-hour blood sugar level after oral glucose. One possible reason for the preservation of glucose tolerance in this study is the low dose of diuretic used.

Another way of establishing a causal relationship between thiazides and glucose intolerance is to look at whether withdrawing the drug improves glucose tolerance. Ames and Hill confirmed the findings of Murphy et al. that glucose tolerance improved significantly when diuretic therapy was withdrawn.

The question that naturally arises is whether a small number of patients are particularly susceptible to the diabetogenic effect of thiazides or whether thiazides produce an overall shift toward hyperglycemia in all patients. In two studies of potential or established diabetics, only a proportion of the subjects showed an increase in hyperglycemia, but the numbers studied were small and the period of treatment was short. On the other hand, in the much larger and longer-term EWPHE study, it appeared that diuretics produced an overall shift toward hyperglycemia in most of the individuals studied.

The epidemiological consequences of thiazide-induced glucose intolerance remain unknown. Of interest is the observation from the Whitehall study that coronary heart disease mortality was doubled in subjects who fell into the diagnostic category of impaired glucose tolerance short of frank diabetes mellitus. These patients appeared to be at greater risk of large vessel disease but remained free of the small vessel disease that is typical of diabetes. It is quite likely, therefore, that thiazides shift a large proportion of patients from normal to this category of impaired glucose intolerance. By the long-term use of thiazides, we may be reducing the mortality associated with hypertension but increasing the mortality due to impaired glucose tolerance.

**Mechanism of Thiazide-induced Glucose Intolerance**

Although diuretic-induced hyperglycemia is well documented, the mechanisms underlying this effect remain obscure. It seems likely that changes in potassium are at least contributory, although they may be mediated by a reduction in insulin release. In several large studies, hyperglycemia developed mainly in patients who became hypokalemic. This was not confirmed in other studies in which smaller numbers of subjects were evaluated. Rapoport and Hurd studied seven patients with chlorothiazide-induced glucose intolerance and demonstrated significant reversal of this thiazide effect when potassium chloride supplementation was given with the diuretic.

It is of interest also that several other syndromes that are characterized by hypokalemia have been shown to be associated with glucose intolerance. These include primary hyperaldosteronism, Bartter’s syndrome, and Cushing’s syndrome. Furthermore, when potassium depletion was induced in healthy persons by having them ingest a cation-exchange resin for 7 days, glucose tolerance decreased but partially recovered four to seven days after the resin was stopped. Despite this, the hypoglycemic response to administered insulin was unaffected by potassium depletion, suggesting that glucose intolerance in this case is not due to tissue resistance to insulin. Rowe et al. extended our knowledge of potassium deficiency-induced glucose intolerance by employing the glucose-clamp technique. This experimental technique allows the investigator to assess separately the pancreatic response to glucose and tissue sensitivity to insulin. It appears that potassium depletion in healthy subjects is associated with a diminished insulin response to glucose, while tissue sensitivity to insulin is unchanged. Others found identical results in two healthy persons who became hypokalemic while taking hydrochlorothiazide. This diminished pancreatic response did not occur when diuretic therapy was supplemented with potassium.

Despite this indirect evidence suggesting a relationship between thiazide-induced potassium depletion and decreased insulin response, remarkably few prospective clinical studies have examined this by measuring plasma insulin levels in diuretic-treated patients, and those that did produced conflicting results. Guigliano et al. found that furosemide reduced the glucose-induced secretion of insulin in healthy humans, but studies in diabetic subjects suggested that while diuretics do elevate the blood sugar, they do not clearly reduce the insulin response to glucose except in the case of diazoxide. The results of animal studies are also contradictory. In the mouse, diuretic treatment for 14 days did not alter the hypoglycemic response to insulin, which argues against an effect on tissue sensitivity to insulin. Benzothiadiazine diuretics do, however, inhibit glucose uptake in skeletal muscle and
adipose tissue in vitro, which suggests a peripheral mechanism for this phenomenon. Therefore the current position must be that thiazide diuretics do induce glucose intolerance, especially in diabetic patients and also in healthy persons. There is good evidence to suggest that changes in body potassium are at least contributory to this effect, but whether this effect is predominantly due to insulin deficiency or to insulin resistance remains unknown.

**Beta-adrenergic Receptor Antagonists**

In essential hypertension, the main alternatives to thiazide diuretics are β-adrenergic receptor antagonists; however, concern has been expressed with regard to their use in diabetic patients. This concern stems from the fact that beta blockade may influence catecholamine-mediated metabolic effects and such effects may be particularly important in diabetes mellitus. It must be appreciated, however, that beta blockers are not homogeneous drugs. One property of particular relevance is the β1,β2 selectivity of each drug, especially since many metabolic effects are attributed to β2-adrenergic receptors.

**Hypoglycemia**

The first clinical situation of note is that of hypoglycemia in which several possible adverse effects of beta blockade have been found. The restoration of a normal blood glucose level is dependent on hepatic glycogenolysis and increased gluconeogenesis, both of which are dependent to varying extents on increased circulating catecholamines, glucagon, and cortisol. In fact, insulin-induced hypoglycemia is the most potent stimulus to the adrenal medulla known in humans. It should be appreciated that blood glucose recovery is considerably slower in diabetic patients than in healthy volunteers. This may be due to reduced glycogen depots, reduced glucagon release, and/or autonomic neuropathy.

Lager et al. studied the effect of propranolol (40 mg), metoprolol (50 mg), or placebo on insulin-induced hypoglycemia in seven patients with insulin-dependent diabetes. Deacon et al. compared propranolol, atenolol, acebutolol, and placebo in the same situation in 12 patients with non-insulin-dependent diabetes. In both of these studies, propranolol delayed the recovery of the blood glucose concentration and prevented the rise in free fatty acids and blood lactate after hypoglycemia. The precise reason for the slow recovery after a nonselective beta blocker is unclear. It is not due to any impairment in release of the various counterregulatory hormones, and is more likely caused by impairment of both glycogenolysis and gluconeogenesis. The β-adrenergic receptors mediating glycogenolysis in liver and skeletal muscle are thought to be of the β2 subtype, which explains why cardioselective beta blockers do not delay glucose recovery. In addition, however, it seems likely that part of their effect is due to inhibition of the release of gluconeogenic substrates such as lactate.

A further consideration is whether beta blockers might potentiate the hypoglycemic effect of insulin itself. Of interest, in these studies the only drug to produce such an effect was acebutolol, although this finding was disputed. Acebutolol is a cardioselective agent with membrane-stabilizing properties, and it may be these that potentiate hypoglycemia, since atenolol did not have this effect. Consistent with this is the observation that drugs with membrane-stabilizing properties inhibit glucose release from the liver in response to a low blood glucose concentration.

In any diabetic, the onset of hypoglycemia should be recognized early so that preventive measures can be taken. Many hypoglycemic symptoms are due to increased sympathoadrenal activity. It has been shown that palpitations are noticed much less after propranolol, although sweating is more pronounced. Since sweating is predominantly a parasympathetic function, propranolol may act to alter the sympathetic-parasympathetic balance during hypoglycemia.

Since some beta blockers potentiate hypoglycemia, some delay recovery, and some reduce awareness of symptoms, it might be considered that these drugs would increase the frequency of unconscious hypoglycemic episodes in insulin-dependent diabetes. Barnett et al. however, followed 150 patients with insulin-dependent diabetes for 8 months and showed that the frequency of hypoglycemic unconsciousness was the same in those treated with a beta blocker as in controls, and this was despite the fact that 86% of the treated group were taking nonselective beta blockers. Therefore the above hazards of beta blockade during hypoglycemia may be more theoretical than practical, but it seems sensible to use cardioselective in preference to nonselective beta blockers.

A final concern with regard to hypoglycemia is that the hemodynamic response is undoubtedly altered by nonselective beta blockade. During hypoglycemia, increased catecholamines normally stimulate β1-adrenergic receptors, causing vasodilatation and a decrease in diastolic blood pressure. In the presence of nonselective beta blockade, however, increased catecholamines lead to unopposed α-adrenergic receptor stimulation, causing peripheral vasoconstriction and rise in blood pressure. Such a rise in blood pressure might be detrimental in a patient with preexisting hypertension; even if it were of short duration, it could facilitate the bursting effect of hypertension, as in a cerebral hemorrhage.

**Glycemic Control**

It is well known that the stimulation of β-adrenergic receptors in the pancreas causes insulin release and it is therefore possible that beta blockers worsen glycemic control by inhibiting insulin release. It is not clear what contribution, if any, these receptors make in the physiological situation where insulin is released in response to the ingestion of a mixed meal. Most investigators have studied this by observing the insulin and sugar responses to either oral or intravenous glucose, which are both rather unphysiological stimuli.
Cerasi et al. found that the blockade of β-adrenergic receptors by an intravenous infusion of propranolol resulted in significant inhibition of the initial as well as the late insulin responses to glucose infusion in healthy subjects. This could alternatively be due to unopposed stimulation of pancreatic α-adrenergic receptors, which are known to inhibit insulin release. Several studies, however, have found no effect of propranolol on insulin secretion or glucose tolerance after acute treatment. It is possible that the variation in the acute response in these studies reflects variation in endogenous sympathoadrenal activity in different studies; that is, beta blockers may not affect the insulin response to glucose but may affect the additional variable factor of catecholamine-induced insulin response.

Rather than being concerned about the effects of a single dose of a beta blocker on the contrived situation of a glucose tolerance test, we should be more interested in the effect of long-term therapy on overall glycemic control. Wright et al. studied hypertensive patients with diabetes mellitus and gave them propranolol (80 mg twice a day), metoprolol (100 mg twice a day), or placebo, each for 1 month in a double-blind crossover study. All 20 patients had non-insulin-dependent diabetes and 16 were taking oral hypoglycemic agents. Fasting, prelunch, and midafternoon venous blood samples were taken to measure blood sugar and serum insulin (Figure 3). The mean blood sugar concentration was higher after propranolol (10.7 mmol/L) and metoprolol (10.1 mmol/L) than after placebo (8.9 mmol/L). The rise with propranolol was not significantly greater than after metoprolol, although Waal-Manning reported improved glucose tolerance and insulin secretion in patients with mild diabetes changed from a nonselective beta blocker to metoprolol. It is possible that this small glycemic effect of beta blockade is due either to increased α-adrenergic recep-

tor-mediated hepatic glycogenolysis and/or to decreased insulin secretion. Wright’s observation that postprandial serum insulin levels were not different between placebo and beta blockade does not exclude an insulinopenic drug effect. After beta blockade, sugar levels were high but insulin levels unchanged, which suggests that the insulin levels were inappropriately low and may therefore still have contributed to the elevated sugar levels.

Therefore the mean blood sugar increases by the small margin of 1.0 to 1.5 mmol/L when those with non-insulin-dependent diabetes are treated with beta blockers. This potential risk must be weighed against the potential benefits of controlling hypertension with drugs that have proved to be both effective and well tolerated. In addition, some adjustment can be made in the patient’s antidiabetic regimen to compensate for this slight increase in sugar, although in a few patients, such an adjustment will require the institution of insulin therapy. With regard to hypoglycemic attacks, it appears that although there are small, demonstrable, potentially harmful effects, they are of doubtful clinical significance and can probably be avoided by choosing a cardioselective beta blocker.

**Calcium Antagonists**

Calcium antagonists are being used increasingly in the treatment of essential hypertension. Many investigations have focused attention on their effects on glucose tolerance because calcium influx is an essential step in insulin release and because nifedipine, diltiazem, and verapamil have all been shown consistently to inhibit insulin release in vitro in the perfused rat pancreas. It has, however, proved difficult to reproduce this inhibitory effect in the whole animal, and results have been extremely variable in studies of humans with normal glucose tolerance.

Several studies have been published on the effect of calcium antagonists in diabetic patients. Donnelly and Harrower found no significant effect on either glucose or insulin levels during an oral glucose tolerance test after nifedipine (10 mg three times/day) for 1 month, and similar negative results were noted when the same dosage was given for three months. In contrast, Guigliano et al. performed glucose tolerance tests before and after 10 days of treatment with nifedipine (30 mg/day) in 10 subjects with impaired glucose tolerance. Nifedipine impaired both glucose tolerance and the insulin response to glucose, although the effect was small. The factors responsible for these discrepancies remain unclear, but it is quite possible that there is interindividual variation in susceptibility to the diabetogenic effects of these drugs, and there are case reports of patients in whom nifedipine precipitated marked glucose intolerance. In the majority of patients, however, the short-term effect of nifedipine on glucose tolerance appears to be either small or nonexistent. Further studies are required on the effect of calcium antagonists on overall glycemic control over longer periods of time.

**Figure 3.** Blood sugar concentrations in diabetic patients at four assessments. I = initial; PI = after placebo for four weeks; M = after metoprolol for four weeks; Pr = after propranolol for four weeks. Bars represent means. (Reprinted from Wright et al. with permission.)
Alpha Agonists and Antagonists

There is now strong in vitro evidence for the involvement of pancreatic α2-adrenergic receptors in insulin release. This could obviously be of importance to hypertensive patients with diabetes, since many different antihypertensive drugs interfere with α2-adrenergic receptor function.

Guthrie et al. studied the effect of clonidine (0.2 mg/day) for 10 weeks in 10 patients with hypertension and diabetes. Whereas the glycemic response to intravenous glucose was increased by clonidine (α2 agonist), it did not significantly change overall diabetic control as assessed by glycosylated hemoglobin, 24-hour urinary glucose excretion, and fasting serum glucose. This highlights the fact that data obtained from short-term studies of the effect of various drugs on oral glucose tolerance may give misleading results. More studies are required examining overall glycemic control over longer periods of time.

Prazosin is an antihypertensive drug that blocks α1-adrenergic receptors. Barbieri et al. noted that prazosin (3 mg/day) for 1 week improved glucose tolerance and increased the insulin response during a glucose tolerance test in six patients with chemical diabetes. As prazosin is an antagonist principally at α1-adrenergic receptors, this effect would not have been expected and may reflect some degree of α2 antagonist. Theoretically, selective α2 antagonism with new drugs such as idazoxan might improve glucose tolerance but they increase blood pressure, making them unsuitable for use in hypertensive patients.

Conclusions

This review concentrated on the effect of various antihypertensive drugs on glucose tolerance in diabetic subjects. Many other factors also need to be considered. Both beta blockers and diuretics have a deleterious effect on the plasma lipid profile, although the long-term significance of these effects is unclear. Furthermore, diabetic subjects are at risk for such symptoms as impotence and postural hypotension, which are also recognized side effects of several antihypertensive drugs. Currently, the main recommendation must be that after the institution of antihypertensive therapy in a diabetic, the patient should be reassessed not only for side effects but for the biochemical indexes of glycemic control, potassium, and lipids. Consequently on this, antihypertensive therapy may have to be changed or antidiabetic therapy increased to compensate. We should at least try to ensure that we are not inflicting a greater side effect burden or risk than that of the hypertension originally.

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