DRUG SAFETY CONCEPT

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Drug Administration in Patients with Diabetes Mellitus

Safety Considerations

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Summary

Diabetes mellitus is associated with alterations in a number of key metabolic pathways. Despite theoretical concerns, clinically significant alterations in the pharmacokinetic properties of commonly prescribed drugs are relatively uncommon. Indeed, dose adjustment is rarely required in the setting of well controlled diabetes mellitus. However, significant alterations in drug handling may occur in the context of poor metabolic control or in the presence of complications such as nephropathy.

Metformin use may be complicated by lactic acidosis. Fortunately, this is a rare occurrence providing that the agent is not used in circumstances in which it is contraindicated. Indeed, the risk of death from metformin-related lactic acidosis is similar in magnitude to the risk of death related to hypoglycaemia in sulphonylurea-treated patients.

The novel hypoglycaemic agent troglitazone may be associated with abnor-

malities in liver function in approximately 2% of patients. Discontinuation of treatment is followed by normalisation of liver enzyme levels. Current prescribing information recommends frequent monitoring of liver function tests and immediate cessation of therapy if abnormalities develop.

In addition to disturbances in intermediary metabolism, diabetes mellitus may also lead to chronic microvascular and marcovascular complications. Thus, in addition to the use of drugs for the control of blood glucose, patients with diabetes mellitus are likely to be prescribed medication for associated conditions such as cardiovascular disease. Such medication includes the ACE inhibitors which are contraindicated in patients with bilateral renal artery stenosis. This complication may be theoretically more common in patients with diabetes mellitus because of accelerated atherosclerosis. However, in clinical practice this is an uncommon occurrence in the absence of clinical features that should alert the treating clinician that an individual patient might be at high risk. Although caution should also be used with β-blocker therapy in patients with diabetes mellitus, current evidence suggests that, like ACE inhibitors, these drugs may be particularly useful in this patient group.

Diabetes mellitus is a common disease associated with chronic complications leading to significant end organ damage. For instance, the incidence of death from cardiovascular disease is increased 2-fold in men with diabetes mellitus and 4- to 5-fold in women with diabetes mellitus compared with the age-matched general population.[1] Thus, in addition to the use of drugs for the control of blood glucose, patients with diabetes mellitus are likely to be prescribed medication for associated conditions such as cardiovascular disease.[2]

The present review examines issues of drug safety arising from the potential for altered drug handling in diabetes mellitus as well as specific issues related to drugs commonly used in the treatment of the disease and its associated complications.

1. Effect of Diabetes Mellitus on Drug Handling

Diabetes mellitus is associated with alterations in a number of key metabolic pathways. However, despite theoretical concerns, clinically significant alterations in the pharmacokinetic properties of commonly prescribed drugs are relatively uncommon.[3] Indeed, dose adjustment is rarely required in the setting of well controlled diabetes mellitus, though potentially significant alterations in drug handling may occur in the setting of poor metabolic control or in the presence of complications such as neuropathy and nephropathy.

1.1 Absorption

Oral absorption of most drugs is generally unaffected by the presence of diabetes mellitus. However, delayed gastric emptying due to gastroparesis diabeticorum or poor glycaemic control may decrease the rate and extent of absorption of some drugs such as ampicillin[4] and tolazamide.[5] In addition, gastroparesis may result in delayed postprandial glucose peak causing early-phase hypoglycaemia and late-phase hyperglycaemia when short acting insulins are used.[6] Intramuscular absorption of drugs may also be slower in diabetes mellitus.

1.2 Protein Binding

Binding of a variety of drugs to albumin and α_1 acid glycoprotein may be reduced in the presence of poor metabolic control.[3] This may be due to glycation of plasma proteins and/or displacement of drug from plasma proteins by free fatty acids, the level of which are increased in the context of poor metabolic control.[7] However, in clinical practice these changes are rarely significant and

apply mostly to highly protein bound drugs such as warfarin[8] and diazepam.[7]

1.3 Distribution

Despite a probable expansion of extracellular fluid volume in experimental[9] and human[10] diabetes mellitus, the limited data obtained in humans do not suggest a consistent effect on the volume of drug distribution.[11,12]

1.4 Hepatic Metabolism

Diabetes mellitus may impair hepatic metabolism of some drugs. The mechanisms underlying this effect are uncertain but may reflect diabetes mellitus–related liver changes such as fatty infiltration.[13] For instance, conjugation reactions with paracetamol (acetaminophen) may also be impaired where the magnitude of impairment appears dependent on the degree of glycaemic control.[14] With regard to oxidative metabolic processes, studies examining the effect of diabetes mellitus have revealed conflicting results as have those comparing differences in hepatic metabolism between type 1 (insulin-dependent) and type 2 (non–insulin-dependent) diabetes mellitus.[11-13,15] Overall, the effect of diabetes mellitus on hepatic metabolism is probably not of major clinical significance in the presence of reasonable glycaemic control.

1.5 Renal Elimination

Because of the early increase in glomerular filtration rate in patients with type 1 and possibly type 2 diabetes mellitus,[16] the plasma concentrations of drugs that are predominantly renally excreted may fall.[17,18] However, with declining renal function in association with nephropathy (which affects approximately one-third of patients with diabetes mellitus), elimination of renally excreted drugs becomes impaired, as in patients with nondiabetic kidney disease,[19] and appropriate dose adjustments are required.

1.6 Pharmacodynamics

Responses to drugs may be altered in patients with diabetes mellitus. Most studies have evaluated the haemodynamic effects of administration of vasoactive medications such as isoprenaline (isoproterenol), epinephrine (adrenaline) and ACE inhibitors for which both increased and decreased responsiveness have been described.[20-23] Furthermore, caution is needed with the interpretation of these data as serum concentrations were not measured and changes in responsiveness may thus reflect alterations in pharmacokinetic as well as pharmacodynamic properties.

2. Drugs Used to Control Hyperglycaemia in Patients with Diabetes Mellitus

2.1 Metformin

The biguanides phenformin (phenethylbiguanide) and metformin (dimethylbiguanide) were introduced as orally active glucose-lowering drugs for the treatment of diabetes mellitus more than 40 years ago. Because of its association with lactic acidosis, phenformin was withdrawn from the market in many countries in the 1970s. The high incidence of phenformin-associated lactic acidosis is now thought to have been in part due to an inherited inability in some patients to metabolise phenformin thereby leading to its accumulation and toxicity.[24] Similar pharmacogenetic traits of reduced enzymatic drug modification are thought to contribute to the toxicity of other drugs such as perhexilene and isoniazid. However, metformin, which is not metabolised but excreted unchanged, has continued to be available in most countries with the exception of the US where it was introduced only 3 years ago.

Minor adverse effects such as abdominal discomfort, nausea and loose bowel actions are common with metformin, especially during the initiation of therapy. In addition, absorption of cyanocobalamin (vitamin B12) and folic acid may be impaired with long term use, although the plasma

levels of these vitamins does not usually fall below clinically significant levels.[25]

The principal severe adverse effect associated with metformin therapy is lactic acidosis. While metformin therapy is accompanied by increased plasma lactate concentrations these are mostly within the normal range, possibly reflecting increased conversion of glucose to lactate within the mucosa of the small intestine.[26] Fortunately, unlike phenformin, metformin-related lactic acidosis (MRLA) is quite rare with an incidence of 0.027 to 0.084 cases/1000 patient years, but the mortality rate is 30 to 50%.[27] In the majority of reported cases of MRLA contraindications to metformin use were present. These contraindications relate to potential drug accumulation and conditions associated with tissue hypoxia or impaired lactate metabolism (see table I). However, opinions vary regarding what degree of renal, liver, cardiac or lung dysfunction should be viewed as a contraindication to metformin use. Furthermore, many patients with type 2 diabetes mellitus have coexistent cardiac or renal disease. Indeed, in a recent report, 54% of the patients treated with metformin at a university hospital diabetes mellitus clinic had a concomitant condition(s) considered to be a relative or absolute contraindication to this agent[28] emphasising the need for continued vigilance.

Although metformin use may be accompanied by an elevation in plasma lactate level to approximately 2 mmol/L, this biochemical parameter is frequently within the normal range and is of doubtful use in predicting subsequent lactic acidosis in the clinical setting. In addition to observing the listed contraindications for the initiation of therapy, patients should also be periodically re-evaluated with regard to suitability for continuing metformin use, particularly in the context of age-related decline in renal function. Furthermore, certain acute illnesses such as septicaemia, myocardial infarction (MI) or pneumonia, which may follow unpredictable patterns, should lead to immediate withdrawal of metformin therapy.

In clinical practice, metformin is well tolerated in the absence of contraindications and unlike the sulphonylureas, metformin *per se* is not associated with hypoglycaemia. Indeed, the risk of dying from MRLA (0.0240/1000 patient years) is similar to that of death due to hypoglycaemia in glibenclamide (glyburide) treated patients (0.0332/1000 patient years).[29]

Table I. Contraindications to metformin use

Renal impairment
Cardiac failure
Chronic liver disease
Chronic lung disease
Acute illness (e.g. septicaemia, myocardial infarction, trauma or other conditions where tissue perfusion may be impaired or hypoxaemia may develop)
Chronic vascular disease where tissue perfusion may be significantly impaired such as peripheral vascular disease
History of lactic acidosis

2.2 Sulphonylureas

The sulphonylureas act primarily on the pancreatic islet β-cell to stimulate insulin secretion. This release of insulin follows an interaction between the sulphonylurea and specific membrane-associated receptors that induce closure of adenosine triphosphate (ATP)–dependent potassium (K_{ATP}) channels leading to an influx of calcium into the cell ultimately resulting in insulin granule exocytosis.[30] These K_{ATP} channels are also present in the myocardium and vascular smooth muscle cells and preliminary studies suggest an interaction between glibenclamide and cardiovascular K_{ATP} channels.[31] However, the clinical relevance of these findings is unclear as are the potential benefits of more β-cell specific sulphonylureas such a glimepiride.

Although jaundice, leucopenia and haemolytic anaemia have been reported with sulphonylurea therapy, the principal adverse effect of the sulphonylureas is hypoglycaemia. The prevalence of severe sulphonylurea-induced hypoglycaemia requiring hospital admission is highly variable with reports of between 0.38 and 4.2 episodes per 1000 patient years.[32] The case fatality rate for severe sulphonylurea-induced hypoglycaemia is high, varying from 4.3 to 10%.[32,33]

Individual sulphonylurea drugs have different pharmacokinetic properties with chlorpropamide and glibenclamide having longer durations of action than glipizide, gliclazide or tolbutamide.[34] However, the contribution of duration of action to the likelihood of hypoglycaemia is not entirely clear. For instance, the higher frequency of hypoglycaemic episodes reported with glibenclamide in comparison with tolbutamide[35] may be confounded by prescribing patterns whereby physicians using tolbutamide may not be aiming to achieve as tight glycaemic control as those using glibenclamide. However, at identical plasma concentrations glipizide was noted to have a greater effect on hepatic glucose production than glibenclamide[36] and may thus predispose to nocturnal hypoglycaemia. It does seem prudent, then, to avoid long acting sulphonylureas in patients thought to be at high risk of hypoglycaemia. Such patients would include those with impaired renal function, poor nutrition, history of excessive alcohol (ethanol) consumption and age greater than 70 years.[34]

The sulphonylureas are mostly well absorbed orally, highly plasma protein bound and metabolised in the liver with residual drug and its metabolites excreted in the urine and in some cases also in the faeces. The pharmacokinetic properties of the individual drugs become clinically significant in the setting of renal impairment (including age-related decline in glomerular filtration) where the parent drug or its active metabolites may accumulate and lead to prolonged hypoglycaemia. Therefore, in the presence of reduced renal function, use of gliclazide and glipizide, which do not have active metabolites and where intact drug is minimally excreted in the urine, may be preferable.[30]

Drug interactions are a further potential cause of sulphonylurea-associated hypoglycaemia. As the sulphonylureas are all highly plasma bound caution should be used when they are administered with other drugs that may compete for plasma protein binding sites such as sulphonamides, warfarin, phenylbutazone and salicylates.[30] The rate and extent of absorption of sulphonylureas may be increased in association with elevations of gastric pH.[37] This may have important implications for concomitant therapy with antacids, histamine H_2 receptor antagonists and proton pump inhibitors such as omeprazole (see table II). Additional pharmacokinetic drug interactions include competitive inhibition of sulphonylurea metabolism, inhibition of urinary excretion and diminution of the counter-regulatory responses to hypoglycaemia (see table II).[32,38]

2.3 Newer Agents

Two new agents have recently been added to the armamentarium of antidiabetic drugs: the thiazolidinedione troglitazone and the α-glucosidase inhibitor acarbose.

2.3.1 Thiazolidinediones

Troglitazone is the first of a new group of drugs, the thiazolidinediones, which act primarily by increasing insulin sensitivity. Troglitazone is rapidly absorbed following oral administration [time to reach peak concentration following drug administration (t_{max}) 2 to 3h] and absorption is increased significantly by food. Steady-state concentrations of the drug are generally reached after 3 to 5 days administration. Although troglitazone is metabolised through various cytochrome P450 enzyme pathways, clinically significant interactions with agents that share the same pathways of hepatic enzymatic degradation have not thus far been observed.

Based on preclinical testing and premarketing clinical testing, reported adverse event rates have generally been similar in placebo and troglitazone treated groups.[39] In a Japanese study of 284 patients, treatment-related laboratory abnormalities developed in 9.2% of patients receiving troglitazone (compared with 5.1% of placebo-treated patients) and consisted predominantly of a fall in haemoglobin level, haematocrit and red blood cell count which were viewed to be a consequence of an increase in extracellular fluid volume.[40] In addition, reversible heart enlargement without significant microscopic changes was observed in mice and rats in long term studies with troglitazone, at

Table II. Clinically important drug interactions with antidiabetic drugs. Bold type in column two denotes interactions that: (i) involve commonly used drugs; (ii) involve common drug combinations used to treat the same condition or conditions that often coexist; or (iii) may have serious or potentially fatal consequences[38]

Primary drug	May interact with	Potential result	Implications for management and how to avoid
Biguanides (metformin)	Alcohol (ethanol)	Risk of hyperlacticacidaemia	Instruct the patient to avoid excessive quantities (moderate to large) of alcohol, and to be aware of and to report early symptoms of lactic acidosis (vomiting and malaise, abdominal pain, diarrhoea)
Sulphonylureas [tolbutamide, chlorpropamide, tolazamide, acetohexamide, glibenclamide (glyburide), glipizide, gliclazide]	**ACE inhibitors** **Perhexilline**	Increased insulin sensitivity with potential for hypoglycaemia (case reports)	Monitor for hypoglycaemia when ACE inhibitors or perhexilline are added to stable antidiabetic therapy
	β-Blockers	Hypoglycaemic activity may be increased in some patients and early symptoms of hypoglycaemia may be masked (less likely with β_1-selective agents). Hyperglycaemia may occur in some patients due to decreased insulin sensitivity and release	Altered doses of sulphonylureas may be needed in some patients. β-Blockers prevent the release of lactate from muscle which is normally subsequently converted in the liver to glucose. In the absence of lactate, hypoglycaemia may result, particularly when the liver contains little or no glycogen (e.g. after prolonged fasting, in ketosis, in any patients with liver disease, or in alcoholics)
	Alcohol	Disulfiram-like intolerance (facial flushing, headache) of alcohol in some cases, particularly with chlorpropamide. Hypoglycaemic activity may be increased with acute alcohol ingestion if food intake is restricted (e.g. malnutrition, prolonged fasting)	Instruct the patient about the possibility of alcohol intolerance and to avoid moderate to large quantities of alcohol; intolerance of small quantities of alcohol more likely with chlorpropamide. Educate patient to maintain adequate nutrition
	Anabolic steroids	Increased hypoglycaemic activity of some sulphonylureas induced by some anabolic steroids	Advise patients with diabetes mellitus taking sulphonylureas against usage of anabolic steroids
	Antacids **Histamine H_2-receptor antagonists** **Omeprazole**	Increased absorption of tolbutamide, glibenclamide and glipizide with potential for hypoglycaemia	Avoid these combinations or monitor for hypoglycaemia closely
	Barbiturates Phenytoin Rifampicin (rifampin) [and other enzyme-inducing drugs]	May make diabetic control more difficult by decreasing the hypoglycaemic effect of the sulphonylurea	Likely to be a problem with compounds extensively metabolised in the liver (e.g. tolazamide, tolbutamide, glibenclamide, acetohexamide). Avoid occasional use of barbiturates as hyponosedatives. Substitute a benzodiazepine or consider cognitive or relaxation therapies as alternatives
	Chloramphenicol	Hypoglycaemic activity of tolbutamide and chlorpropamide markedly increased	Avoid this combination. Substitute another antibacterial drug (but not sulfonamides or ciprofloxacin; see below)
	Ciprofloxacin	Reports of hypoglycaemia after commencement of ciprofloxacin in patients on glibenclamide	Avoid combination if possible. Warn patient of possible increased risk of hypoglycaemia and increase frequency of blood glucose monitoring
	Clofibrate	Severe hypoglycaemia has been reported with tolbutamide and clofibrate	A reduced dose of tolbutamide may be needed in some patients. Increase frequency of blood glucose monitoring
	Corticosteroids Diuretics (e.g. thiazides)	May make diabetic control more difficult	Modify dose of sulphonylurea if necessary
	Dicoumarol	Hypoglycaemic activity of tolbutamide and chlorpropamide markedly increased	Avoid this combination; use of warfarin may decrease risk of interaction

doses 14 times greater than the therapeutic dose used in humans. There was no deterioration in cardiac function observed with these changes. Subsequently, cardiac size was specifically examined in clinical studies of up to 96 weeks duration. In those studies, no clinically significant differences in heart size (or function) were noted with troglitazone therapy.

Since the introduction of troglitazone, a number of cases of hepatic failure been reported with its use. A review of placebo-controlled data indicates that elevations in ALT levels to 3 times the upper limit of normal developed in 1.9% of patients treated with troglitazone compared with 0.6% of patients receiving placebo.[41] In all patients, cessation of troglitazone therapy resulted in subsequent normalisation of ALT levels. As a result of this liver toxicity, troglitazone has been voluntarily withdrawn by the manufacturer in the UK and in the US current prescribing recommendations suggest that ALT levels should be measured before therapy, the monthly for the first 6 months of treatment, every 2 months for the remainder of the first year and periodically thereafter.[42]

Because of the ability of the agents to augment the hypoglycaemic action of either insulin or sulphonylurea therapy, combination therapy using these agents with troglitazone should be approached cautiously.

2.3.2 Acarbose

Acarbose is a reversible inhibitor of α-glucosidase, acting principally in the small intestine to reduce the rate of glucose production and absorption thereby blunting the postprandial glucose peak. Though antihyperglycaemic, acarbose does not itself induce hypoglycaemia but may predispose to it if coadministered with insulin or a sulphonylurea. The adverse effects of acarbose are mostly the result of intestinal carbohydrate fermentation reflecting the pharmacology of the drug, and include flatulence, diarrhoea, abdominal discomfort and borborygmi in approximately two-thirds of patients.[43] However, these symptoms tend to improve within several weeks of continued acarbose therapy. In addition abnormal liver func-

Fluconazole Ketoconazole	Hypoglycaemia reported with fluconazole at a dose of 100 mg/day and various sulphonylureas, and with ketoconazole and tolbutamide	Use alternative antifungal such as itraconazole if possible, or instruct patient to anticipate hypoglycaemia with dose adjustment to sulphonylurea based on blood glucose monitoring
Fluoxetine **Nonselective MAOI** (e.g. phenelzine, isocarboxazid, tranylcypromine)	Enhanced or prolonged hypoglycaemic response to sulphonylureas	Monitor blood glucose closely when MAOIs or fluoxetine are added to a stable oral antidiabetic drug regimen
Oxyphenbutazone Phenylbutazone	Hypoglycaemic coma has been reported on many occasions with phenylbutazone and chlorpropamide, acetohexamide, glibenclamide or tolbutamide	Avoid this combination. Substitute another NSAID such as ibuprofen, indomethacin or naproxen
Salicylates (large doses)	Hypoglycaemic activity of chlorpropamide enhanced	Avoid this combination. Substitute another NSAID such as ibuprofen, indomethacin or naproxen
Sulfonamides Sulfinpyrazone	Hypoglycaemia secondary to decreased clearance of tolbutamide, chlorpropamide, glipizide and glibenclamide	Avoid these combinations. Substitute another antibacterial agent (except chloramphenicol or ciprofloxacin which, under certain circumstances, can increase the activity of the sulphonylureas) **Note:** This risk of drug-induced hypoglycaemic reactions is increased in the presence of associated renal impairment or liver dysfunction, with restricted food intake, and in the elderly

Abbreviations: MAOI = monoamine oxidase inhibitor; NSAID = nonsteroidal anti-inflammatory drug.

tion tests have also been reported in association with acarbose therapy, though the clinical significance of these reversible changes is uncertain.[44]

2.4 Insulin

Although drug-induced hypoglycaemia is less frequent in type 2 diabetes mellitus compared with type 1 diabetes mellitus, a proportion of the observed difference between the two diabetes mellitus types may reflect different goals for long term glycaemic control. Prospective studies do suggest that oral hypoglycaemic agents are less likely to be associated with severe hypoglycaemia when compared with insulin, though the risk of hypoglycaemia may differ according to the sulphonylurea used. For instance, in a study,[45] patients with type 2 diabetes mellitus that was not controlled by diet were randomly assigned to receive treatment with either insulin or sulphonylurea. Although the treatment goal, a fasting plasma glucose level of <8.0 mmol/L, was the same in both groups, the frequency of severe hypoglycaemia was 6.6% in insulin-treated patients – more than double that of those receiving glibenclamide (3.7%) or chlorpropamide (2.0%) over a 3 year period.[45]

In type 1 (and probably also type 2) diabetes mellitus the likelihood of severe hypoglycaemia increases commensurately with the goals of glycaemic control. For instance, the 2% difference in haemoglobin A_{1c} level between the intensive and conventionally treated groups in the Diabetes Control and Complications Trial (DCCT)[46] was associated with a 3-fold difference in the likelihood of significant hypoglycaemia requiring assistance. Furthermore, the incidence of severe episodes with seizure or coma was also substantially higher in the intensively treated group at 16 and 5 episodes/100 patient years, respectively.[46]

While short-acting soluble insulins may be more likely to cause hypoglycaemia, their use is necessary in the vast majority of patients with type 1 diabetes mellitus and insulin-requiring type 2 diabetes mellitus in whom at least fair glycaemic control is contemplated. However, the relatively new ultra short-acting insulin analogue insulin lispro is not associated with any greater likelihood of hypoglycaemia than is conventional short-acting soluble insulin.[47] Indeed several studies suggest a reduction in hypoglycaemic reactions with this agent.[48]

3. Drugs Used to Treat Diseases Associated with Diabetes Mellitus

3.1 Antihypertensive Therapy

Hypertension is twice as common in patients with diabetes mellitus as in the age and gender-matched general population.[49] Furthermore, complications of diabetes mellitus (e.g. atherosclerotic vascular disease and nephropathy) are greatly accelerated in the presence of hypertension.[50] Thus, achievement and maintenance of normotension via use of antihypertensive therapy is a major therapeutic goal in the hypertensive patient with diabetes mellitus.

There are a considerable number of treatment options in the management of the patient with diabetes mellitus and systemic hypertension. All classes of antihypertensives effectively lower blood pressure. Therefore the choice of agent is dependent upon specific benefits to the patient with diabetes mellitus weighed up against the potential for adverse effects in that patient group.

3.1.1 ACE Inhibitors

ACE inhibitors are frequently indicated in patients with diabetes mellitus because in addition to their antihypertensive action, ACE inhibitors have been shown to have renoprotective,[51] cardioprotective[52] and possibly retinoprotective actions.[53,54] Moreover, they have been demonstrated to improve insulin sensitivity.[55] Nevertheless, care must be exercised with the use of ACE inhibitors in patients with diabetes mellitus.

Diabetes mellitus is associated with the syndrome of hyporeninaemic hypoaldosteronism. This syndrome usually presents as unexplained hyperkalaemia and is particularly common if renal impairment is also present.[56] Therefore, the hyperkalaemia accompanying hyporeninaemic hypoaldosteronism can be exacerbated by concom-

itant use of ACE inhibitors. However, in patients without pre-existing problems (plasma potassium level <6 mmol/L) the likelihood of significant hyperkalaemia may be lower than anticipated. For instance, in a study of patients with type 1 diabetes mellitus and chronic renal impairment, only 3 of 207 patients treated with captopril developed hyperkalaemia.[51] However, it is possible that higher rates may be found in patients with type 2 diabetes mellitus and extreme caution is needed if concomitant therapy with potassium sparing diuretics or potassium supplements is undertaken. Indeed, the regular measurement of plasma electrolytes is warranted in all patients with diabetes mellitus receiving treatment with ACE inhibitors.

Diabetes mellitus is associated with accelerated atherosclerosis.[1] Therefore, diseases such as bilateral renal artery stenosis (RAS) or unilateral stenosis in a solitary kidney may, theoretically, be more common in this disease. The introduction of an ACE inhibitor in this setting may critically reduce glomerular filtration by reducing efferent arteriolar tone[57] leading to lowered filtration pressure and potentially, acute renal failure.

While autopsy studies have suggested that RAS may be more common in diabetes mellitus[58] it is likely that the reported stenoses were not functionally significant. Few studies have been performed to screen for RAS in patients with diabetes mellitus and hypertension. In 1988 Ritchie and colleagues[59] noted that RAS was a common finding in a cross-sectional study of patients with hypertension and type 2 diabetes mellitus. However, more detailed assessment by the same group using functional studies such as radioisotopic renal scanning and bilateral synchronous renal vein renin measurements suggested that RAS was unlikely to be a major cause of the patients' hypertension. Thus, since there are no clinically convincing data to support the notion that patients with diabetes mellitus and hypertension have a much higher prevalence of RAS compared with nondiabetic patients with hypertension, the presence of diabetes mellitus *per se* does not represent a contraindication to the use of ACE inhibitors nor warrant routine investigation to exclude RAS prior to the initiation of treatment

Nevertheless, there are several clinical features which should alert the treating clinician that an individual patient with diabetes mellitus may be at higher risk of RAS. These factors include male gender, old age, history of smoking and evidence of peripheral or coronary artery disease.[60] Therefore, in the setting of clinical suspicion of RAS appropriate investigation prior to commencing ACE inhibitor therapy seems prudent. In addition, plasma potassium and creatinine levels should be measured routinely in all patients prior to and within 1 week of commencing treatment with ACE inhibitors to determine whether a significant deterioration in renal function has developed as a consequence of bilateral renal artery stenosis. The marked elevation in plasma creatinine level that occurs with the use of ACE inhibitors in the context of bilateral RAS needs to be differentiated from the more minor elevations that may occur with the use of these agents, particularly in the setting of volume depletion and concomitant diuretic, situations which do not necessitate withdrawal of therapy.

Most ACE inhibitors (and their active metabolites) are predominantly excreted via the kidney. Therefore, in the setting of significant renal impairment in patients with diabetes mellitus, adjustment of ACE inhibitor dose may be required.

3.1.2 Calcium Antagonists

The effect of calcium antagonists on the progression of diabetic nephropathy has not been fully delineated. Nevertheless, these agents do not impair glucose tolerance or have adverse effects on lipid profiles[61,62] and may therefore be suitable for patients with diabetes mellitus and hypertension, particularly those intolerant of ACE inhibitors.

Controversy regarding the use of calcium antagonists has arisen in the context of a recent case-control study of antihypertensive therapies which suggested an excess mortality in patients taking calcium antagonists. However, in the study of Psaty and co-workers,[63] the excess mortality appears to be confined to short-acting calcium antag-

onists and only a small number patients included in the study had diabetes mellitus.

More recently, the results of a trial comparing the effectiveness of a long-acting dihydropyridine calcium antagonist nisoldipine with the ACE inhibitor enalapril on the development and progression of complications of type 2 diabetes mellitus [the Appropriate Blood Pressure Control in Diabetes (ABCD) trial] were published.[64] This study, which included patients with symptomatic heart disease and nephropathy, had a normotensive and a hypertensive treatment arm. The investigators terminated the trial in the hypertensive arm of the study (470 patients) because there were fewer MIs (fatal and nonfatal) in the ACE inhibitor treated group compared with the calcium antagonist group.

Subsequently, the results of another trial comparing an ACE inhibitor with a dihydropyridine calcium antagonist have also been published.[65] In this study, the Fosinopril and Cardiovascular Events Trial (FACET), 380 patients with type 2 diabetes mellitus and hypertension, but without known heart disease or nephropathy were randomised to receive either fosinopril or amlodipine. However, if blood pressure was inadequately controlled, the other study drug was added. After 3.5 years follow-up, patients randomised to receive fosinopril had significantly fewer major vascular events (stroke, MI, hospitalised angina) compared with those treated with amlodipine. This improved cardiovascular outcome in ACE inhibitor–treated patients was also seen in patients who received both fosinopril and amlodipine. These findings suggest that the better cardiovascular outcome in patients who received fosinopril may reflect a beneficial effect of fosinopril rather than a detrimental effect of amlodipine.

3.1.3 β-Blockers

β-Blockers are effective blood pressure lowering agents, but are associated with adverse metabolic effects of relevance to patients with diabetes mellitus. For instance, β-blockers may worsen glycaemic control[66] and have adverse effects on plasma lipid levels by increasing triglyceride levels and lowering high density lipoprotein (HDL) cholesterol levels.[67] These effects are particularly relevant to patients with type 2 diabetes mellitus where these increased triglyceride and decreased HDL levels may form part of the syndrome of insulin resistance.[68] Additional concerns with the use of β-blockers in patients with diabetes mellitus include a reduction in hypoglycaemic awareness and diminished counter-regulatory metabolic responses such as glycogenolysis.

The effects of β-blockers on the cardiovascular system are complex. For instance, β-blockers may shorten claudication distance and worsen symptoms in patients with peripheral vascular disease.[69] However, favourable effects may be seen in patients with ischaemic heart disease or those with cardiac failure as described recently in patients screened for participation in the Bezafibrate Infarction Prevention (BIP) Study. Analysis of baseline characteristics and 3-year mortality data indicated that the use of β-blockers in patients with diabetes mellitus and coronary artery disease was associated with a total mortality rate of 7.8% in patients receiving β-blockers compared to 14% in those who were not (44% relative reduction).[70] Subgroup analyses from several other trials also suggest that the ability of β-blockers to reduce post-MI mortality is at least similar if not greater in patients with diabetes mellitus compared with patients without diabetes mellitus.[71] Furthermore, though previously contraindicated, β-blockers may be of more benefit to patients with diabetes mellitus and post-MI cardiac failure, than to those patients with diabetes mellitus who have normal cardiac function.[72] Indeed, in a recent study with the β-blocker carvedilol, patients with diabetes mellitus and cardiac failure derived even greater mortality benefits than did nondiabetic heart failure patients.[73]

3.1.4 Diuretics

Diuretics may also impair glucose tolerance, although this is generally dose-dependent[74] and, at low doses, a degree of antihypertensive efficacy may be maintained without loss of glycaemic con-

trol. An additional problem with both thiazide diuretics and β-blockers is erectile dysfunction.[75]

3.1.5 Other Antihypertensive Drugs

α-Blockers are relatively free of major metabolic adverse effects and are therefore suitable for antihypertensive therapy in patients with diabetes mellitus. Indeed, these agents may improve insulin sensitivity.[76] However, first dose postural hypotension may be particularly problematic in the patient with diabetes mellitus and orthostatic hypotension secondary to autonomic neuropathy.

Potassium sparing agents such as spironolactone and amiloride should be used with caution in patients with diabetes mellitus because of the possibility of triggering severe hyperkalaemia in association with hyporeninaemic hypoaldosteronism (see section 3.1.1).

3.2 Lipid Lowering Drugs

Cardiovascular disease is the commonest cause of morbidity and mortality in patients with diabetes mellitus. Patients with diabetes mellitus and heart disease have a worse prognosis compared with their nondiabetic counterparts[77] and may also respond less favourably to revascularisation by angioplasty.[78,79] The reasons for the increased risk of cardiovascular disease in patients with diabetes mellitus is incompletely understood. However, quantitative and qualitative abnormalities in serum lipid levels are likely to be contributory. Although a large number of different lipid lowering drugs are available, the 2 groups of drugs which are most commonly used in diabetes mellitus are the HMG CoA reductase inhibitors ('statins') and the fibric acid derivatives.

3.2.1 HMG CoA Reductase Inhibitors

Several large clinical trials have demonstrated the beneficial effects of the HMG CoA reductase inhibitors in reducing cardiovascular and total mortality when used as either primary[80] or secondary preventative strategies.[81,82] More recently, *post hoc* analyses of secondary intervention trials with simvastatin and pravastatin have confirmed that the beneficial effects observed in patients without diabetes mellitus extend to those with diabetes mellitus.[83,84] Furthermore, the safety and tolerability of the HMG CoA reductase inhibitors appears similar in patients with and without diabetes mellitus.[85-87]

The most common safety concern in patients receiving HMG CoA reductase inhibitors is abnormal liver function tests, principally elevated transaminase levels. While mostly mild, transaminase levels exceed the apparent safe level of 3 times the upper limit of the reference range in approximately 1.5% of patients.[88] Although clinically significant liver disease is extremely rare in this group of drugs, their cessation is recommended if the safety limit is exceeded and in all reported cases liver function tests have returned to normal. Since abnormal liver function test results are not uncommon in patients with diabetes mellitus, possibly as a consequence of fatty infiltration, these should be measured prior to commencing drug treatment and checked periodically thereafter.

Less common, but more significant is the development of myopathy. This adverse effect may take the form of a poorly understood nonspecific muscle aching with normal plasma creatinine kinase levels [89] or the combination of muscle pain, weakness and elevated creatinine kinase levels [>10 times the upper limit of normal (ULN)] which occasionally progresses to rhabdomyolysis with myoglobinuric acute renal failure. In many other patients the creatinine kinase level is coincidentally mildly elevated as a consequence of exercise or injury and returns to normal with cessation of exercise and recovery from injury. Myopathy with creatinine kinase levels >10 times ULN is fortunately rare with reported incidence rates of 0.08 to 0.09% for lovastatin, simvastatin and pravastatin.[90] The risk of myopathy is increased with concurrent use of cyclosporin, erythromycin, gemfibrozil and nicotinic acid.

With regard to the newer HMG CoA reductase inhibitors, fluvastatin and atorvastatin, more widespread usage will be needed before the relative risks of myopathy with these agents can be ascertained.

3.2.2 Fibric Acid Derivatives

In clinical practice the fibric acid derivatives are commonly used particularly in the mixed dyslipidaemia which commonly develops in patients with type 2 diabetes mellitus. Their use was met with concern following the increased mortality reported with the use of clofibrate in the WHO Cooperative Trial for primary prevention of coronary heart disease.[91] This reported increase in cancer and noncardiovascular death with clofibrate has not been adequately explained. In the Helsinki Heart Study, the reduction in cardiovascular events described in the study group was also noted in a *post hoc* subgroup analysis of patients with diabetes mellitus.[92]

Gemfibrozil treatment was associated with a minor increase in surgery for gall stones, appendicitis, cataracts and skin cancers. In addition, more cases of intracranial haemorrhage and deaths due to violence or accidents were also found in the gemfibrozil-treated group.[93] More recently, an 8.5 year follow-up study of the Helsinki Heart Study found the number of adverse events to be mostly similar in the 2 treatment groups with 32 versus 37 strokes, 16 versus 14 violent deaths in gemfibrozil- and placebo-treated patients, respectively.[94] 51 patients in each group were diagnosed with cancer.[94]

3.2.3 Combination Therapy with Fibric Acid and HMG CoA Reductase Inhibitors

Combination therapy with fibric acid derivatives and HMG CoA reductase inhibitors may lead to greater improvements in lipid parameters when compared with monotherapy alone. Because patients with diabetes mellitus frequently have significant mixed dyslipidaemia, treatment with a single agent often fails to achieve target levels for HDL cholesterol, low density lipoprotein (LDL) cholesterol and triglycerides. More than 20 trials have examined combination drug therapy using either clofibrate, gemfibrozil, bezafibrate or fenofibrate in combination with either lovastatin, simvastatin, pravastatin. These trials are reviewed in a paper by Shepherd.[90]

More recently studies on the safety and efficacy of fluvastatin with either gemfibrozil[95] or bezafibrate[96] have also been undertaken. The overall incidence of drug-related myopathy was approximately 1.0% and in no cases did rhabdomyolysis or myoglobinuria develop. Although most cases of severe myopathy have incriminated either lovastatin or simvastatin in combination with gemfibrozil, this may simply reflect the greater clinical exposure of patients to these drugs. The relative myotoxicity of individual HMG CoA reductase inhibitors or fibric acid derivatives remains uncertain. Indeed, as drug-induced myopathy is relatively rare, most reports will come from postmarketing surveillance.

4. Conclusion

Diabetes mellitus is a common disease associated with chronic complications. Hypoglycaemic drug therapy is mostly well tolerated provided that appropriate precautions are taken. Treatment of associated cardiovascular disease is also a major priority in the patient with diabetes mellitus. Drugs used to treat concomitant hypertension and dyslipidaemia are mostly well tolerated. Current evidence suggests that such drugs are equally and possibly more effective in patients with diabetes mellitus and are not accompanied by any significant worsening of their safety profiles.

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