REVIEW ARTICLE

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Drug-Induced Hypoglycaemia
An Update

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Abstract

Drugs are the most frequent cause of hypoglycaemia in adults. Although hypoglycaemia is a well known adverse effect of antidiabetic agents, it may occasionally develop in the course of treatment with drugs used in everyday clinical practice, including NSAIDs, analgesics, antibacterials, antimalarials, antiarrhythmics, antidepressants and other miscellaneous agents. They induce hypoglycaemia by stimulating insulin release, reducing insulin clearance or interfering with glucose metabolism. Several drugs may also potentiate the hypoglycaemic effect of antidiabetic agents. Administration of these agents to

individuals with diabetes mellitus is of most concern. Many of these drugs, and depending on clinical setting, may also induce hyperglycaemia. Drug-induced hepatotoxicity and nephrotoxicity may lead in certain circumstances to hypoglycaemia. Some drugs may also induce hypoglycaemia by causing pancreatitis. Drug-induced hypoglycaemia is usually mild but may be severe. Effective clinical management can be handled through awareness of this drug-induced adverse effect on blood glucose levels. Herein, we review pertinent clinical information on the incidence of drug-induced hypoglycaemia and discuss the underlying pathophysiological mechanisms, and prevention and management.

Drugs are the most frequent cause of hypoglycaemia in adults.[1] Drug-induced hypoglycaemia as a cause of acute medical admissions ranges from 0.1% to 1.7%[2] and in a recent study, 20% of hospital admissions attributed to adverse drug reactions were related to hypoglycaemia.[3] The median length of hospital stay for drug-induced hypoglycaemia was 4 days.[4] It is estimated that each hospital admission for severe hypoglycaemia costs around £1000, which is considerable.[5] The leading cause of drug-induced hypoglycaemia is represented by antidiabetic agents, particularly insulin and sulphonylureas. In the UKPDS (UK Prospective Diabetes Study), for patients with type 2 diabetes mellitus and over 6 years of follow-up, the prevalence of major hypoglycaemia (requiring medical attention or admission to hospital) was 2.4% of those using metformin, 3.3% of those using a sulphonylurea, and 11.2% of those using insulin.[6] The incidence of hypoglycaemia induced by non-antidiabetic drugs is unknown, due to several factors, including the lack of a standardized definition of hypoglycaemia, lack of data from clinical trials, under-reporting of adverse drug reactions by physicians, and the lack of evidence of a causal relation between hypoglycaemia and the suspected drug.

Drug-induced hypoglycaemia has a substantial clinical impact in terms of mortality. In diabetic patients, it also prevents optimal glycaemic control. Severe hypoglycaemia is considered a contributing factor towards death in 2–6% of diabetic patients.[7-9] Recent reports are more alarming and indicate that 6–10% of patients with type 1 diabetes die as a result of hypoglycaemia.[10-12] However, it was not always possible to confirm whether the deaths were directly related to hypoglycaemia, since all diabetic patients had serious associated co-morbidities.

With the expansion of the diabetic population, the increasing use of antidiabetic agents and the increase in the number of drugs recently introduced, drug-associated hypoglycaemia becomes inevitably a major and common concern in clinical practice. In this review, we shed light on the potential drugs causing hypoglycaemia, the mechanisms underlying iatrogenic hypoglycaemia, and pertinent issues for the optimal management of drug-induced hypoglycaemia.

Data were identified from MEDLINE and SCOPUS from January 1960 to December 2009, and from *Reactions Weekly* from 1992 to December 2009, regardless of the language. We used the keywords 'hypoglycaemia' and 'glucose metabolism disorders' with the subheading 'drug-induced', 'drug-interaction'. Certain drugs were directly inserted as keywords, such as 'insulin', 'sulphonylureas' and 'antidiabetic drugs'. Searches also included the terms 'blood' and 'glucose/drug effects'. If there were relevant articles in many languages that described the same topic, only English or French articles were analysed. Identified articles were evaluated to determine whether any of their references contained additional relevant publications. Information from reviews focusing on this topic has also been considered.[13,14] We excluded articles with insufficient clinical or laboratory data.

In this review, we focus only on drug-induced hypoglycaemia. Alcohol and herbal remedies are excluded from this review. Drug-induced hepatotoxicity and nephrotoxicity may lead, in certain

circumstances, to hypoglycaemia. Drugs may also induce hypoglycaemia by causing pancreatitis.

1. Definition and Clinical Manifestations of Hypoglycaemia

There is really no veritable consensus definition of hypoglycaemia. Currently, hypoglycaemia may be defined either biochemically or clinically. Biochemically, hypoglycaemia occurs when the plasma glucose level falls below an arbitrary value. However, a wide range of glucose levels may represent biochemical hypoglycaemia, and the difficulty arises in determining at what glucose level it starts.[15] Based on a report from the American Diabetes Association (ADA), hypoglycaemia may be defined as a venous blood glucose concentration of ≤3.9 mmol/L (70 mg/dL) in diabetic patients.[16] The ADA Workgroup argued that this is the glucose level at which hormonal counter-regulation is activated in non-diabetic subjects, and that antecedent hypoglycaemia of this modest degree can reduce the secretion of the counter-regulatory systems (glucagon and adrenaline [epinephrine]) in response to a subsequent episode of hypoglycaemia. However, many clinicians investigating non-diabetic patients would regard these levels of blood glucose as being within the normal fasting range, and would not consider it to indicate hypoglycaemia. They consider that this level proposed by the ADA is higher than the glucose levels required to produce symptoms in non-diabetic individuals (approximately 2.8–3.1 mmol/L [50–55 mg/dL]) and substantially higher than those that do so in individuals with well controlled diabetes.[17] An arbitrary cut-off level of 3.5 mmol/L (63 mg/dL) to define the onset of hypoglycaemia in clinical practice is also considered more appropriate by these clinicians.[15]

The definition proposed by Whipple is still the most useful and defines pathological hypoglycaemia as a triad of low plasma glucose, hypoglycaemic symptoms, and resolution of symptoms with correction of the blood sugar.[1]

Although the symptoms of hypoglycaemia related to drugs are nonspecific, in some instances drug-induced hypoglycaemia may be differentiated from other possible aetiologies by evaluating the temporal relationship between drug administration, onset of symptoms and changes in blood glucose levels. Drug withdrawal and rechallenge may be helpful to confirm the diagnosis.

Rapid detection of symptoms of drug-induced hypoglycaemia and immediate treatment with frequent monitoring of the patient are mandatory. The symptoms of mild to moderate hypoglycaemia include features such as palpitations, sweating, tingling, hunger, nausea, tremor and headache.[18] Later, and if hypoglycaemia is not promptly treated, neuroglycopenic symptoms are inevitable. They include blurred vision, psychopathic behaviour, confusion, convulsions, focal neurological deficit, and coma. Furthermore, repeated episodes of hypoglycaemia may over time lead to the syndrome of hypoglycaemia unawareness.[19] Cognitive dysfunction resulting in confusion and coma is not preceded by warning symptoms.[19] Loss of warning of hypoglycaemia is associated with delayed and reduced neuroendocrine responses to falling blood glucose levels, leading frequently to severe hypoglycaemia. It occurs as a consequence of frequent and recurrent iatrogenic hypoglycaemic events and is closely linked to defects in hormonal counter-regulation, in particular to the blunted adrenaline response.[20] Hypoglycaemia unawareness seems also to develop as the duration of diabetes increases, and is common among insulin-treated patients. β-Adrenergic receptor antagonists (β-blockers) can blunt hypoglycaemia awareness. However, several drugs such as caffeine and theophylline are thought to have an attenuating effect on the syndrome of hypoglycaemia unawareness.[21]

2. Causative Drugs

Drug-induced hypoglycaemia may occur when an antidiabetic agent is given therapeutically to a diabetic patient. It can also complicate an intentional or accidental overdose of an antidiabetic agent in non-diabetic patients. Antidiabetic agents may interact with some other drugs taken by the patient, leading to an enhancement of their hypoglycaemic effect. Rarely, the hypoglycaemic effect may be a direct or an undesirable effect of a drug that is not primarily an antidiabetic agent.[22] Administration of these agents to individuals

Table I. Non-antidiabetic drugs inducing hypoglycaemia in patients without diabetes

Drug classes
Cardiovascular
Amiodarone,[23] alprenolol,[24] atenolol,[25] carvedilol,[26] clonidine,[27] disopyramide,[28] ethacrynic acid,[29] felodipine,[30] hydralazine and procainamide,[31] nadalol,[32] nifedipine,[33] perhexilene,[34] pindolol,[35] propranolol,[36] telmisartan[37]
Antibacterial
Ceftriaxone,[38] ciprofloxacin,[39] cotrimoxazole,[40] doxycycline,[41] ethionamide,[42] isoniazid,[43] piperacillin-tazobactam,[44] sparfloxacin[45]
Antimalarial
Hydroxychloroquine,[46] mefloquine,[47] pentamidine,[48] quinine,[49] sulfadoxine/pyrimethamine[50]
Antiviral
Amprenavir,[51] entecavir,[52] ganciclovir,[53] stavudine,[54] zidovudine and zalcitabine[55]
Antifungal
Ketoconazole,[56] voriconazole[57]
Antiepileptic
Gabapentin,[58] phenytoin,[59] topiramate,[60] valproate[61]
Miscellaneous
Chlorpromazine,[62] dexmedetomidine,[63] donepezil,[64] etomidate,[65] haloperidol,[66] sertraline,[67] trimeprazine,[68] zuclopenthixol[69]

with diabetes is of most concern; however, there have also been reports of these agents possibly inducing hypoglycaemia in individuals without diabetes (table I).[23-69] Many of these drugs, and depending on clinical setting, may also induce hyperglycaemia. A systematic review showed that most exposures were consistent with appropriate dosing rather than overdose, and hypoglycaemia episodes were usually symptomatic and severe.[70] Reported cases usually described patients who were elderly, had renal or hepatic insufficiency, were using insulin or a sulphonylurea, or had severe systemic disease.

2.1 Antidiabetic Agents

2.1.1 Regular Human Insulin

Hypoglycaemia is one of the most frequent complications of insulin therapy, and up to 25–30% of insulin-treated diabetic patients experience one or more severe hypoglycaemic episodes every year.[71]

Insulin can induce hypoglycaemia if high doses are given, if insufficient carbohydrate is taken or a meal is missed, or as a result of excessive physical activity. In addition, concomitant diseases such as renal disease or hepatic disease, and alcohol ingestion are all factors to consider in assessing hypoglycaemia in a patient with diabetes treated with insulin.[1]

The hospitalization rate following hypoglycaemia has been reported to be 9.1 per 1000 patient-years for insulin.[72] In the DCCT (Diabetes Control and Complications Trial), the incidence of severe hypoglycaemia induced by insulin was approximately three times higher in the intensive therapy group than in the conventional therapy group. In the intensively treated group, there were 62 hypoglycaemic episodes per 100 patient-years compared with 19 such episodes per 100 patient-years in the conventionally treated group.[73] In the US Veterans Affairs Cooperative Study in Type 2 Diabetes the frequency of mild hypoglycaemic episodes was reported as 1.5 and 16.5 episodes per patient per year in the conventionally and intensively treated groups, respectively.[74] The incidence of severe hypoglycaemia seems to be lower in type 2 diabetes than in type 1 diabetes; in fact, the rate of severe hypoglycaemia in type 2 diabetes is about 10% of that in type 1 diabetes.[75] The lower incidence of severe hypoglycaemia in type 2 diabetes may result from insulin resistance, which is often quite severe. This difference, however, may disappear with increasing duration of insulin therapy.[76] Regardless of the type of diabetes, other factors have been associated with a higher incidence of severe insulin-induced hypoglycaemia. These factors include the degree of glycaemic control and a previous history of severe hypoglycaemic reactions. Errors in the timing of insulin injection and the type of insulin may also lead to hypoglycaemia.[1]

2.1.2 Insulin Analogues

The currently available rapid-acting insulin analogues are insulin lispro, insulin aspart and insulin glulisine. They have shown superior lowering of postprandial blood glucose levels compared with regular insulin.[77] Based on their pharmacodynamic properties, they may prevent or at least improve postprandial hyperglycaemia and are less likely to lead to hypoglycaemia. Indeed, rapid-acting insulin analogues have been developed to more closely replicate the physiology of meal-related and basal insulin secretion.[78]

It is not surprising that hypoglycaemia occurs earlier with a rapidly acting analogue than with regular insulin.

Although the pharmacokinetic and pharmacodynamic properties of rapid-acting insulin analogues are better than those of regular human insulin, the frequency of severe hypoglycaemia does not appear to be significantly different between these two forms of insulin in all studies. In a Cochrane review the median incidence (number of episodes per 100 person-years) of severe hypoglycaemia in type 1 diabetic patients was 21.8 (range 0–247.3) with rapid-acting insulin analogues and 46.1 (0–544) with regular insulin. In type 2 diabetes, the median incidence was 0.3 (range 0–30.3) with the insulin analogues and 1.4 (range 0–50.4) with regular insulin.[79]

In several studies, the incidence and risk of severe hypoglycaemia have been reported to be reduced with insulin aspart and insulin lispro compared with human regular insulin.[80-83] Conversely, Garcia et al.,[84] reported a similar frequency of severe hypoglycaemia during treatment with insulin lispro compared with human regular insulin. In fact, rapid-acting insulin analogues seem to offer a little benefit over conventional insulin in terms of glycaemic control or reduced hypoglycaemia but do not appear to significantly decrease the incidence of severe hypoglycaemia. Furthermore, there is no convincing evidence to switch patients from existing conventional therapy with human regular insulin to these insulin analogues if they have appropriate glycaemic control without troublesome hypoglycaemia. However, appropriate use of rapid-acting insulin analogues should improve quality of life, since patients can 'inject and eat'.

In terms of an optimal basal pharmacokinetic/pharmacodynamic profile, the long-acting insulin analogues (insulin glargine and insulin detemir) became an important option to replace basal insulin for patients with type 1 diabetes. Insulin glargine has been compared with regular human insulin in 4385 patients with type 2 diabetes. There was no significant difference in confirmed or severe episodes of hypoglycaemia between the two types of insulin.[85] However, in a meta-analysis there were fewer episodes of nocturnal and symptomatic hypoglycaemia when long-acting insulin analogues (detemir or glargine) were compared with human regular insulin.[86] Furthermore, the risks of severe hypoglycaemia and severe nocturnal hypoglycaemia were significantly reduced with insulin glargine compared with human regular insulin with at least equivalent glycaemic control.[87] Vague et al.[88] reported a 22% reduction in overall hypoglycaemia and a 34% reduction in nocturnal hypoglycaemia with insulin detemir compared with regular human insulin. The lower rate of severe and nocturnal hypoglycaemia induced by insulin detemir is probably due to the low coefficient of variation in serum insulin levels between injected doses seen with this insulin. When comparing short- and long-acting insulins, insulin glargine seems to induce significantly fewer hypoglycaemic events than insulin lispro.[89]

Because of the ability of continuous subcutaneous insulin infusion (CSII) to closely mimic the normal insulin profile, this method seems to be a very useful tool for the prevention of hypoglycaemia. Although, many studies have reported no significant difference in the frequency of severe hypoglycaemia between CSII and multiple daily injections (MDIs), other recent studies have shown significant reductions in severe hypoglycaemia with CSII compared with MDIs.[90,91] Jakish et al.[92] demonstrated in a large cohort that CSII in children is associated with significantly reduced rates of hypoglycaemia when compared with MDI. In a large meta-analysis, Pickup and Sutton[93] reported that the rate of severe hypoglycaemia in type 1 diabetes was markedly lower during CSII than MDI.

Insulin-induced hypoglycaemia has been documented due to deliberate misuse, essentially for attracting attention and sympathy and in suicide attempts. The true incidence of this factitious insulin-induced hypoglycaemia is unknown. Its diagnosis is based on the finding of high or extremely high serum insulin concentrations in combination with suppression of C peptide and, possibly, the presence of insulin antibodies.

2.1.3 Sulphonylureas

Sulphonylureas have been a part of medical practice for the treatment of type 2 diabetes for

nearly 50 years. By the 1960s, first-generation sulphonylureas were marketed, including tolbutamide and chlorpropamide, though these are rarely prescribed today. Second-generation sulphonylureas (glibenclamide [glyburide], gliclazide and glipizide) emerged in the 1970s and 1980s. The newest second-generation sulphonylurea, glimepiride, was introduced in the late 1990s. Sulphonylureas act mainly by augmenting insulin secretion through stimulating the closure of adenosine triphosphate-sensitive potassium channels of the pancreatic β cells followed by opening of calcium channels. The release of insulin continues while there is ongoing drug stimulation and β cells are fully functional. Sulphonylureas do not affect insulin synthesis but only insulin secretion. Consequently, they can cause a fasting but not a reactive type of hypoglycaemia.

Hypoglycaemia is the most frequent complication in patients with diabetes taking sulphonylureas.[94] Sulphonylurea-induced hypoglycaemia may occur because insulin release is initiated even when glucose levels are below the normal threshold for glucose-stimulated insulin release (approximately 5 mmol/L).[95] It occurs particularly if the doses of sulphonylureas taken are high or if meals are missed. Sustained physical exercise, advancing age, coexisting renal failure or advanced liver disease, duration of therapy, concomitant use of insulin, drug interactions and concomitant use of β-blockers are also risk factors for developing hypoglycaemia in patients treated with sulphonylureas.[96] Individuals with genetically determined low cytochrome P450 (CYP) 2C9 activity have been recently reported with an increased risk of sulphonylurea-associated severe hypoglycaemia.[97] Sulphonylurea-induced hypoglycaemia is usually subclinical or minor. It also may be severe or even fatal, persists for many hours, and often mandates immediate admission to hospital. It occurs within the first days of treatment, but can also appear weeks or months later, even without apparent modification in dosage. The incidence and severity of sulphonylurea-induced hypoglycaemia range widely across studies. Variation may be due to differences in definitions, methodology of studies and data collection. Overall, the reported frequency of sulphonylurea-induced hypoglycaemia has varied from 1.8% to 59%.[98,99] For example, in a review of UK medical records of 33 243 sulphonylurea users, the annual risk for a first episode of sulphonylurea-induced hypoglycaemia was 1.8%.[100] Severe hypoglycaemia due to sulphonylurea use was rare. It is more likely to occur in older individuals and in those with underlying cardiovascular or renal impairment.[101] The mortality risk from severe sulphonylurea-induced hypoglycaemia has been estimated to be 0.014–0.033 per 1000 patient-years.[98,102] In addition to fatal cases related to sulphonylurea, 5% of survivors may have permanent neurological impairment.[99] Although direct comparisons between drugs in the same study population are rare, chlorpropamide and glibenclamide conferred higher risk for hypoglycaemia compared with other sulphonylureas. During an estimated 26 125 person-years of observation among diabetic patients, Sugarman[72] reported an incidence of severe hypoglycaemia of 5.8 and 16.0 per 1000 patient-years for chlorpropamide and glibenclamide, respectively. In a prospective study, the incidence of severe hypoglycaemia with glimepiride was significantly lower than with glibenclamide, at 0.86 per 1000 person-years versus 5.6 per 1000 person-years.[97] In a meta-analysis, the risk of major hypoglycaemic events was over four times higher for glibenclamide compared with other second-generation sulphonylureas.[103] Overall, hypoglycaemia rates with glimepiride, glipizide and gliclazide appear to be lower than those with glibenclamide and chlorpropamide.

In a 6-month, head-to-head, multicentre study, hypoglycaemia with a blood glucose level of <3 mmol/L occurred significantly less frequently with gliclazide modified release (3.7% of patients) compared with glimepiride (8.9% of patients).[104] There are no published reports comparing glimepiride directly with glipizide for hypoglycaemia.

The reasons for the difference in rates of hypoglycaemia are variable. Differences in chemical structure, and pharmacokinetic and pharmacodynamic properties between sulphonylureas may lead to differences in the rates of hypoglycaemic episodes. Chlorpropamide and glibenclamide have long half-lives, and are significantly dependent on renal excretion. Furthermore, the metabolites

of glibenclamide have a relatively long half-life with significant hypoglycaemic activity that depends also on renal excretion.[94] The long duration of effect of both glibenclamide and chlorpropamide requires prudent use in elderly individuals, whose renal function declines with age. In fact, there is an important potential for accumulation of these drugs and their metabolites resulting in severe and protracted hypoglycaemia. Doses of glibenclamide should either be markedly reduced or avoided in patients with moderate renal dysfunction and in elderly patients. However, dose adjustment is not required for glimepiride or gliclazide. At present there are insufficient data to support their use in patients with end-stage renal disease, for which insulin remains the preferred option.[105]

In a systematic review comparing the safety of antidiabetic agents, Bolen et al.[106] revealed that minor and major hypoglycaemic episodes were more frequent in patients receiving second-generation sulphonylureas (especially glibenclamide) than in those receiving metformin or thiazolidinediones. Second-generation sulphonylureas and repaglinide (one of the meglitinides) conferred similar risks for hypoglycaemia. Comparative data on acarbose and nateglinide with sulphonylureas were not conclusive.

Sulphonylurea-induced hypoglycaemia does not occur only in patients with diabetes. Severe hypoglycaemia has been reported in patients treated with chlorpropamide for diabetes insipidus.[107] Unintended use of sulphonylureas remains a common cause of unexplained hypoglycaemia in non-diabetic persons, especially in children and the elderly. Sulphonylurea overdose with suicidal intent can lead to severe hypoglycaemia. Since their introduction into therapy, sulphonylureas have been used to induce factitious hypoglycaemia.

Drug interaction may also lead to severe hypoglycaemia even at therapeutic dosages of sulphonylureas.[108] The hypoglycaemic effect of sulphonylureas is potentiated by other anti-diabetic agents. The incidence of minor and major hypoglycaemia was higher with combination therapy that included sulphonylureas compared with metformin or sulphonylurea monotherapy. The hypoglycaemic effect of sulphonylureas is potentiated also by some non-antidiabetic drugs, and many drug interactions have been reported (table II).[109-139]

2.1.4 Biguanides

Metformin is considered to be the first-choice drug for treatment of obese patients with type 2 diabetes.

Monotherapy with conventional doses of metformin is not expected to cause hypoglycaemia, as the drug does not exert its effects through an increase in insulin secretion.[140] Metformin also does not modulate the glucose counter-regulatory mechanism. However, mild hypoglycaemia has been reported in 2.8% of 4072 cases of poisoning exposures to metformin.[141]

The ADOPT study (A Diabetes Outcome Progression Trial) has reported rates of self-reported hypoglycaemia around 9.8% for metformin over the 5 years of treatment. Severe episodes were reported in only one patient.[142] Metformin-induced hypoglycaemia is more commonly reported in combination regimens with insulin or an insulin secretagogue, presumably as a function of potentiation by metformin of the other therapy.[143] In a 24-week trial of metformin or nateglinide alone and in combination, rates of symptomatic hypoglycaemia determined by self-monitoring were 10% in the metformin group compared with 12.8% in the nateglinide group, and 26.6% in the metformin + nateglinide group.[145] During a 7-year period, the associations of metformin + glibenclamide and metformin + insulin were implicated in 15% of drug-induced hypoglycaemic coma.[8] Alcohol may also increase the risk of lactic acidosis as well as hypoglycaemia.[145] Hypoglycaemia associated with lactic acidosis induced by metformin may be a consequence of liver failure.[145] Precautions should be taken if metformin is given with drugs that may impair renal function.

2.1.5 α-Glucosidase Inhibitors

Acarbose, the first α-glucosidase inhibitor to be marketed, was introduced in the early 1990s. Recently, two additional agents of this class, miglitol and voglibose, have been introduced in some countries. Due to their mode of action, α-glucosidase inhibitors do not stimulate insulin

Table II. Drug interactions with sulphonylureas leading to hypoglycaemia

Interacting drug	Sulphonylureas implicated	Suggested mechanisms	References
NSAIDs (azapropazone phenylbutazone, salicylates)	Tolbutamide, chlorpropamide, glibenclamide (glyburide)	Displacement of sulphonylureas from protein binding sites. Reduced renal secretion. Inhibition of metabolism of sulphonylureas	109-111
Fibrates (bezafibrate, ciprofibrate, gemfibrozil, clofibrate)	Glibenclamide, tolbutamide	Displacement of sulphonylureas from plasma protein binding sites. Reduced renal secretion. Inhibition of metabolism of sulphonylurea	112-115
Azoles (miconazole, fluconazole, ketoconazole)	Glipizide, tolbutamide, glibenclamide, gliclazide	Inhibition by azoles of sulphonylurea-metabolizing enzymes (cytochrome P450 [CYP] isoenzyme CYP2C9)	116-119
Sulphonamides (cotrimoxazole, sulphaphenazole, sulphamethizole, sulphafurazole, sulphadimidine)	Chlorpropamide, glibenclamide, gliclazide, tolbutamide	Inhibition of metabolism of sulphonylureas. Displacement of sulphonylureas from protein binding sites	113,120-123
Macrolides (clarithromycin, erythromycin)	Glibenclamide, glipizide, tolbutamide	Displacement of sulphonylureas from protein binding sites	124,125
Histamine H_2-receptor antagonists (cimetidine, ranitidine)	Gliclazide, glibenclamide	Cimetidine inhibits metabolism of the sulphonylurea by the liver, thereby increasing its effects	113,126-128
ACE inhibitors (captopril, enalapril, lisinopril, perindopril)	Glibenclamide, gliclazide	Unknown	129
Quinolones (gatifloxacin, ciprofloxacin, levofloxacin)	Glibenclamide, glimepiride, glipizide	Unknown	130-134
Allopurinol	Gliclazide	Unknown	113
Chloramphenicol	Tolbutamide	Inhibition of metabolism of sulphonylurea	135
Cibenzoline	Gliclazide	Unknown	113
Dextropropoxyphene-paracetamol (acetaminophen)	Unspecified sulphonylurea	Unknown	113
Disopyramide	Gliclazide	Unknown	136
Heparin calcium	Glipizide	Displacement of sulphonylureas from their plasma protein binding sites	137
Nicardipine	Gliclazide	Unknown	113
Sertraline	Glibenclamide	Unknown	138,139

secretion, and therefore monotherapy does not provoke hypoglycaemia.[146] The UKPDS found that there was no difference between acarbose and placebo for the risk of hypoglycaemic episodes.[147] In a 24-week, double-blind, randomized trial, in which acarbose was compared with vildagliptin, no hypoglycaemic episodes were reported for either treatment group. There were also no cases of hypoglycaemia reported with acarbose, even in patients predisposed to hypoglycaemia, such as the elderly.[148] Although α-glucosidase inhibitors, when given alone, do not carry the risk of hypoglycaemia, they cause a moderate additional blood glucose-lowering effect when used with other antidiabetic agents. In fact, hypoglycaemia was only reported when an α-glucosidase inhibitor was used in combination with a sulphonylurea or insulin.[105] α-Glucosidase inhibitors delay the digestion and absorption of disaccharides such as sucrose, but do not affect monosaccharides. Therefore, patients who take these drugs must use a monosaccharide such as glucose or glucagon, grape juice or honey to treat hypoglycaemia. However, when glucose is not available, milk with lactose sugar can be used as an alternative. Indeed, acarbose only slightly inhibits lactase. In severe cases of hypoglycaemia, glucagon can also be used.

2.1.6 Thiazolidinediones

Thiazolidinediones rarely cause hypoglycaemia when used in monotherapy.[149] However,

they can contribute to hypoglycaemia in patients receiving glucose-lowering drugs such as insulin or insulin secretagogues.[150] Hypoglycaemia may occur several weeks after adding a thiazolidinedione to a sulphonylurea.[151] The dose of the latter may require reduction and a self-monitoring of blood glucose, which can be a useful safety measure if this combination is used.

In a 24-week, multicentre, randomized, open-label, parallel trial, rosiglitazone was associated with a significantly lower average rate of confirmed hypoglycaemic events than insulin glargine, when used in combination with metformin plus a sulphonylurea (3.4 vs 7.7 events per patient-year).[153]

A prospective, randomized, controlled trial in 5238 patients with type 2 diabetes who had evidence of macrovascular disease, comparing the addition of pioglitazone or placebo with usual diabetic treatment (metformin, sulphonylurea and insulin, either individually or in combinations), found that the incidence of symptoms compatible with hypoglycaemia was significantly higher in the pioglitazone plus usual treatment group (28% vs 20%), although the incidence of severe hypoglycaemia that resulted in admission to hospital was not significantly different (0.7% vs 0.4%).[153] Furthermore, the ADOPT study has reported rates of self-reported hypoglycaemia of around 11.6% for rosiglitazone over the 5 years of treatment. Severe episodes were reported in only one patient.[142] In a *post hoc* analysis of pooled data, from patients aged >65 years with type 2 diabetes in four multicentre, randomized, double-blind, parallel-group trials, pioglitazone monotherapy was associated with the lowest incidence of hypoglycaemia (1.4%) compared with metformin alone (2.4%) or sulphonylurea alone (9.9%).[154] In an open-label, active-controlled study, St John Sutton et al.[155] showed that patients treated with rosiglitazone therapy had a lower incidence of hypoglycaemia (1.9%) than those treated with glibenclamide therapy (7.1%).

2.1.7 Meglitinides

As with sulphonylureas, the main adverse effect of this class is hypoglycaemia. In a randomized, parallel-group, open-label, clinical trial, repaglinide was compared with nateglinide.[156] In the trial, 7% of patients treated with repaglinide (five subjects with one episode each) had minor hypoglycaemic episodes (blood glucose <2.8 mmol/L) versus no patients with nateglinide. Renal failure and insufficient calorie intake are considered possible risk factors for developing hypoglycaemia in patients treated with meglitinides.[157,158] Meglitinides should be administered prior to meals to reduce the risk of hypoglycaemia. A multicentre, randomized, double-blind study comparing repaglinide with glibenclamide showed that the risk of mild/moderate hypoglycaemia was 1% for both treatments.[159] Other studies comparing repaglinide with sulphonylureas have shown that the risks of severe hypoglycaemia (blood glucose <2.5 mmol/L) were 1.3% and 3.3%, respectively.[160] A small study of 8 weeks duration, which included 51 patients receiving nateglinide and 50 receiving glibenclamide, reported four times higher symptomatic hypoglycaemic events with glibenclamide than with nateglinide.[161] Overall, no consistent significant differences were reported between sulphonylureas and meglitinides for the number of hypoglycaemic episodes.[162] Hypoglycaemia seems to be more frequent with repaglinide compared with metformin.[162]

In a study comparing nateglinide and troglitazone, mild hypoglycaemia occurred in 1.3% of patients treated with either nateglinide or troglitazone, and in 7.3% of patients treated with nateglinide plus troglitazone.[163]

Severe hypoglycaemia secondary to meglitinides following surreptitious use or in suicide attempts has also been reported.[164,165] Meglitinides are metabolized by the CYP3A4 isoenzyme. In addition to CYP3A4, repaglinide is metabolized via CYP2C8, while nateglinide metabolism also involves CYP2C9.[166] They may be exposed to pharmacokinetic interactions. Ciclosporin raises the plasma concentrations of repaglinide and potentiates the blood glucose-lowering effect with a possible increase in the risk of hypoglycaemia.[168]

2.1.8 Incretin Analogues and Dipeptidyl-Peptidase 4 Inhibitors

Exenatide, a synthetic form of exendin-4, is an incretin analogue that increases insulin secretion, suppresses glucagon release and slows gastric

emptying. It is approved for adjunctive glycaemic control in patients with type 2 diabetes who are taking metformin, a sulphonylurea, or a combination of metformin and sulphonylurea. Exenatide does not seem to be commonly associated with any increased risk of hypoglycaemia when used as monotherapy, which is consistent with its glucose-dependent insulinotropic effect. When it occurred, exenatide-induced hypoglycaemia was generally mild to moderate. Rates of mild to moderate hypoglycaemia were reported as 36%, 14% and 3% for groups of patients receiving exenatide 10 μg, 5 μg and placebo, respectively.[168]

Compared with insulin glargine, rates of symptomatic hypoglycaemia with exenatide were similar, but nocturnal hypoglycaemia occurred less frequently with exenatide (0.9 vs 2.4 events/patient-year for insulin glargine).[169]

There is an increased risk of hypoglycaemia with exenatide if used in association with sulphonylureas.[170] Initial reduction of sulphonylurea dosage may be necessary to limit the risk of hypoglycaemia.[171] However, it is not necessary to adjust metformin dosing when used in combination with exenatide.[172]

Sitagliptin, a dipeptidyl-peptidase 4 inhibitor, is currently approved for use in patients with type 2 diabetes in many countries. It may be administered with or without food. In a randomized, placebo-controlled, double-blind, 18-week trial, 530 patients with type 2 diabetes diagnosed within the past 5 years received sitagliptin 100 mg once daily or placebo.[173] In this study, despite substantial lowering of fasting and postprandial glucose in patients treated with sitagliptin, there were no reports of hypoglycaemia. In a 24-week analysis of the addition of sitagliptin to the existing therapy versus placebo therapy in patients inadequately controlled on glimepiride and metformin therapy, rates of hypoglycaemia were 12.2% with sitagliptin, compared with 1.8% for placebo.[174] However, the majority of episodes may be explained by precipitating factors such as fasting or delayed meals.

Vildagliptin, another dipeptidyl-peptidase 4 inhibitor, was well tolerated and hypoglycaemic events were rare. The incidence of hypoglycaemia was generally below 1%.[175] In a randomized, double-blind study in drug-naive patients with type 2 diabetes, the incidence of hypoglycaemic events was slightly higher in the group receiving only vildagliptin 100 mg (3.6%) than in the group receiving only vildagliptin 50 mg (1.2%) or placebo (0.6%).[176] There were no reports of severe hypoglycaemia, and no patients discontinued vildagliptin due to hypoglycaemia.

2.1.9 Pramlintide

Pramlintide, a synthetic injectable analogue of human amylin, is approved in the US for use in patients with type 1 or 2 diabetes who are using mealtime insulin or a combination of insulin and metformin and/or a sulphonylurea. It reduces postprandial glucose, and increases satiety, resulting in reduced food intake and weight loss. There is a 2-fold increase in severe hypoglycaemia in diabetic patients treated with pramlintide compared with placebo.[177] The incidence of pramlintide-induced hypoglycaemia seems to decrease as patients continue therapy.[178] Severe hypoglycaemic episodes can also occur with pramlintide-insulin combination use.

2.2 Non-Antidiabetic Agents

2.2.1 NSAIDs

Salicylates such as aspirin (acetylsalicylic acid) have hypoglycaemic properties. In the past, they have been used in relatively high doses for the treatment of diabetic patients. However, their use has been discontinued because of the toxicity associated with the large doses needed to maintain lower blood glucose levels.[179,180] In non-diabetic patients, salicylates rarely induce symptomatic hypoglycaemia.[181] In children, however, salicylate overdose can induce severe, even fatal, hypoglycaemia.[182] The majority of drug-induced hypoglycaemic episodes in 2-year-old children or younger are related to salicylate poisoning.[14] Application of topical salicylates may also lead to severe hypoglycaemia.[183] Although the exact mechanisms of salicylate-induced hypoglycaemia remain uncertain, several possible hypotheses have been postulated. Salicylates may influence glucose metabolism by reducing hepatic gluconeogenesis and increasing insulin secretion.[184] Reduced insulin clearance and enhanced plasma

insulin response have also been proposed as possible mechanisms.[185] In diabetic patients, salicylates may displace sulphonylureas from protein binding sites and inhibit their renal excretion, leading to hypoglycaemia.[186] Molecular mechanisms include a possible action of salicylates on endogenous prostaglandin E_2 production. In fact, salicylate-associated hyperinsulinaemia with reduced gluconeogenesis can be ameliorated by an infusion of prostaglandin E_2.[187]

In addition to salicylates, a few NSAIDs can rarely induce hypoglycaemia. Phenylbutazone and azapropazone may produce hypoglycaemia when concomitantly used with sulphonylureas.[109,188] Indobufen, ibuprofen, fenclofenac and nimesulide may also cause hypoglycaemia when used in patients receiving sulphonylurea therapy.[189-191] In experimental settings, indometacin and piroxicam may potentiate the effects of hypoglycaemic treatments.[192] A recent study found that a low dose of meclofenamic acid, an NSAID, excites β cells by inhibiting the adenosine triphosphate-sensitive potassium channel activity, thus increasing insulin secretion. The authors suggested that meclofenamic acid inhibits the adenosine triphosphate-sensitive potassium channel through an extracellular mechanism, which may partially explain the hypoglycaemic effect of certain NSAIDs.[193]

2.2.2 Analgesics

Paracetamol (acetaminophen) overdose can lead to symptomatic hypoglycaemia, probably because of hepatic necrosis.[194] Hypoglycaemia has also been associated with paracetamol at therapeutic analgesic doses, particularly in children.[195] There are isolated cases of hypoglycaemia in non-diabetic patients taking dextropropoxyphene alone, sometimes associated with advanced age, chronic renal insufficiency or accidental poisoning.[196,197] The combination dextropropoxyphene-paracetamol may induce hypoglycaemia in diabetic patients taking a sulphonylurea.[113] The exact mechanism of dextropropoxyphene-induced hypoglycaemia is still obscure. There is a possible potentiated effect of insulin release by dextropropoxyphene. A non-micro-receptor agonism or non-competitive *N*-methyl-D-aspartate receptor antagonism has also been suggested by some authors.[198] Two cases of hypoglycaemia related to tramadol have been reported, one in a non-diabetic 88-year-old woman and another in a diabetic 8-year-old girl.[199] An experimental study[200] suggests that the μ-opioid receptor is the principal target involved in this hypoglycaemic mechanism.

2.2.3 Antibacterials

Fluoroquinolones are a class of widely used antibacterials that act by inhibiting bacterial DNA replication and transcription, leading to rapid cell death. Although they are known to have a good safety profile, they may produce dysglycaemic disorders. Gatifloxacin has been reported to induce both hypoglycaemia and hyperglycaemia.[201] Ciprofloxacin, levofloxacin and moxifloxacin may also produce severe hypoglycaemia.[202] The mechanisms by which these agents produce hypoglycaemia are complex and still unclear, probably related to an increase in the levels of insulin. Some hypotheses suggest that there is a high affinity of fluoroquinolones for the adenosine triphosphate-sensitive potassium channels in the pancreatic β cells, leading to insulin secretion.[203] Alteration in glucose homeostasis seems to occur more frequently in patients taking oral hypoglycaemic agents and in patients with chronic renal failure.[132]

Cotrimoxazole (trimethoprim-sulfamethoxazole), another widely used antibacterial, alone or in combination with a sulphonylurea, can lead to hypoglycaemia. High doses of cotrimoxazole given alone have been reported to induce hypoglycaemia in adults with AIDS, in patients with renal failure, in the elderly and in children.[204,205] However, in standard therapeutic doses and even in association with insulin, it does not appear significantly to affect glucose homeostasis.[206] Strevel et al.[40] reported 14 cases of cotrimoxazole-induced hypoglycaemia. The authors concluded that renal insufficiency was the most prevalent predisposing risk factor for this adverse effect. In all cases, intravenous glucose administration was required, and in six cases there was protracted (>12 hours) hypoglycaemia.

Cotrimoxazole may potentiate the hypoglycaemic effect of sulphonylurea agents.[122] It has

structural similarities to sulphonylureas and enhances insulin release, therefore facilitating the occurrence of hypoglycaemia in susceptible individuals.[207,208] Sulphonamides are also inhibitors of CYP2C9, by which many of the sulphonylureas are metabolized, such as tolbutamide. Trimethoprim alone may cause interactions mediated via inhibition of CYP2C9 and CYP2C8. It raised the plasma concentrations of repaglinide probably by inhibiting its CYP2C8-mediated biotransformation.[209] The possibility of an increased risk of hypoglycaemia should be considered during concomitant use of trimethoprim and repaglinide in diabetic patients.[209] Sulphonamides may also displace the sulphonylureas from their protein binding sites.[210] Caution should be observed when cotrimoxazole is added to the regimen of patients receiving sulphonylureas. Tetracycline may induce hypoglycaemia by reducing the need for insulin or by inducing hepatorenal failure.[211,212] Doxycycline has also been associated with hypoglycaemia.[41]

2.2.4 Antimalarials

Hypoglycaemia can occur in patients with falciparum malaria, either spontaneously or during treatment with antimalarial drugs.[213] It is a frequent complication encountered in falciparum malaria and is often associated with a poor prognosis. Typical symptoms of hypoglycaemia may not be clinically evident in comatose patients and may be missed if regular monitoring of blood glucose is not performed. In fact, coma may be attributed wrongly to cerebral malaria rather than to antimalarial-induced hypoglycaemia.[214] The latter has been reported with quinine, mefloquine, sulfadoxine-pyrimethamine, and hydroxychloroquine.[50,215,216] However, it is mainly reported with quinine therapy and seems to be dose-dependent. In pregnancy, hypoglycaemia may be particularly amplified, severe and difficult to manage. Severe hypoglycaemia occurs in 50% of pregnant women with severe malaria treated with quinine.[217] Children, the malnourished and patients with renal failure appear also to be particularly at risk. Hypoglycaemia induced by quinine may also occur in persons not infected with malaria. It has been reported occasionally following the use of oral quinine for leg cramps.[218] Similarly, hydroxychloroquine, in addition to its use as an antimalarial drug, has become one of the most commonly prescribed drugs in the treatment of many rheumatic diseases such as rheumatoid arthritis and systemic lupus erythematosus. In a prospective, multicentre, observational study involving 4905 patients with rheumatoid arthritis, Wasko et al.[219] reported that the use of hydroxychloroquine was associated with a reduced risk of diabetes. Hydroxychloroquine may induce hypoglycaemia in both diabetic and non-diabetic patients with rheumatoid arthritis.[46,220]

Antimalarial drugs can stimulate insulin release from the pancreas, probably through the activation of voltage-sensitive calcium channels by inhibition of potassium conductance.[216,222,223] In addition to the enhanced insulin release by antimalarial drugs, a marked glucose uptake by parasitized red cells can lead to severe hypoglycaemia in treated patients with falciparum malaria.

Octreotide, a somatostatin analogue, is considered to be effective in the treatment of profound hypoglycaemia induced by quinine.[223] It inhibits insulin release and reduces the need for large volumes of intravenous dextrose.

2.2.5 Pentamidine

Hypoglycaemia is a common metabolic abnormality associated with the use of pentamidine. It is sudden, often recurrent, and may be fatal.[224] It can occur within a few hours to days after the commencement of pentamidine therapy. Risk factors for pentamidine-induced hypoglycaemia include longer treatment duration, high dosage, impaired renal function, and severe clinical condition with shock and anoxia.[225] The overall incidence of pentamidine-associated hypoglycaemia with AIDS is several-fold higher than previously reported for patients without AIDS.[226] Pentamidine produces a multiphasic effect on blood glucose levels. It may be toxic to the β cells, inducing early cytolytic release of insulin leading to β cell destruction seen in an experimental setting.[227] The release of insulin can lead to severe hypoglycaemia followed by persistent hyperglycaemia secondary to the destruction of islet cells. As pancreatic destruction progresses, patients may become diabetic. Diabetes induced by pentamidine

may persist despite withdrawal of the drug, and may require insulin therapy. In these diabetic patients, plasma C-peptide levels were lower than normal values, and the β-cell secretory responses to stimuli were poor. Islet cell antibodies and insulin antibodies were also not detected.[224,228] Pentamidine isethionate seems to be less toxic to islet cells than pentamidine mesylate.[229] However, because of toxicity and the availability of alternative agents, pentamidine is now used infrequently.

2.2.6 β-Adrenergic Receptor Antagonists (β-Blockers)

β-Blockers have been reported to cause severe hypoglycaemia in diabetic patients.[230,231] Although administration of selective β-blockers may be associated with hypoglycaemia, they are probably safer than nonselective agents.[232] Nonselective β-blockers are associated with an increased risk of insulin resistance, increased levels of serum triglyceride and glucose, and decreased high-density lipoprotein cholesterol levels.[233] A number of studies in diabetic patients found no statistically significant increase in the risk of hypoglycaemia in patients with diabetes receiving insulin or sulphonylureas and also taking either cardioselective β-blockers or non-selective β-blockers.[235]

Overall, and despite the lack of conclusive evidence regarding their possible association with hypoglycaemia, if diabetic patients need treatment with a β-blocker, a selective agent should always be chosen.

Propranolol-induced hypoglycaemia has also been observed in non-diabetic patients with renal disease, poor nutrition or liver disease.[235] Prolonged fasting or severe exercise are serious risk factors for hypoglycaemia due to β-blockers.[24,236] In infants, hypoglycaemia has been observed with propranolol or nadolol during treatment of cyanotic heart disease or thyrotoxicosis.[237] Hypoglycaemia may also occur in neonates from women taking β-blockers for cardiac arrhythmias, hypertension or thyrotoxicosis.[238] Treatment with β-blockers seems to be also associated with delayed recovery from hypoglycaemia and elevation of the glycaemic threshold (lower plasma glucose levels required for symptoms) in patients with diabetes, probably by blocking the sympathetic β-stimulation and the mobilization of glucose from the liver.[233] However, other studies have shown no increase in the severity or incidence of hypoglycaemic events.[239] The retained sympathetic activity and the ability to suppress endogenous insulin production are seen in patients with type 2 diabetes.[232]

The mechanism of β-blocker-induced hypoglycaemia is multifactorial. It involves enhanced insulin action with a resultant increase in peripheral glucose uptake by muscles, inhibition of hepatic glucose production, and inhibition of lipolysis.[240]

β-Blockers may also be associated with the development of hyperglycaemia.[241] The use of β-blockers appears to increase the risk of diabetes, but the proven benefits of β-blockers in reducing the risk of cardiovascular events generally outweigh the risk.[242]

2.2.7 Antiarrhythmics

Disopyramide, a quinidine-like agent, is used as an antiarrhythmic drug for treatment of ventricular and supraventricular rhythm disturbances. It has been mainly reported to cause severe hypoglycaemia at high concentrations.[243] However, it can induce hypoglycaemia even at therapeutic concentrations.[28] It is one of the most common causes of non-antidiabetic drug-induced hypoglycaemia. Older age, impaired renal function and hepatic disease are considered as risk factors for disopyramide-induced hypoglycaemia.[243,244] Furthermore, other factors such as anorexia and low bodyweight also increase the risk of hypoglycaemia.[245] The risk of hypoglycaemia is greater when disopyramide is used in combination with glimepiride, insulin and certain antibacterials.[249,250] Disopyramide has been found to inhibit β-cell adenosine triphosphate-sensitive potassium channels.[247] It stimulates insulin secretion leading to hyperinsulinaemic hypoglycaemia. Quinidine (diastereoisomer of quinine), a type Ia antiarrhythmic drug, may induce hypoglycaemia. It may increase plasma insulin concentrations.[248] It is more likely to cause hypoglycaemia, particularly in children, pregnant women and in individuals with renal failure. Cibenzoline, another antiarrhythmic drug, may also lead to hypoglycaemia at toxic plasma concentrations.[249] Renal impairment presents a serious risk

factor, as cibenzoline's half-life is prolonged in this situation.[250]

2.2.8 ACE Inhibitors

The association between ACE inhibitors (ACEIs) and the occurrence of hypoglycaemia remains controversial. In fact, a nested case-control study revealed that both among users of insulin and among users of oral antidiabetic drugs, the use of ACEIs was significantly associated with an increased risk of hospital admission for hypoglycaemia.[129] Isolated cases of severe hypoglycaemia in non-diabetic patients associated with both captopril and ramipril therapy have also been reported.[251] In another study, the use of these drugs in diabetic patients has been associated with a 3- to 4-fold increase in the risk of hypoglycaemia.[252] However, other studies did not confirm this finding.[253,254] The EUCLID study showed also that there was no difference in hypoglycaemic events or in glycaemic control in diabetic patients between lisinopril and placebo groups at any time during the study.[255]

The mechanisms of hypoglycaemia and improvement of glucose tolerance during ACEI therapy are complex and have not been clearly elucidated. Some authors have reported that ACEI therapy may be associated with an improvement of blood flow and microcirculation in skeletal muscles. ACEIs may improve insulin sensitivity.[259] In addition, enhancement of insulin and glucose delivery to the insulin-sensitive tissues may facilitate insulin signalling at the cellular level and improvement of insulin secretion by the β cells.[257] However, other authors failed to show any effect of ACEIs on glucose metabolism.[258,259] Furthermore, high natural ACE activity has been associated with a higher risk of severe hypoglycaemia.[260]

2.2.9 Fibrates

Fibrates are widely used in the treatment of hyperlipidaemia. They are mainly efficacious in lowering serum triglyceride levels and raising levels of high-density lipoprotein cholesterol. They activate the peroxisome proliferator activated receptor-α and stimulate a large panel of genes controlling the β-oxidation and catabolism of fatty acids. Although fibrates are known to be generally safe, they may induce hypoglycaemia. This adverse effect occurs more frequently in diabetic patients treated with sulphonylureas. Fibrates are highly bound to albumin: they displace the sulphonylureas from their plasma protein binding sites, improving their hypoglycaemic effects.[115] Gemfibrozil seems to inhibit the CYP2C8 and CYP3A4 and thus inhibits the metabolism of repaglinide.[261] Moreover, the blockade of the CYP2C8-mediated metabolism of rosiglitazone and pioglitazone by gemfibrozil may induce hypoglycaemia as well as the inhibition of the CYP2C9-mediated metabolism of glimepiride and other sulphonylureas.[115,262,263] Clofibrate may decrease glucose serum levels independent of any concomitant use of antidiabetic medication.[264]

The concurrent use of sulphonylureas and fibrates requires frequent adjustment of the dosage of the antidiabetic medications.

2.2.10 Antidepressants

Antidepressants have been reported to be associated with both hyperglycaemia and hypoglycaemia. However, the association with hypoglycaemia seems to be pronounced for antidepressants with affinity for the serotonin reuptake transporter.[67,265] In fact, serotonergic antidepressants such as fluoxetine reduce hyperglycaemia, normalize glucose homeostasis and increase insulin sensitivity.[266] Sertraline has also been associated with hypoglycaemia.[67] Venlafaxine overdose can also lead to severe hypoglycaemia.[267] Monoamine oxidase inhibitors have been reported to induce hypoglycaemia in a very few reports when used in large doses.[268] These drugs may stimulate insulin release.[269] The hydrazine group in these drugs seems to be incriminated in the genesis of hypoglycaemia. Tricyclic antidepressant drugs such as imipramine, nortriptyline, maprotiline and doxepin can induce hypoglycaemia in both diabetic and non-diabetic patients.[139,270,271] Nefazodone may also lead to hypoglycaemia, especially in diabetic patients.[272]

2.2.11 Miscellaneous Agents

In addition to the drugs listed in table III, many miscellaneous agents may also induce hypogly-

Table III. Miscellaneous drugs inducing hypoglycaemia and their suggested mechanism

Drug	Clinical setting	Suggested mechanism	References
Dexmedetomidine	Overdose in a child with patent ductus arteriosus	Unknown	63
Etanercept	Diabetic patient with rheumatoid arthritis	Increase of insulin sensitivity	273
Etomidate	Chronic right ventricular failure and recurrent atrial tachyarrhythmias. Hypoglycaemia may be severe	Long-term use of etomidate has been associated with adrenal suppression	65
Erlotinib	Patient with non-small-cell lung cancer	Unknown	274
Gabapentin	Patient with end-stage renal disease	Hyperinsulinaemia	58
Haloperidol	Patient with chronic lymphocytic leukaemia. Hypoglycaemia may be severe	Increase of insulin secretion	66
Halothane	Regular dose in a child with malignant hyperthermia. Hypoglycaemia may be severe	Liver toxicity	275
Imatinib	Patient with gastrointestinal stromal tumour	Inappropriate insulin secretion	276
Isoniazid	Premature infant	Hyperinsulinaemia	43
Levothyroxine	Liver impairment	Unknown	277
Lidocaine (lignocaine)	Overdose. Transient hypoglycaemia	Unknown	278
Lithium	Neonate whose mother had taken lithium throughout pregnancy	Enhanced insulin action	279,280
Mercaptopurine	Acute leukaemia in children. Hypoglycaemia may be severe	Decrease in hepatic glycogen stores. Altered hepatic glycogenesis	281
Phenytoin	Overdose in patient with status epilepticus	Increase in insulin secretion. Enhancement of sensitivity of the tissues to insulin	59
Ritodrine	Neonates born from mothers who have received this drug. Hypoglycaemia may be severe	Increase of insulin secretion by β-adrenergic stimulation	282
Salbutamol	Neonates born from mothers taking salbutamol therapy for premature labour. Overdose in children. Hypoglycaemia may be severe	Increase of insulin secretion by β-adrenergic stimulation	283,284
Selegiline	Patient with Parkinson's disease. Hypoglycaemia may be severe	Unknown	285
Varenicline	Smoking cessation. Hypoglycaemia may be severe	Improvement of insulin sensitivity. Interference with hypoglycaemia awareness	286

caemia[273-286] (table III). These drugs may induce hypoglycaemia in their own right, i.e. not only when combined with a drug used for the treatment of diabetes, and those that work only by exacerbating the hypoglycaemic potential of antidiabetic drugs.

3. Prevention and Management

It is preferable to prevent rather than to treat drug-induced hypoglycaemia. One of the most important ways to prevent hypoglycaemia is to educate the patient. Thomson et al.[287] showed that 88% of patients taking oral antidiabetic drugs and 32% of insulin-treated patients denied any knowledge of hypoglycaemia. Teaching patients how to recognize, treat and prevent hypoglycaemia is essential. Furthermore, patients should be educated about hypoglycaemia risk factors. Information regarding onset and duration of action or times to peak effect of oral anti-diabetic agents or insulin preparations should also be provided to diabetic patients in a comprehensible manner. The choice of an insulin regimen that does not peak during sleep is mandatory for the prevention of nocturnal hypoglycaemia. If physical activity can be anticipated, insulin should be lowered in advance. Furthermore, in order to prevent severe hypoglycaemic episodes, it is prudent to switch patients taking long-acting sulphonylureas who develop recurrent hypoglycaemic

episodes to short-acting sulphonylureas. Despite patient education, hypoglycaemic episodes are sometimes difficult for patients to discriminate from other feelings of malaise. Every treated diabetic patient who develops a neurological or psychiatric disorder or coma has to be considered to be hypoglycaemic until proven otherwise. Ingestion of glucose tablets or carbohydrate in the form of juice, a soft drink, milk, crackers or a meal will always give rapid relief of symptoms if the diagnosis is hypoglycaemia. For the treatment of mild to moderate hypoglycaemia, 15–25 g of carbohydrate is usually needed;[288,289] 5 g of carbohydrate will increase the plasma glucose concentration by about 15 mg/dL. This should be repeated in 15–20 minutes if symptoms have not improved or the monitored blood glucose remains low.

Intravenous administration of glucose (25 g) is the preferred treatment for severe hypoglycaemia and when neuroglycopenic symptoms limit carbohydrate consumption. Parenteral glucagon (1 mg subcutaneously) may be an alternative, especially in patients with type 1 diabetes who may have to be treated by family members for severe hypoglycaemia.[289]

The removal or adjustment of the doses of the offending drug is mandatory. Confrontation and psychiatric referral may be necessary for patients with a factitious hypoglycaemia. In the case of sulphonylurea-induced hypoglycaemia, and if intravenous glucose replacement is insufficient, octreotide is recommended. Diazoxide may also be used.[290] It has been proposed as a treatment option in cotrimoxazole-induced prolonged hypoglycaemia. Patients with sulphonylurea-induced hypoglycaemia should not be given glucagon, since it will stimulate insulin secretion. Continued observation and frequent food intake are often required because recurrence after temporary recovery is common. Octreotide may also minimize the number and severity of hypoglycaemic events associated with massive nateglinide overdose.[291]

4. Conclusions

Drugs are the most frequent cause of hypoglycaemia in adults. In addition to antidiabetic agents, many other drugs have the potential to cause hypoglycaemia. Drug-induced hypoglycaemia can be severe and may cause significant morbidity. However, this adverse effect can be prevented and/or minimized with awareness of the problem and the judicious use and close monitoring of the suspect drug(s).

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