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Management of Antidiabetic Medications in Overdose

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Contents

Abstract

The drugs used to treat diabetes mellitus are diverse and involve several classes. However, these drugs can be roughly separated into hypoglycaemic agents, such as insulin and the sulphonylureas, and antihyperglycaemic agents, such as the biguanides, the α-glucosidase inhibitors and troglitazone.

Reports of insulin overdose are rare. The major effects of insulin overdose are secondary to the insult to the CNS produced by hypoglycaemia. The mainstay of insulin overdose management is glucose replacement therapy. Sulphonylureas are the most commonly used oral antihyperglycaemic agents in the management of type 2 (non–insulin-dependent; NIDDM) diabetes mellitus. Sulphonylureas primarily cause serum glucose reduction by stimulating the release of preformed insulin from the pancreatic islets. The mainstay of sulphonylurea overdose management is glucose replacement therapy, and in severe cases, reduction of insulin release. In the large majority of patients intravenous glucose supplementation will be sufficient to maintain euglycaemia.

Repaglinide, a meglitinide analogue, is a new nonsulphonylurea oral hypoglycaemic agent. In overdose, this drug may produce prolonged hypoglycaemia similar to the sulphonylureas.

The primary problem with biguanide overdose is the potential for lactic acidosis. The management of biguanide overdose is largely supportive and directed at correcting the metabolic acidosis along with associated complications.

The α-glucosidase inhibitors, acarbose, voglibose and miglitol competitively and reversibly inhibit the α-glucosidase enzymes (glucoamylase, sucrase, maltase and isomaltase) in the brush border in the small intestine, which delays the hydrolysis of complex carbohydrates. They appear unlikely to produce hypoglycaemia in overdose, but abdominal discomfort and diarrhoea may occur.

Troglitazone is the first thiazolidinedione antidiabetic drug available. There are no data on overdose, probably because of its very recent introduction.

Overdoses with antidiabetic drugs produce major morbidity, with many cases requiring intensive care medicine and prolonged hospital stays. However, fatalities are rare when treatment is initiated early. The management of the hypoglycaemic drugs (insulin and sulphonylureas) is based primarily on restoring and maintaining euglycaemia via intravenous dextrose supplementation. In the case of the sulphonylureas, reduction of insulin secretion via pharmacological intervention may also be necessary. With biguanides the main risk appears to be cardiovascular collapse secondary to profound acidosis. The management focus is on restoring acid-base balance with hyperventilation and the use of insulin to shift the utilisation of glucose from the nonoxidative pathway to the oxidative pathway. Use of haemodialysis has shown equivocal results but may be valuable in metformin overdose.

Diabetes mellitus is generally divided into 2 varieties: type 1 (insulin-dependent; IDDM), caused by an autoimmune destruction of pancreatic β cells, and type 2 (non–insulin-dependent; NIDDM), a disorder characterised by both impaired insulin secretion and insulin resistance. A primary feature of both types of diabetes mellitus is the marked loss of glycaemic control.

The prevalence of diabetes mellitus is believed to be about 5 to 6% of the population but may vary according to ethnic grouping.[1-3] In general, approximately 15% of patients with diabetes mellitus will have the type 1 variety.[4] Approximately 80% of patients will have the type 2 variety and about 5% who appear to have type 2 may actually have a slowly progressive form of type 1.[5]

The drugs used to treat diabetes mellitus are diverse and involve several classes. However, these drugs can be roughly separated into hypoglycaemic agents, such as insulin and the sulphonylureas, and antihyperglycaemic agents, such as the biguanides, the α-glucosidase inhibitors and troglitazone. The effects seen in overdose with these agents tend to be secondary to either hypoglycaemia or lactic acidosis. The risk of severe outcome from these overdoses is somewhat effected by the presence or absence of diabetes mellitus itself. Persons without diabetes mellitus tend to be at greater risk of severe outcome with insulin and sulphonylurea overdose, while those with diabetes mellitus tend to be at greater risk for severe outcome with biguanide overdose.[6-8] This review focuses on the effects seen after overdoses of these antidiabetic drugs and provides practical treatment recommendations for the management of these overdoses. The adverse effects associated with long term therapy and idiosyncratic events will not be covered.

1. Why Do Overdoses Occur?

In general, overdoses of antidiabetic drugs fall into 2 categories: intentional and accidental.

Intentional overdose may occur for: malicious reasons in cases of homicide;[9] recreational reasons in an attempt to 'get high';[10] or in a suicide

attempt.[11] Depression, a known risk factor for suicide, is higher in the population of people with diabetes than the general population.[12] In adolescents, surreptitious insulin overdose may occur for manipulative reasons.[12,13] In some cases, it may not be until after strong clinical evidence and direct confrontation by the physician that the patient will admit to a suicide attempt.[14] Clinicians need to be aware of the possibility of suicide intent in cases of unexplained hypoglycaemia and treat, if present, the concomitant psychiatric illnesses in those patients with diabetes mellitus.[12]

Accidental ingestions of oral hypoglycaemics occur commonly in children and any unexplained hypoglycaemia in a child should arouse the suspicion of accidental sulphonylurea ingestion.[15,16] A second reason for accidental ingestion may be drug dispensing errors. Several reports have been published of the inadvertent dispensing of sulphonylureas and the subsequent hypoglycaemia in the unsuspecting patient.[17,18] And finally, while not necessarily an overdose, drug interactions with the antidiabetic drugs may cause profound hypoglycaemia and may need to be part of the investigation in any hypoglycaemic patient.[19] In 1 compilation of 1418 patient reports of drug-induced hypoglycaemia, sulphonylureas were responsible for 70% of these cases, but insulin and the biguanides were also responsible for a number of cases.[19]

2. Insulin

Episodes of insulin-induced hypoglycaemia are a common occurrence in the population of those with type 1 diabetes mellitus, with an estimated incidence at 9 to 26%.[20-22] However, reports of insulin overdose are rare, with less than 100 total cases published in the literature since insulin was first introduced more than 70 years ago.[14,23] There is a belief that the number of published cases represents only a small portion of a much larger incidence of insulin overdose.[12-14,23] In most published cases, insulin overdose has occurred because of recreational, suicidal or homicidal reasons.[6,7,9,13,23,24] Onset of hypoglycaemia for unexplained reasons should increase the suspicion of a possible insulin overdose, with possible suicidal or malicious intent.[9,12,14]

The primary difference between insulin-induced hypoglycaemia caused by therapeutic misadventures, missed meals or drug interactions, and insulin overdose–induced hypoglycaemia, is the much larger doses of insulin used in latter. In insulin overdose, the demand for glucose is significantly greater and more prolonged.[6,14,23,25] Because of this increased demand Roberge et al.[14] suggest that initial poor response to intravenous and oral glucose during a hypoglycaemic event should raise the suspicion of an insulin or sulphonylurea overdose. People without diabetes mellitus are more likely than people with diabetes mellitus to present with decreased blood sugar and develop recurrent hypoglycaemia after insulin overdose.[6,7] This may be because of a lack of insulin antibodies and insulin resistance in the individual without diabetes mellitus.

Acute insulin overdose results in hypoglycaemia and subsequent seizures and coma. Severity of intoxication should be based on clinical findings rather than the speculated amount injected.

2.1 Pharmacokinetics

Endogenous insulin synthesis occurs in the β-cells of the pancreas with the manufacture of proinsulin. Proteolytic cleavage of the proinsulin results in the formation of insulin and the connecting peptide (C-peptide), which is metabolically inactive. Under normal conditions, equal amounts of insulin and C-peptide are secreted by the β-cells. This is occasionally used as a diagnostic clue because injection of exogenous insulin contains no C-peptide and will result in elevated insulin levels with normal or depressed C-peptide levels.[9] Insulin facilitates the penetration of glucose and amino acids through cell membranes of skeletal and heart muscle, as well as increases glucose utilisation via lipid and glycogen catabolism. The action of insulin is mediated by a membrane-bound receptor, so that the pharmacological effect of the different in-

sulins, once bound to the receptor, is identical. Insulin is not absorbed from the gastrointestinal tract.

Commercial insulin preparations differ in onset, peak and duration of effect after subcutaneous injection (table I). Generally, onset of action in overdose of the various insulins may not vary from those described in therapeutic use, but duration of action may be more prolonged. Large injections of insulin may produce a prolonged action due to the 'depot' effect, with the slow release of insulin from the injection site.[6,23] This may produce a need for external glucose supplementation for 24 to 96 hours.[14,25-27] The hypoglycaemic affect of insulin may be increased by monoamine oxidase inhibitors, alcohol (ethanol), β-blockers, salicylates, fenfluramine, clofibrate and tetracyclines. Hepatic or renal impairment may prolong the half-life of insulin and subsequently prolong any potential hypoglycaemic effects.

2.2 Overdose

The major effects of insulin overdose are secondary to the insult to the CNS produced by hypoglycaemia (table II). In some cases, if presentation to the diagnostician or emergency room is early, the patient may appear with no initial neurological deficits.[14,27] The level of consciousness may deteriorate to lethargy or coma with seizures.[23] Hypoglycaemic coma may mimic coma secondary to other aetiologies such as head trauma, cerebrovascular accident or ingestion of other drugs. In severe cases, the patient may present with status epilepticus.[23] If the hypoglycaemia has been prolonged there may be cerebral oedema.[28] Pupils may show no reaction to light or may be dilated. The initial cardiovascular response to hypoglycaemia is tachycardia and, in some cases, palpitations. However prolonged hypoglycaemia may lead to bradycardia and cardiovascular collapse. Hypokalaemia has been reported,[6,23] but this is most likely because of a shift of potassium from the extracellular compartment to the intracellular compartment, rather than detection of a true potassium deficit.[29] Cases of insulin-induced neurological sequelae have usually been associated with cases of delayed recognition of the overdose and subsequent prolonged periods of hypoglycaemia without treatment.[23]

2.3 Overdose Management

The mainstay of the management of insulin overdose is glucose replacement therapy and correction of hypokalaemia. The onset of hypoglycaemia in insulin overdose will depend on the type of insulin injected, but will generally be within 12 hours of injection.[23] This is in contrast to onset of hypoglycaemia from therapeutic misadventures which may be up to 18 hours post injection.[21] This is due mainly to the larger amounts of insulin injected in the overdose situation.

The duration of hypoglycaemia appears to be related to the amount and type of insulin used in the overdose. Initial management should include an intravenous bolus of 50% dextrose in water

Table I. Pharmacokinetics of various insulins under therapeutic circumstances

Insulin preparations	Onset of effect (h)	Peak of effect (h)	Duration of effect (h)
Rapid-acting			
Insulin injection (regular)	0.5-1		8-12
Prompt insulin zinc suspension (semilente)	1-1.5	5-10	12-16
Insulin lispro® insulin solution	0.25	0.5-1.5	6-8
Intermediate			
Isophane insulin (neutral protamine human) suspension	1-1.5	4-12	24
Insulin zinc suspension (lente)	1-2.5	7-15	24
Long-acting			
Protamine zinc insulin suspension	4-8	14-24	36
Extended insulin zinc suspension (ultralente)	4-8	10-30	>36

(D50W) solution. Following this should be a continuous infusion of 10 or 20% dextrose, titrated to blood glucose levels in the euglycaemic range. It is estimated that maximum glucose requirement may vary according to the patient but that 375 to 600 mg/kg/h should compensate for maximal hypoglycaemia.[14] In severe cases, this may require infusions of dextrose concentrations of 20% or greater, with occasional boluses of 50% dextrose in water to reduce the risk of fluid overload. For example, a 75kg patient might potentially require 10.8 litres of 10% dextrose infusion over 24 hours to maintain euglycaemia. Continuous infusion of high concentration dextrose (>10%) should be managed through a central line. In addition, oral intake of high glucose foods provides another route of glucose supply that may decrease the fluid volume demand in these cases. In some cases, dextrose infusions may be tapered off as oral intake is added to the regimen. Finally, oral alimentation will be needed to for hepatic glycogen store repletion.

Duration of therapy will vary according to the patient and the amount and type of insulin injected. Cessation of therapy should be followed by at least 2 successive blood glucose levels greater than 5.6 mmol/L (100 mg/dl) over an 8-hour period. Use of glucagon (1mg intramuscular) should probably only be considered in the rare circumstance that intravenous access or dextrose are unavailable. Glucagon requires adequate hepatic glycogen stores, which are likely to be quickly exhausted in the insulin overdose patient.

Electrolytes should be measured, especially potassium, magnesium and phosphorous. Potassium replacement should be guided by repeat serum potassium levels.[14] Arem and Zoghbi[23] reported the need for 300 mmol of KCl over 4 days in 1 patient to maintain a normal serum potassium level. However, potassium imbalances have generally not produced a clinical problem if managed appropriately. In 1 group of 10 insulin overdose patients with serum potassium below 3.5 mmol/L, none became symptomatic from hypokalaemia and all responded to oral or parenteral potassium.[6]

Table II. Effects of hypoglycaemia

Mild
Diaphoresis, light-headedness, dizziness, agitation or confusion, tachycardia, palpitations
Moderate
Obtundation, coma, hypokalaemia, single discrete seizures, hemiparesis
Severe
Status epilepticus, cerebral oedema, hypotension, ventricular tachycardia, cardiovascular collapse, metabolic acidosis

Surgical excision of the injection site has been suggested in some instances.[24,30,31] Since the majority of these cases are managed safely with simple dextrose infusion, this procedure may not be necessary.[6] However, surgical excision may significantly reduce the need for a prolonged intensive care stay. This procedure should be considered if the injection is recent (less than 2 to 3 hours), massive and of a long acting insulin.[3,14]

3. Sulphonylureas

Sulphonylureas are the most commonly used oral antidiabetic agents in the management of type 2 diabetes mellitus.[32,33] Not surprisingly, they are also the most commonly encountered oral antidiabetic drug overdose, with more than 3000 overdoses reported to poison centres in the US annually.[15] Sulphonylureas were discovered accidentally in 1942 by Janbon and colleagues,[34] while investigating the antibacterial activity of sulphonamide compounds. Subsequent work led to the development of the sulphonylurea class of drugs. Carbutamide and tolbutamide were the first 2 sulphonylureas produced, of which tolbutamide was the first widely used member.

Sulphonylureas are divided into 2 classes or generations, with the first generation containing tolbutamide, chlorpropamide, acetohexamide, and tolazamide and the second generation including glibenclamide (glyburide), glipizide, glimepiride and gliclazide. Of the available drugs, glibenclamide, chlorpropamide and glipizide are the most widely used, with more than 75% of the market.[32,33] The second generation sulphonylureas

Table III. Onset and duration of effects of sulphonylureas[a]

Drug	Available dose (all as tablets) [mg]	Time to maximal effect (h)	Half-life (h)	Duration of therapeutic effect (h)	Comments
Acetohexamide	250, 500	3		12-18	Active metabolite hydroxyhexamide[b]
Chlorpropamide	100, 250	2-7	24-48	Up to 72	20% cleared by kidneys as parent drug[b]
Tolazamide	100, 250, 500	4-6	4-8	16-24	
Tolbutamide	250, 500	3-4	3-28	6-10	
Glipizide	5, 10	1-3	7	16-24	
Glipizide/extended release	5, 10	6-12	7[c]	24	
Glibenclamide (glyburide)	1.25, 2.5, 5	4	10	24	Active metabolite 4-hydroxyglyburide[b]
Micronised glibenclamide	1.5 and 3	3-4	4	24	Active metabolite 4-hydroxyglyburide[b]
Glimepiride	1, 2, 4	2-3	5-9.2	24	

a Based on therapeutic dosage situations.

b Renal impairment will prolong half-life and duration of effect.

c Will be altered by kinetics of long absorption period.

are significantly more potent on an equimolar basis, but all are believed to have a similar mechanism of action, based on a sulphonlyurea receptor on the β-cells of the pancreatic islets.[35,36]

Sulphonylureas primarily cause serum glucose reduction by stimulating the release of preformed insulin from the pancreatic islets. In a manner similar to glucose, sulphonylureas reduce conductance to the adenosine triphosphate (ATP)–sensitive potassium channel on the β-cells of the pancreatic islets.[35,36] This action, in turn, causes calcium influx, intracellular kinase activation and release of preformed insulin from secretory granules.[37] There have been suggestions of extra-pancreatic effects of sulphonylureas but these do not play a role in the overdose patient. The clinical effects seen in overdose are the result of subsequent hyperinsulinaemia and hypoglycaemia.

3.1 Pharmacokinetics

Sulphonylureas are readily absorbed from the gastrointestinal tract with the exception of tolazamide, which is absorbed somewhat more slowly. Oral bioavailability is complete for all sulphonylureas.[38] The 2 key parameters in sulphonylurea overdose management and patient disposition decisions are onset and duration of effect (table III). Peak plasma levels occur within a range of 1 to 8 hours of ingestion and there is good evidence that acute response is related to dose or blood concentration of the drug.[38]

The onset of hypoglycaemia in acute overdose occurs in less than 8 hours.[16,39] In accidental chronic misdosing due to therapeutic error or cases of build up of active metabolites due to renal failure, onset of symptomatic hypoglycaemia may be delayed for several days.[40,41]

There is extensive hepatic biotransformation of the sulphonylureas; those with active metabolites are glibenclamide and acetohexamide. Both active metabolites, hydroxyglyburide and hydroxyhexamide are renally cleared and renal impairment has caused incidents of prolonged hypoglycaemia.[41] Acetohexamide is different from the other sulphonylureas in that the parent drug is inactive and requires bioactivation by the liver to hydroxyhexamide.

The duration of action of the sulphonylureas is generally of greater clinical importance than the individual half-lives in the overdose patient. The supra-therapeutic doses taken by the acute overdose patient may prolong the duration of effect, but the onset will remain the same. The long elimination half-life of chlorpropamide and the partial re-

nal excretion of the active parent drug may explain its propensity to produce prolonged hypoglycaemia. Additionally glibenclamide, despite a reported short half-life in acute studies, may put patients at risk for prolonged hypoglycaemia due to prolonged and continued uptake by the pancreatic islets.[38]

3.2 Overdose

The cascade of symptoms from sulphonylurea overdose reflect the patient's hypoglycaemic state. It should be noted that, because clinical evidence of hypoglycaemia may not occur in individuals without diabetes mellitus until blood glucose drops below 2.3 mmol/L (40 mg/dl) the patient may initially seem asymptomatic, with only laboratory evidence of hypoglycaemia. However, a rapid fall in blood glucose may produce symptoms (table II), regardless of the initial or subsequent blood glucose level. An infant or small child may be difficult to feed. Nausea, vomiting and abdominal pain may also occur. This may be followed by increasing CNS depression, seizures and coma if the patient's blood glucose continues to fall. Most other effects reflect persistent hypoglycaemia and may include hemiparesis, permanent neurological sequela, hypotension, metabolic acidosis and cardiovascular collapse.[42,43]

For the most part, serious adverse outcomes have been rare. Two recent large studies described 278 sulphonylurea ingestions in children with the only significant findings being the laboratory changes of low blood glucose and transient CNS depression.[16,44] This lack of serious outcome may have been due to the small amounts usually ingested by children as well as early assessment and treatment. By contrast, in 2 studies of 101 mainly intentional adult sulphonylurea overdoses, 5 deaths and 5 cases of severe permanent neurological impairment occurred.[10,45] Cases of sulphonylurea-induced neurological sequelae have usually been associated with cases of delayed recognition of the ingestion (12 to 48 hours) and subsequent prolonged periods of hypoglycaemia without treatment.[42,43,46-49]

3.3 Overdose Management

The mainstay of sulphonylurea overdose management is glucose replacement therapy and, in severe cases, reduction of insulin release. Activated charcoal would be expected to bind all sulphonylureas and is recommended in the large overdoses usually seen with suicide attempts. A 50 to 100g dose is recommended and is most effective if administered within 1 hour of the overdose.[50] The value of activated charcoal in the unintentional paediatric patient, who has typically ingested 1 or 2 tablets, has not been established. Emesis is not recommended because of the risk of subsequent CNS depression.

For patients with acute overdose, direct clinical observation with repetitive blood glucose measurements every 1 to 2 hours during the first 8 hours post-ingestion is recommended.[16] During this period the patient should have free access to food. If the blood glucose remains above 3.4 mmol/L (60 mg/dl) during this period, a benign outcome is expected. If the blood glucose falls below 3.4 mmol/L the patient should be admitted for continued observation and medical management. Once hypoglycaemia has been established in a sulphonylurea overdose patient, they should be medically monitored for at least 24 hours due to the potential for a prolonged duration of hypoglycaemic effect. Several studies have found poor correlation between the history of dose ingested and the severity of the clinical course.[10,16] The patient history of the dose ingested should not be used to guide management decisions.

In the large majority of cases intravenous glucose supplementation will be sufficient to maintain euglycaemia.[10,16,44] Occasional boluses of D25W or D50W may be necessary. In the cases refractory to glucose supplementation, it may be necessary to reduce insulin secretion.[10,39,51,52] Octreotide, a long acting somatostatin analogue, is capable of inhibiting glucose-stimulated β cell insulin release.[53] In a study of patients in simulated glipizide overdose by Boyle et al.,[39] octreotide was shown to be superior to glucose alone or diazoxide in maintaining euglycaemia. In this study, 8 pa-

tients acting as their own controls received 1.45 mg/kg of glipizide, with a 2-week washout period between arms of the study. In 4 of the 8 of the patients octreotide completely eliminated the need for external glucose supplementation and in all 8 patients external dextrose demand was significantly less than in the diazoxide or dextrose study arms. Octreotide can be given subcutaneously or intravenously at 50μg for adults and 1 μg/kg in children. If necessary, it can be repeated every 12 hours.

An alternative therapy would be diazoxide, which will reduce calcium influx into the β-cells and thereby reduce insulin secretion.[10,52] However, use of diazoxide is not universally recommended.[3] The suggested dosing of diazoxide is 300mg intravenously slowly over 1 hour for adults or 1 to 3 mg/kg in children.

For reasons similar to those of insulin overdose, glucagon should probably only be considered in the rare circumstance that intravenous access or dextrose are unavailable.

4. Repaglinide

Repaglinide, a meglitinide analogue, is a new nonsulphonylurea oral hypoglycaemic. To date, there have been no cases of overdose. However, its action on closing of the ATP-sensitive potassium channel in β-islet cells is similar to the sulphonylureas and in overdose would be expected to produce a similar hyperinsulinaemic picture as the sulphonylureas.[54] It is rapidly absorbed, extensively metabolised by the liver and excreted predominantly in the bile, with no known active metabolites. Reported elimination half-life is less than 1 hour. However, duration of hypoglycaemic action in dogs has lasted up to 24 hours.[55] In overdose this drug may produce prolonged hypoglycaemia similar to the sulphonylureas.

5. Biguanides

Originally developed in the 1920s, the biguanides were not investigated for their antihyperglycaemic properties until 1950s.[56,57] Of the 3 biguanides originally produced (metformin, phenformin and buformin) only metformin is still in wide usage.[58,59] Phenformin initially received wide usage but was withdrawn in many countries during the 1970s because of an association with lactic acidosis.[8,60] Occasional reports of lactic acidosis from phenformin usage continue to occur from the few countries where it remains in use.[61,62] Metformin is prescribed as both monotherapy in type 2 diabetes mellitus patients and combination therapy for both type 1 (along with insulin) and type 2 (along with sulphonylureas) diabetes mellitus patients. Metformin reduces hepatic glucose production, reduces intestinal absorption of glucose, decreases fatty acid oxidation and improves insulin sensitivity.[58,63]

The primary problem with biguanide overdose is the potential for lactic acidosis, which carries a high potential mortality risk. In 1 study of biguanide-induced lactic acidosis, the mortality rate was 50%.[64] Concomitant disease factors, such as renal failure, hepatic disease, cardiovascular disease, infectious process and alcoholism, may increase the risk of lactic acidosis in patient using biguanides.[64] In contrast to the many reports of adverse events from therapeutic use, published reports of metformin or phenformin overdose have been rare, but may be under reported.[3,65-70] In 1 study of inquiries to a poison centre in the UK about oral antidiabetic medications, 26% (19 of 76 cases) involved metformin.[3]

The pathogenesis of lactic acidosis in biguanide overdose is complex and not completely understood.[8,71] Biguanides, which accumulate in much higher concentrations in the intestines than other tissues, double lactate production by the intestine.[71] This increases portal lactate levels and subsequently decreases the pH of the liver, causing a decrease in lactate metabolism due to suppression of pyruvate carboxylase.[72] In addition, high concentrations of metformin, such as those seen in overdose or significant drug accumulation due to renal failure, decrease glucose utilisation and increase lactate production by hepatocytes.[71] Cumulatively, these actions will produce an accumulation of lactate in the blood.

Table IV. Pharmacokinetics of biguanides

Drug	Gastrointestinal absorption	Hepatic biotransformation	% Cleared by kidneys as parent drug	Half-life (h)	Protein binding	Volume of distribution (L/kg)
Metformin	80	No	100 GF, TS	2.6-8[a]	0%	1
Buformin		No	100 GF, TS	4-6[a]		3.1
Phenformin	50%	Yes, by hydroxylation	0	2-4[b]	20%	5-10

a Will be prolonged with renal failure or renal impairment.

b Will be prolonged with hepatic impairment.

GF = glomerular filtration; **TS** = tubular secretion.

Peripherally, metformin increases glucose uptake by muscles and in overdose conditions may promote increased nonoxidative metabolism.[63,71] Furthermore, diabetes mellitus itself may increase the risk of lactic acidosis in these patients, secondary to the abnormal lactate metabolism that is part of the disease.[8] Patients with diabetes mellitus may be at somewhat of a greater risk than individuals without diabetes mellitus in overdose of biguanides because of their underlying abnormal lactate metabolism. This is in contrast to the sulphonylureas where the person without diabetes mellitus may be at greater risk because of adequate insulin stores, normal β-cell function and a lack of insulin resistance.

5.1 Pharmacokinetics

All biguanides are incompletely absorbed (table IV): approximately 80% of a metformin dose is absorbed, with a bioavailability of 50 to 60%.[63] The reduced bioavailability may be from binding by the intestinal wall.

There are several important differences in the pharmacokinetics of the biguanides. Metformin has a low volume of distribution, is not protein bound and is entirely renally cleared. All these factors suggest that significant amounts of metformin may be available for dialysis in the overdose situation. At the same time, cases of renal failure or significant renal impairment may be at greater risk of lactic acidosis due to the prolonged half-life of the drug. Phenformin has a large volume of distribution making it a poor candidate for effective removal by dialysis.

5.2 Overdose

There have been few acute cases of biguanide overdoses published.[3,65-70] However, there are significantly more data on toxic effects from biguanides during therapeutic use. With the exception of the gastrointestinal symptoms and rare incidence of hypoglycaemia, most clinical effects from biguanide overdose are secondary to the profound lactic acidosis produced by these drugs. In acute overdose, nausea, vomiting and abdominal pain are prominent.[65,66,69,70] Gastrointestinal bleeding has occurred, but to date has not been severe.[69] Hypoglycaemia is usually not seen with biguanide exposure.[64-66,70] However, it may occur if there is a period of prolonged fasting prior to and during the overdose.[69,73-74]

Lactic acidosis may be severe. In 1 series, the mortality rate was 50%.[64] Onset of acidosis may take several hours, so that an observation period of 6 to 8 hours post ingestion for these patients is appropriate.[66] With the onset of lactic acidosis the patient may experience Kussmaul's respirations, confusion, lethargy, coma or seizures.[66,69] Hypotension, tachycardia and ventricular arrhythmias may be seen.[61,69,70] Additionally, myocardial infarctions have occurred during severe lactic acidosis from biguanides.[61,64] Any severe cardiovascular impairment may worsen peripheral perfusion and increase production of peripheral lactate by skeletal muscle, worsening the acidosis. In severe cases there may be a risk of renal failure.[61,74] Serum potassium is often elevated secondary to metabolic acidosis.

5.3 Overdose Management

The management of biguanide overdose is largely supportive and directed at correcting the metabolic acidosis along with associated complications. Activated charcoal would be expected to bind all biguanides and should be used in cases of acute overdose.

Management of lactic acidosis with the use of sodium bicarbonate is controversial.[75,76] It has been proposed that use of large doses of sodium bicarbonate to correct acidosis have no place in the management of biguanide overdose.[77] Use of large doses of sodium bicarbonate in biguanide-induced lactic acidosis may increase intracellular acidaemia, decrease cardiac output, increase lactate production and paradoxically worsen the acidosis. A better method is for intubated patients to be hyperventilated to reduce the pCO_2 to 25 to 30mm Hg. This will allow the patient to blow off CO_2 generated by the acidosis, potentially restore hepatic and cardiac intracellular pH and allow lactate metabolism to continue.[77] If bicarbonate is to be used, low doses, aimed at increasing the base excess by 4 to 6 mmol/L, should be given. This can generally be accomplished by using a mmol amount equal to 2 times the patient's bodyweight in kilograms. If there is evidence of renal impairment, consideration should be given to haemodialysis.

In the case of metformin, haemodialysis has been effective in restoring acid-base balance.[78-80] Dialysis will be able to remove circulating lactate, metformin, correct hyperkalaemia and restore acid-base balance. However in the case of phenformin, haemodialysis provided no greater benefit than supportive care and bicarbonate therapy.[64] Because of its large volume of distribution, phenformin would be expected to be a poor candidate for dialysis.

Intravenous insulin therapy has shown promise and may be more effective than bicarbonate therapy in reversing the biguanide-induced lactic acidosis.[64,76,77,81] A major action of insulin is the dephosphorylation of the enzymes pyruvate dehydrogenase and glycogen synthase, increasing their activity, which in turn will reduce lactate production and increase glycogen deposition. Misbin[8] found increased survival in patients treated with insulin (81%) *vs* bicarbonate therapy (49%) or haemodialysis (52%). However, Luft et al.[64] found no such association. Guariglia et al.[76] reported success with the addition of thiamine to insulin therapy in an effort to reactivate the pyruvate-oxidative therapy. The initial insulin dose is 10 to 20 units every 4 hours, along with 5 to 12.5g dextrose. The dose can be titrated to achieve restoration of the acid/base balance or correction of acidosis.

Sodium dichloroacetate has been suggested as a potential therapy for lactic acidosis secondary to biguanide overdose. Sodium dichloroacetate stimulates pyruvate dehydrogenase activity, potentially decreasing lactate production, and may increase myocardial glucose oxidation and contractility.[82] In a controlled clinical trial in the treatment of lactic acidosis from multiple causes, dichloroacetate produced significant decreases in lactate levels and increases in pH and circulating bicarbonate.[82] However, there was no improvement in haemodynamics or survival. This may have been because the underlying disease processes in these patients was of greater significance that the acidosis itself. Sodium dichloroacetate has shown poor efficacy when tried as the sole therapy in a patient with phenformin-induced lactic acidosis.[83,84] Further evaluation of sodium dichloroacetate is needed before it can be recommended.

Hypoglycaemia, if it occurs, is easily managed with intravenous glucose.[69] Hypotension should be managed with fluid replacement and vasopressors. However, care should be exercised in the fluid management of patients with renal impairment.

6. α-Glucosidase Inhibitors

Acarbose is a complex pseudo-tetrasaccharide obtained from the fermentation processes of the microorganism *Actinoplanes utahensis*.[85,86] Acarbose competitively and reversibly inhibits the α-glucosidase enzymes (glucoamylase, sucrase, maltase and isomaltase) in the brush border in the

small intestine, which delays the hydrolysis of complex carbohydrates. There are no published reports of acarbose in overdose. This may be because acarbose is only recently available.[85,87] However, judging from published reports of clinical trials and pharmacokinetic data, it seems unlikely acarbose will cause significant injury in overdose.

Less than 2% of acarbose is absorbed as the parent drug, possibly due to its large molecular size.[87] Unabsorbed acarbose is extensively metabolised in the gut, with about 34% absorbed. Approximately 50% is excreted in the faeces. Since acarbose acts locally, its pharmacological effects are not dependent on systemic absorption. Reported adverse effects are primarily gastrointestinal in nature: bloating, flatulence, diarrhoea and abdominal pain.[85,88-90] In overdose diarrhoea could be expected. Acarbose does not stimulate endogenous insulin release, has not caused hypoglycaemia with monotherapy and would not be expected to cause hypoglycaemia in overdose.[85,88,91] Significant liver injury has been reported in chronic therapy.[92,93] However, these have been suspected to be idiosyncratic events.[92,93] Elevations of hepatic transaminases have been noted in clinical trials and it would be prudent to check transaminases in the case of a massive overdose.

Voglibose, another α-glucosidase inhibitor, is not widely available. In addition to α-glucosidase inhibition similar to acarbose, voglibose may have some inhibitory effect on insulin secretion.[94] In single dose administration it appeared less effective than acarbose in sparing insulin secretion.[95] There are no reports of overdose and little clinical information to guide therapy in overdose. Administration of voglibose increases the secretion of glucagon-like peptide-1, which may produce a hypoinsulinaemic response.[94,96] It appears unlikely that voglibose will cause significant hypoglycaemia in overdose.

Miglitol is another α-glucosidase inhibitor. There are no published cases of overdose. It is rapidly and completely absorbed in low doses but at higher doses a saturation of absorption becomes evident.[97] There is no protein binding and it is cleared renally without apparent hepatic biotransformation.[97] It has an estimated half-life of 0.4 to 1.8 hours. Like other α-glucosidase inhibitors it appears to have no other clinically relevant extraintestinal effects.[98,99] It appears unlikely to produce hypoglycaemia in overdose, but abdominal discomfort and diarrhoea may occur.

7. Troglitazone

Troglitazone is the first thiazolidinedione antidiabetic drug available. There are no data on overdose, probably because of its very recent introduction. Troglitazone is rapidly absorbed with a peak serum concentration in approximately 2 to 3 hours. It is highly protein bound (99%) and has a large volume of distribution of 10.5 to 26.5 L/kg. It is extensively metabolised and excreted in the faeces via biliary excretion.[100] Troglitazone reduces systemic vascular resistance and diastolic pressure.[101,102] It has not produced hypotension in therapeutic trials and it is unknown if it will produce hypotension in overdose.[101] Troglitazone does not effect insulin secretion and has not produced hypoglycaemia in monotherapy. Troglitazone differs from metformin and the biguanides in that troglitazone and metformin affect 2 distinct metabolic pathways: troglitizone uses an anabolic pathway, whereas metformin uses a catabolic pathway.[103] Because of this troglitazone would not be expected to cause lactic acidosis and indeed, lactic acidosis has not been reported in clinical trials, and troglitazone does not appear to increase lactate production.[100,103] Thiazolidinediones act by binding to the peroxisome proliferator-activated γ-receptors (PPAR-γ) in the cell nucleus that moderate diverse metabolic pathways involving lipoprotein lipase, glucose transporters and insulin-signalling pathways.[100,104]

Until more data are available it would be prudent to provide close monitoring and supportive care for the patient who has overdosed on troglitazone. Haemodialysis, haemoperfusion and diuresis would be of little or no value because of the large volume of distribution, high protein bind-

ing and biliary excretion of this drug, and are not recommended.

8. Conclusions

Overdoses with antidiabetic drugs produce major morbidity, with many cases requiring intensive care medicine and prolonged hospital stays. However, fatalities are rare when treatment is initiated early.

The management of the hypoglycaemic drugs (insulin and sulphonylureas) is based primarily on restoring and maintaining euglycaemia via intravenous dextrose supplementation. The primary organ system effected in the CNS, which relies on glucose as its sole source of energy. In the case of the sulphonylureas, reduction of insulin secretion via pharmacological intervention may also be necessary. Cases of insulin- and sulphonylurea-induced neurological sequelae have usually been associated with cases of delayed recognition of the overdose and subsequent prolonged periods of hypoglycaemia without treatment. Prompt recognition and adequate treatment of these hypoglycaemic events is a key to a successful outcome.

In biguanides the main risk appears to be cardiovascular collapse secondary to profound acidosis. The management focus is on restoring acid-base balance with hyperventilation and the use of insulin to shift the utilisation of glucose from the non-oxidative pathway to the oxidative pathway. Use of haemodialysis has shown equivocal results but may be valuable in metformin overdose.

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