POISONING.COMM

January 2007

Volume 2, Issue 1

Drug Induced Hypoglycaemia – New Insights into an Old Problem

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Features

Inside This Issue

Hypoglycaemia is a common, potentially fatal, yet preventable problem. The aetiology of hypoglycaemia is variable, but drug-induced hypoglycaemia remains the commonest cause. Determining the aetiology of hypoglycaemia poses little difficulty in patients known to be taking oral hypoglycaemic agents (OHAs). However, it becomes a challenge in those without a history of such exposure. The Hospital Authority Toxicology Reference Laboratory (TRL) received 51 referrals for suspected drug-induced hypoglycaemia in patients without a history of current hypoglycaemic agent use in the period between June 2005 and March 2006. In 23 (45%) of these patients, OHAs and/or their metabolites were detected by toxicology screening. The causative OHAs were found to be gliclazide and glibenclamide in 14 and 8 patients, respectively. For the remaining patients, glimepiride, nateglinide and rosiglitazone were detected. The possible sources of OHAs deduced on the basis of available clinical information are shown in Table 1.

Table 1 Possible sources of OHA in positive cases

Possible source of OHA	No. of cases (Total = 23)
Resident of Residential Care Home for the Elderly with drug administration error confirmed / suspected	9
Took family member's / employer's medication	6
Took stock medication by mistake	2
Patient reported taking an over-the-counter medication, which was not available for analysis	1
Chinese proprietary medicines adulterated with western medications	1
Unknown	4

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The large number of cases identified within such a short period of time suggests that this situation is alarming in Hong Kong. Moreover, the cases reported in this study may represent just the tip of an iceberg. The index of awareness about this phenomenon is variable among clinicians and cases may well be under-recognized and under-reported. Cases of hypoglycaemia without obvious cause should alert health care providers to the possibility of inadvertent OHA use. Missing this aetiology could lead to unnecessary investigation and prolonged hospitalization as well as considerable morbidity and even mortality. There can be a considerable financial impact from hypoglycaemia caused by medication dispensing errors.[1]

The correct diagnosis of hypoglycaemia induced by inadvertent use of OHAs, largely depends on the ability to demonstrate the presence of the offending agent in clinical samples collected during the hypoglycaemic episode. A specially developed method is used in the TRL for the purpose.

We have explored the possible sources of OHAs in our cases. Taking family members' medications by mistake is one common source, particularly in the elderly and children. Education of the general public regarding the safe storage and labelling of medications is therefore a necessary prerequisite to avoid confusion and prevent such inadvertent misuse. Especially for children, there should also be restriction of access to all medications intended for individual family members. Tablet dispensing aids of different colours may also be useful. Colleagues in general practice have a significant role to play in this regard.

For the nine residents in the residential care homes for the elderly (RCHE), errors in medication administration could only be confirmed in one case. Inadvertent OHA ingestion by these residents was seemingly random, since all nine resided in different homes. Lau et al provided evidence of insufficiencies in several areas of medicines management in these facilities, namely: physical storage, quality of storage, medication administration systems (including documentation), and the staff's knowledge about relevant medicines.[2] Under these circumstances, possible medication administration errors merit serious consideration, especially for patients with multiple morbidities and those receiving multiple medications. We therefore recommend that all RCHE should review regularly and, if necessary, rectify their medicines management procedures. Training of RCHE staff on medicines management should be enhanced and include knowledge on proper storage of medicines as well as procedures in administration and documentation.

Hypoglycaemia due to inadvertent use of OHAs is recognized to be a dangerous but preventable condition. Health care providers should be vigilant to the problem, especially if hypoglycaemia remains unexplained. For confirmed cases, underlying sources of any OHAs need to be carefully investigated and remedial / preventive measures should be implemented, if necessary. The importance of targeted toxicological investigation cannot be overemphasized.

Acknowledgements

A more detailed article has been published in the Hong Kong Medical Journal (Hong Kong Med J 2006; 12:334-8). We have obtained the kind permission from the Hong Kong Medical Journal to use the materials for this educational purpose.

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Safety of Oral Antidiabetic Drugs

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Oral antidiabetic drugs can be divided into two groups based on their pharmacodynamics and effect or lack of effect on insulin:

1. The oral hypoglycaemic agents, such as the sulphonylureas and the meglitinides; and
2. The anti-hyperglycaemic agents, such as the biguanides, the a-glucosidase inhibitors, and the thiazolidinediones.

Oral Hypoglycaemic Agents

(1) Sulphonylureas

The sulphonylureas act mainly by increasing insulin secretion. The second generation sulphonylureas are significantly more potent than the first generation agents due to higher affinity for the sulphonylurea receptors.[1] Some of their pharmacokinetic data and usual dosings are shown in Table 1.

Table 1 Pharmacokinetics and dosage of sulphonylurea drugs[3-7]

	Drug	Time to peak level (hr)	Duration of action (hr)	Active metabo-lites?	% Renal excre-tion	Half-life (hr)	Available forms in HK	Maximum daily dose	Usual dosing frequency
First genera-tion	**Chlorpropamide**	3-6	24-72	Yes	100	24-48	250mg	750mg	1
	Tolbutamide	5-8	6-12	Minimal	100	4.5-6.5	500mg	3g	1-3
Second genera-tion	**Glipizide**	2-3	12-24	No	80-85	2-4	5mg	40mg[a]	1-2[a]
	Gliclazide	4-5	24	No	60-80	8-12	80mg	320mg	1-2[b]
	Glibenclamide	2-3	16-24	Yes	50	5-10[c]	2.5, 5mg	20mg	1-2
	Glimepiride	2-4	24	Weakly	60	9	1, 2, 3, 4,	8mg	1
	Gliquidone	1.0-1.5	12-24	In low concen-tration	5	3-4	30mg	180mg	1-3[d]

[a] *15mg is the maximum single dose.*
[b] *Doses above 160mg should be divided into 2 equal parts for twice daily administration.*
[c] *May be as long as 15-20 hr.*
[d] *Maximum single dose is 60mg; doses above 60mg should be divided.*

The principal adverse effect associated with sulphonylureas is hypoglycaemia, which can occur with all agents at all doses.[1] Life-threatening hypoglycaemia may develop in sulphonylurea-naive individuals (adults and children) without diabetes after ingestion of a single therapeutic dose. In patients with type 2 diabetes, on the other hand, hypoglycaemia may also develop while they are taking therapeutic doses.

Overdose of sulphonylureas generally occurs as intentional or accidental ingestions, and most of the latter incidents involve children. Of all the sulphonylurea exposures reported to American Association of Poison Control Centers' Toxic-Exposure Surveillance System (AAPCC-TESS) in 2004, 976 (23.5%) resulted in moderate-to-major toxicity and 9 (0.22%) resulted in fatality.[2] There have been cases of inadvertent dispensing or administration in which non-diabetic patients were given sulphonylureas. In most instances, confusion arose as a result of similarity in spelling and appearance between the intended medication and the sulphonylurea[3], or such errors occur because of inadequate knowledge of the caregivers on medication supervision and administration. Moreover, many other factors may adversely heighten the risks of hypoglycaemia, such as concomitant use of other medications and drug interactions. (Table 2)

The onset of hypoglycaemia after an acute overdose of a sulphonylurea occurs in less than 8 hours.[3] This is consistent with the time to peak effect (approximately 8 hours) for most sulphonylureas. However, the onset of symptomatic hypoglycaemia may be significantly delayed following unintentional chronic administration of larger doses of sulphonylureas than intended.[8] The duration of hypoglycaemia may range from 12 to 24 hours or even longer in cases of large overdose, extended-release preparations, or long-acting preparations such as chlorpropamide or glibenclamide. Prolonged hypoglycaemia may also be observed when a relatively low dose of sulphonylurea is taken by patients with advanced age, or with impaired renal or hepatic function. Elderly patients are at increased risk of developing severe hypoglycaemia due to decreased clearance of the hypoglycaemic agents, impaired counter regulation and decreased cognitive function in this patient group.[9,10]

In adults with hypoglycaemia, autonomic symptoms may include diaphoresis, hunger, emesis, tachycardia, tremor, paraesthesia, and anxiety; and neuroglycopaenic symptoms may include headache, lethargy, weakness, confusion, dizziness and drowsiness. The above symptoms may be followed by coma and seizure if the patient's blood glucose continues to fall. Persistent hypoglycaemia may result in permanent neurologic deficits, hypotension, metabolic acidosis, cardiovascular collapse, and death.[8,11] ß-blockers may attenuate the catecholamine counterregulatory response as well as blunt the autonomic symptoms of hypoglycaemia (except sweating, which is preserved).[1]

(2) Meglitinides

Nateglinide and repaglinide are representatives of this class of agents. They act in a similar fashion as sulphonylureas with a shorter duration of action. Therefore, the risk of the potential prolonged hypoglycaemia resulting from meglitinide overdose is lower than that of sulphonylureas.

Table 2 Pharmacokinetic and pharmacodynamic interactions that may possibly augment the hypoglycaemic action of sulphonylureas and meglitinides[3,6,9,10]

Interaction	Interacting drugs
Reduction in hepatic metabolism	Dicumarol, fluoroquinolone antibiotics, gemfibrozil, histamine-2 blockers, miconazole and related compounds, monoamine oxidase inhibitors, sulphonamides
Impairment in excreting metabolites in urine	Allopurinol, probenecid, salicylates, sulphonamides
Intrinsic hypoglycaemic activity	Alcohol (acute), adrenergic antagonists, angiotensin-converting enzyme (ACE) inhibitors, guanethidine, monoamine oxidase inhibitors, insulin, salicylates

Table 3 Safety Tips on Using Oral Antidiabetic Drugs[1,7,13,15]

In general:
1. Keep all medications away from children (as a mere single therapeutic dose can kill!) 2. Read drug labels and take medications under sufficient lightings. 3. Keep medications in their original containers and avoid pooling of oral antidiabetic drugs with other medications in the same container. 4. Physicians, pharmacy staff and other healthcare professionals should pay special attention to look-alike/sound-alike drugs (both in appearance, colourings and spellings) to prevent prescribing, dispensing and administration errors.
Sulphonylureas: ***(Since hypoglycaemia is a potentially life-threatening toxicity, it is prudent to exercise caution in certain patient groups or avoid things that would increase the risk of such events with its use.)***
1. Watch out for hypoglycaemic symptoms particularly in patients newly or recently initiated with sulphonylureas. 2. Increase vigilance in monitoring the conditions and blood sugar levels of patients with recent hospitalization. 3. Use with caution in patients with hepatic or renal impairment and in frail elderly people. 4. Avoid long-acting sulphonylureas (e.g. chlorpropamide, glibenclamide) in the elderly and in patients with renal impairment. 5. Avoid concomitant alcohol consumption and administration of drugs that might potentiate the effect of sulphonylureas, increase or mask the risk of hypoglycaemia. 6. Ensure drug compliance. 7. Maintain adequate caloric intake and eat meals on regular schedule. 8. Always carry a source of fast-acting carbohydrate e.g. glucose tablets, hard candies etc. to combat hypoglycaemic attack. 9. Check plasma glucose at the onset of hypoglycaemic symptoms.
Biguanides (Metformin):
1. Take with meals. 2. Avoid excessive alcohol intake. 3. Avoid metformin in patients with renal or hepatic impairment, congestive heart failure requiring drug therapy, a history of lactic acidosis, or in elderly over 80 years of age (unless adequate renal function is confirmed as measured by creatinine clearance). 4. Discontinue metformin in clinical situations predisposing to hypoxaemia, e.g. cardiovascular collapse (shock), respiratory failure, acute myocardial infarction, and septicaemia. 5. Withhold metformin in patients undergoing surgery or receiving parenteral iodinated radiographic contrast media.

Anti-hyperglycaemc Agents

(1) Biguanides

Metformin, the only available biguanide, exerts its effect mainly by increasing peripheral utilization of glucose and decreasing gluconeogenesis. It is excreted primarily through the kidney, and elimination is prolonged with renal impairment and increasing age. Metformin is approved for use in children above 10 years old.[12]

In general, the blood glucose lowering effect of metformin will only be seen in diabetics unless one simultaneously ingests ethanol with metformin or another hypoglycaemic agent or; if he or she has co-existing severe hepatic insufficiency. Thus hypoglycaemia is not expected to be of major concern after metformin exposure in healthy subjects. Nevertheless, dose-related gastrointestinal effects, such as nausea, vomiting, diarrhoea and abdominal cramps can occur after acute overdose.[13]

Lactic acidosis, the most devastating effect of metformin poisoning, may occur either in overdose or in patients with predisposing conditions, such as renal failure. Clinical effects of lactic acidosis include agitation, confusion, drowsiness, lethargy, dehydration, hyperventilation, coma and convulsions. If left untreated, it may result in hypotension, cardiovascular collapse, hypothermia and death.[13,14]

(2) a-Glucosidase inhibitors and Thiazolidinediones

These two classes of anti-hyperglycaemics pose minimal risk in acute overdose. Since they do not stimulate the release of endogenous insulin or cause hypoglycaemia with monotherapy, they are not expected to cause hypoglycaemia in overdose.[8] However, both have been implicated in hepatic injury with chronic therapy.

Some safety tips on using oral antidiabetic drugs are shown in Table 3.

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Hypoglycaemia in a non-diabetic elderly subject

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Case Report

An 88-year-old man with a history of Parkinson' s disease on trihexyphenidyl hydrochloride (benzhexol) developed acute confusion at home. Haemoglucostix (H' stix) reading taken by the ambulance crew was 1.9mmol/L. His mental state recovered promptly after receiving intravenous injection of 20ml of 50% dextrose solution. On arrival at the Accident & Emergency Department, his h' stix reading was 8.6mmol/L. He had no fever, anorexia, vomiting or diarrhoea. He had no history of diabetes mellitus and denied taken any other drugs or herbs before admission. He was a non-smoker and non-drinker. He lived with his wife, who had diabetes mellitus on gliclazide. He denied taking his wife' s medication. Physical examination was unremarkable. He was admitted to medical ward. Blood tests including complete blood counts, urea, electrolytes, liver enzymes, thyroid stimulating hormone and morning cortisol levels were unremarkable. His serum creatinine level was 161µmol/L (reference: 62-106µmol/L). His blood glucose level was stabilized with intravenous infusion of 10% dextrose solution at a rate of 80ml per hour, which was stopped one day after admission. Urine sample was sent for screening of oral hypoglycaemic agents. He was discharged home with a follow-up appointment in the medical clinic.

Six days later, he presented again with mental dullness. An h' stix reading of 2.0mmol/L was noted by the ambulance crew. He received 20ml of 50% dextrose solution intravenously and his mental state recovered quickly. He denied taking any non-prescription medication. He was admitted to medical ward. His plasma blood glucose dropped to 1.5mmol/L despite an intravenous infusion of 10% dextrose solution 80ml per hour. The simultaneous serum insulin level was 56.6mIU/L (reference: 6.0-35.0mIU/L). A diagnosis of insulinoma was suspected. Hospital Authority Toxicology Reference Laboratory confirmed the presence of trace amounts of gliclazide metabolite in the patient' s initial urine sample. Further questioning and review of the patient' s medication history showed that he had inadvertently taken his wife' s prescription of gliclazide. He received education about the proper use of his medication before discharge.

Discussion

Hypoglycaemia is a potentially fatal condition.[1] Hypoglycaemia can be caused by drugs, insulinoma, liver failure, renal failure, hormonal deficiencies and reactive hypoglycaemia.[2] Early recognition, prompt treatment and identification of the underlying cause are important in the avoidance of complications and recurrence of hypoglycaemia.

Hypoglycaemia after inadvertent administration of anti-diabetic drugs is well described in the literature.[3,4] One possibility is an accidental substitution of a sulphonylurea for an intended medication with a similar generic or trade name.[3] Taking family members' medications by mistake can also occur, particularly in the elderly and children.[4]

An inadvertent or factitious sulphonylurea overdosage must be considered in every hypoglycaemic patient who denied the use of anti-diabetic drugs. A thorough pill inspection and an interview of patient and care givers for recent changes in pill appearances should be performed. Measurement of serum insulin and C-peptide levels during hypoglycaemia and a blood or urine screen for anti-diabetic drugs may be indicated.[3] In individuals using exogenous insulin, factitious hypoglycaemia can be distinguished from insulinoma by the presence of high insulin levels without a concomitant rise in the C-peptide level, which is suppressed by the exogenous insulin. Sulphonylureas stimulate endogenous insulin and can therefore be detected only by measuring drug levels in plasma or urine. The correct diagnosis of inadvertent use of anti-diabetic drug will help prevent recurrence through patient education as well as avoiding extensive investigations in searching for other causes such as insulinoma.

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Toxicological Surveillance

Between the period of 1 July and 30 September 2006 there were 480 cases of poisoning (excluding infective food poisoning) recorded by the Accident & Emergency Departments of six acute regional hospitals (QMH, PYNEH, UCH, PWH, PMH & TMH). The female to male ratio was approximately 3:2. The incidence was higher in males than females between the ages of 0 to 9 as well as between the ages 55 to 74. The age and gender distribution of patients is shown in Figure 1.

Over 64% of poisoning cases (n=310) occurred at home, while 1.9% (n=9) occurred at workplaces, and 11.6% (n=56) happened at other places such as streets, countryside, and restaurants. The place of exposure for the rest of the cases was unknown.

Vast majority (57.5%) of poison exposures were suicidal in nature while 14.0% and 11.5% of the cases were due to accidents and recreational activities respectively. Therapeutic errors accounted for 5.4% of exposures (Figure 2).

As shown in Figure 3, about 63% of poison exposures were linked with the use of western medicines, while poisoning with multiples agents and household products accounted for 14.6% and 9.8% of the cases respectively. Poisoning by Chinese medicines and environmental chemicals entailed roughly the same proportion (2%).

There were 2 fatalities reported in this quarter. The first case was suicidal with household chemicals. The other case was recreational in which the cause of death was suspected to be multi-factorial awaiting coroner's dismissal.

Figure 1: Age and Gender Distribution of Poisoned Patients (1 Jul 2006 – 30 Sep 2006)

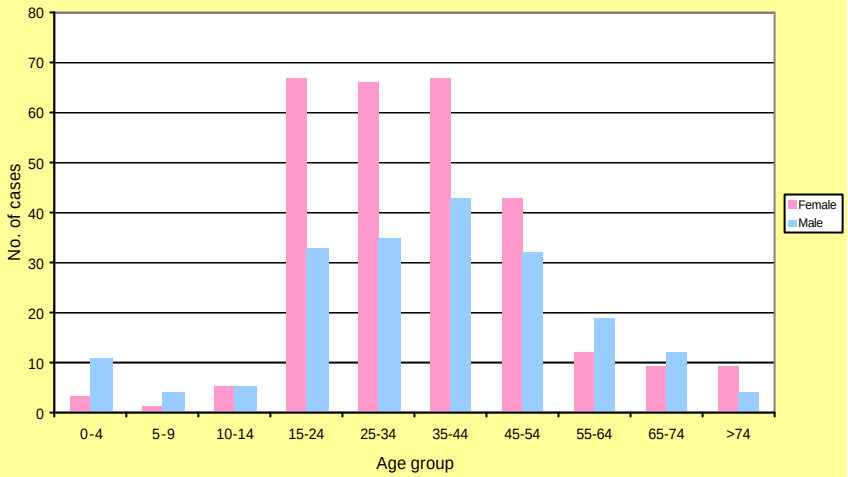


Figure 2: Nature of Poisoning (1 Jul 2006 – 30 Sep 2006)

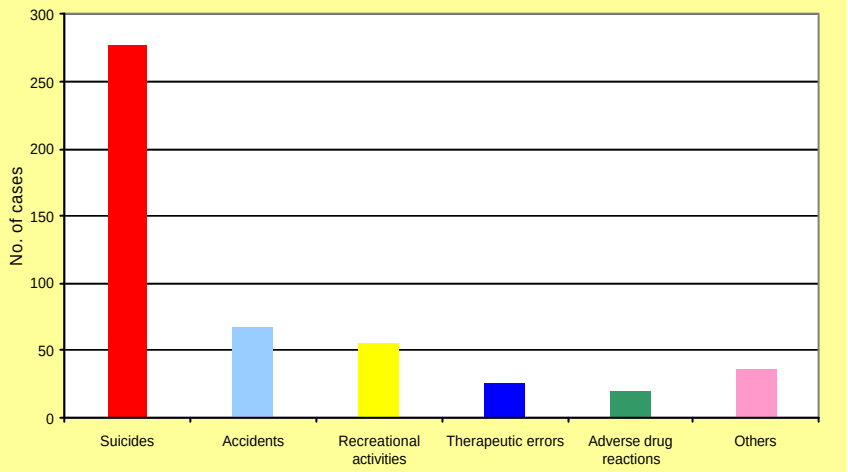
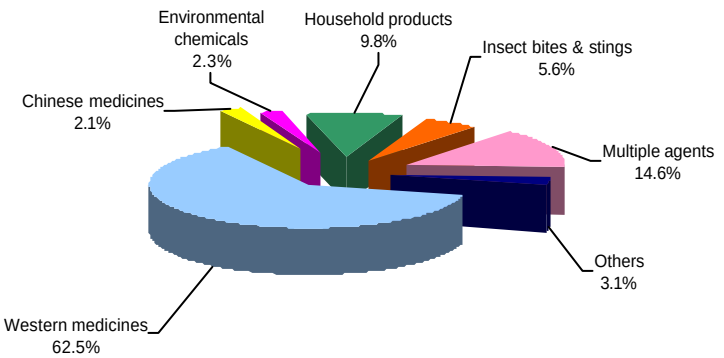


Figure 3: Poisoning Agents Involved (1 Jul 2006 - 30 Sep 2006)



Toxicological Surveillance

There were a total of 17 cases of poisoning in which oral hypoglycaemic agents (OHAs) were involved between July 2005 and September 2006. Out of the 17 cases, 11 cases (65%) happened in patients aged 55 or above. This correlated with the age of onset of type 2 diabetes mellitus. Causes of poisoning included suicides (59%), adverse reactions to the OHAs (24%), accidental ingestion and therapeutic errors (12%). The most common OHAs involved as poisoning agents were metformin (52%), gliclazide (29%), and glibenclamide (14%). This frequency of involvement may be related to their popularity with local prescribers. Table 1 outlines the disposal of patients poisoned by OHAs.

Table 1 Distribution of case disposals from AEDs

Disposal	No. of cases	Percentage (%)
Discharge	3	18%
Discharge against medical advice	1	6%
Admission to general ward	9	53%
Admission to ICU	4	24%
Total	17	100%

The majority of OHAs poisoning (70%) occurred at domestic settings.
Members of the public are advised on the following points to prevent accidental poisoning with medications at home:

On keeping and storage of medicines:

- ★ Keep medicines where children cannot see or reach them.
- ★ Keep medicines in their original containers.
- ★ Keep medicine containers properly closed and preferably in child-resistant containers.
- ★ Do not keep medicines you no longer need.

On taking medicines:

- ★ Always read the label and follow the instructions for use carefully.
- ★ Take note of the ingredients, indications, dosage, warnings and side effects, in order to avoid undesirable results.
- ★ Always put the light on when giving or taking medicines.
- ★ Do not use medicines from unlabelled containers.
- ★ Do not take more than one kind of medication at a time unless under doctors' instructions. Otherwise you may experience harmful drug interaction.
- ★ Do not take Chinese and western medicines at the same time without consulting your doctor.

On the problem with side effects:

- ★ If you are concerned about the side effects or if the medicines affect you in any other way, stop taking them and seek advice from your doctor.

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