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Drug-induced hypoglycaemia—new insight into an old problem

藥物引發的血糖過低——對舊問題的新觀點

Objective. To review the causes of drug-induced hypoglycaemia in patients not taking hypoglycaemic medications.

Design. Retrospective study.

Setting. Regional hospitals in Hong Kong.

Patients. Patients with suspected drug-induced hypoglycaemia without a known history of exposure to hypoglycaemic agents, referred to the Hospital Authority Toxicology Reference Laboratory from June 2005 to March 2006 inclusive.

Main outcome measures. Rate of positive cases, laboratory findings, possible causes, age distribution, and final outcomes.

Results. A total of 51 such patients were referred, in whom the presence of oral hypoglycaemic agents was detected (or inferred) in 23 (45%). In 12 of the 23 patients, oral hypoglycaemic agents could only be detected by target analysis, not through broad-spectrum screening. Gliclazide and glibenclamide were detected in 14 and eight patients respectively, whereas glimepiride, nateglinide and rosiglitazone were detected in the remaining patient. Possible sources of oral hypoglycaemic agents included drug administration errors in residential care homes for the elderly (n=9), mistakenly taking medication of a family member or employer (n=6), taking stock medication by mistake (n=2), taking Chinese proprietary medicine adulterated with oral hypoglycaemic agents (n=1), taking unknown pills bought from a retail pharmacy (n=1), and unknown (n=4). Regarding these 23 patients, 17 (74%) were aged 70 years or above and 21 (91%) recovered uneventfully.

Conclusion. Hypoglycaemia due to inadvertent use of oral hypoglycaemic agents is a recognised problem, particularly in cases where family members living in the same household are taking similar medications. Possible drug administration errors in residential care homes for the elderly should be investigated, and procedures rectified if confirmed. Health care providers should be vigilant to such potential errors, especially in cases of unexplained hypoglycaemia.

Key words:
Hypoglycemia;
Poisoning;
Sulphonylurea compounds

目的：檢討沒有被處方降血糖藥的病人出現藥物引發血糖過低的病例。

設計：回顧式研究。

安排：香港地區性醫院。

病人：2005 年 6 月至 2006 年 3 月期間，沒有接受降血糖藥物但懷疑因藥物引發血糖過低，而轉介至醫院管理局毒理學參考化驗室的病人。

主要結果測量：呈陽性病例比率、化驗結果、可能因素、年齡分布及最終結果。

結果：共有 51 名病人被轉介至是次研究，其中 23 人（45%）被探測（或推斷）體內含有口服降血糖藥。23人中有12人只能透過目標分析方法探測口服降血糖藥，而利用廣譜篩查方法則無法探測到。分別有14名及8名病人，被發現含有藥物「格列齊特」和「格列本」，其餘一名病人體內則含有「格列美」、「使糖立釋錠」和「梵帝雅膜衣錠」。誤服口服降血糖藥的可能來源包括長者院舍藥物管理出錯（9 人）、誤服家人或僱主的藥物（6 人）、誤服舊藥（2 人）、服食了滲入降血糖藥的中藥（1 人）、服食資料不明的藥房藥物（1 人）和原因不明（4 人）。這 23 名病人中，17 人（74%）年齡為 70 歲或以上，而 21 人（91%）康復期間沒重大反應。

結論：因疏忽大意誤食降血糖藥引致血糖過低是一個發現已久的問題，有家庭成員服食同樣藥物者危險性更大。研究認為應調查長者院舍藥物管理出錯的可能，在確定出錯環節後改善程序。醫護人員須對潛在出錯提高警覺，特別對無法解釋的血糖過低病例。

關鍵詞：
血糖過低；
中毒；
磺氨尿素劑化合物

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Introduction

Hypoglycaemia is a common, potentially fatal, yet preventable problem. Patients may present with autonomic symptoms (eg sweating, hunger, paresthesia, tremor, palpitation, anxiety), neuroglycopenic symptoms (eg 'dizziness', weakness, confusion, drowsiness, seizure), which may lead to coma and death if left untreated.[1] Diagnosing hypoglycaemia is not always straightforward, particularly in the elderly, as a significant proportion of such patients may be asymptomatic or present with non-specific symptoms such as altered mental status.[2] The aetiology of hypoglycaemia is variable, and includes: drugs, insulinoma, liver failure, renal failure, hormonal deficiencies and reactive hypoglycaemia.[3] However, drug-induced hypoglycaemia remains by far the commonest.[4] Determining the aetiology of hypoglycaemia poses little difficulty in patients known to be taking parenteral or oral hypoglycaemic agents (OHAs). However, it becomes a challenge in those without a history of such exposure. In May 2005, a cluster of patients with hypoglycaemia who were seen by the same general practitioner was referred to the Toxicology Reference Laboratory (TRL) for suspected drug-induced hypoglycaemia. The general practitioner had allegedly mixed up simethicone with gliclazide.[5-8] The associated publicity triggered a surge of requests to investigate similar possibilities in other patients. This brief report summarises findings pertaining to these subsequent cases.

Methods

All patients with suspected drug-induced hypoglycaemia without a history of OHA exposure, who were referred to the TRL from June 2005 to March 2006 inclusive were investigated. The aforementioned cases seen by the general practitioner were not included. Blood and urine, as well as any available non-prescribed medications (imbibed weeks or months before presentation) were collected from all the patients for toxicological analysis. Samples were analysed by two separate methods, which involved the same preparation procedures. The first was the in-house broad-spectrum toxicology screen by high-performance liquid chromatography with diode array detection (HPLC-DAD).[9] The second entailed OHA targeted analysis by liquid chromatography tandem mass spectrometry (LC/MS/MS).[10] These two methods were able to detect the following OHA parent compounds in serum: glibenclamide, gliclazide, glimepiride, glipizide, glibornuride, gliquidone, chlorpropamide, tolbutamide, acetohexamide, carbutamide, tolazamide, nateglinide and repaglinide. The metabolites of glibenclamide, gliclazide, glimepiride, glipizide, glibornuride and gliquidone in urine could also be detected. For patients whose samples yielded the presence of any OHA (or metabolite) possible sources were elucidated, based on personal drug history, family history of diabetes mellitus (DM) and OHA use, and prior ingestion of non-prescribed medications.

Results

In the period from June 2005 to March 2006, 51 patients without a history of current hypoglycaemic agent use were referred to the TRL for suspected drug-induced hypoglycaemia. In 23 (45%) of these patients, OHAs and/or their metabolites were detected in one or more specimens (serum, urine, and non-prescribed medication). Details pertaining to the latter patients are summarised in the Table. The majority (74%) of them were elderly (aged ≥70 years). Nine patients lived in residential care homes for the elderly (RCHE). Six patients had a history of DM, three of whom were on diet control only. The other three patients (all of whom had renal impairment) claimed to have discontinued their OHA themselves or been asked to do so by their clinicians, at least 1 month prior to their hypoglycaemic episode. We did not observe any increasing or decreasing temporal trend in the number of patients with confirmed OHA-induced hypoglycaemia during the study period.

The causative OHAs were gliclazide and glibenclamide for 14 and eight patients, respectively. For the remaining patient, glimepiride, nateglinide and rosiglitazone were detected. In 12 (52%) of the 23 patients with hypoglycaemia attributable to OHAs, the latter agents were detected only by targeted analysis, not by broad-spectrum screening.

In all, 21 of these 23 patients recovered uneventfully. One of those who recovered underwent computed tomography (CT) of the abdomen and was initially treated for an insulinoma before urine toxicology results became available. The remaining two patients died after developing pneumonia (case 16) and acute coronary syndrome with sepsis (case 17); neither death appeared directly related to hypoglycaemic episodes.

The possible sources of OHA were deduced on the basis of available clinical information. Cases 1 to 9 were RCHE residents (accounting for 39% of these 23 patients), resided in nine different homes. Drug administration error at RCHE was confirmed in one patient only. However, the possibility of drug administration error in the remaining eight cases cannot be ignored. Six (26%) of them (cases 10 to 15) may have mistakenly taken OHAs intended for others. For example, case 10 was a 2-year-old boy who lived with his grandmother, who was a diabetic patient taking glibenclamide. So it was very likely that this child had ingested his grandmother's OHA. Cases 11 to 13 were elderly patients (age range, 82-93 years) who lived with family members taking OHAs. Case 15 was a 24-year-old Indonesian maid, whose employer was a diabetic patient taking gliclazide; she may have mixed up her influenza medications with her employer's OHA. Two patients (cases 16 and 17) had DM with a history of gliclazide use that had been discontinued for some time. Gliclazide was detected in the clinical samples

Table. Clinical details of 23 patients with hypoglycaemia attributable to oral hypoglycaemic agents (OHAs), who were not known to be taking such treatment

Case	Sex/age (years)	Lowest recorded glucose level (mmol/L)	History of DM* and relevant treatment history	OHA detected	Analysis method†	Possible sources of OHAs‡
1	M/85	1.7	Nil	Gliclazide	S: -ve TA: +ve	RCHE resident, cause not determined
2	M/88	1.3	Nil	Glibenclamide	S: +ve TA: +ve	RCHE resident, drug administration error confirmed
3	M/89	1.4	Nil	Gliclazide	S: -ve TA: +ve	RCHE resident, cause not determined
4	M/85	0.6	Nil	Gliclazide	S: -ve TA: +ve	RCHE resident, cause not determined
5	F/81	1.7§	Nil	Gliclazide	S: +ve TA: ND	RCHE resident, cause not determined
6	M/77	0.8§	Nil	Gliclazide	S: +ve TA: +ve	RCHE resident, cause not determined
7	F/78	0.9	Nil	Glibenclamide	S: -ve TA: +ve	RCHE resident, cause not determined
8	F/85	2.5	Nil	Gliclazide	S: +ve TA: +ve	RCHE resident, cause not determined
9	M/88	2.6	Nil	Glibenclamide	S: -ve TA: +ve	RCHE resident, cause not determined
10	M/2	1.9	Nil	Glibenclamide	S: +ve TA: +ve	Took family member's medication
11	F/93	1.7	DM, diet control	Gliclazide	S: -ve TA: +ve	Took family member's medication
12	M/87	1.9§	Nil	Gliclazide	S: -ve TA: +ve	Took family member's medication
13	M/82	2.1	Nil	Gliclazide	S: -ve TA: +ve	Took family member's medication
14	F/56	2.7	Nil	Gliclazide	S: +ve TA: ND	Took family member's medication
15	F/24	2.2	Nil	Gliclazide	S: +ve TA: ND	Took employer's medication
16	M/75	1.8§	DM, Gliclazide stopped already	Gliclazide	S: +ve TA: +ve	Took stock medication by mistake
17	M/96	2.8	DM, Gliclazide stopped already	Gliclazide	S: -ve TA: +ve	Took stock medication by mistake
18	M/32	0.9	Nil	Glibenclamide	S: +ve TA: +ve	Patient reported taking an OTC medication, which was not available for analysis
19	F/48	2.0	DM on CPM	Glimepiride, nateglinide and rosiglitazone	S: +ve TA: +ve	CPM adulterated with western medications
20	M/86	2.3	DM, diet control	Gliclazide	S: -ve TA: +ve	Unknown
21	M/79	1.8	Nil	Glibenclamide	S: +ve TA: +ve	Unknown
22	F/43	1.6	DM, diet control	Glibenclamide	S: -ve TA: +ve	Unknown
23	M/76	1.4	Nil	Glibenclamide	S: -ve TA: +ve	Unknown

* DM denotes diabetes mellitus
† S denotes screening by high-performance liquid chromatography with diode array detection, TA target analysis by liquid chromatography tandem mass spectrometry, ND not done, -ve negative, and +ve positive
‡ RCHE denotes residential care homes for the elderly, OTC over-the-counter, and CPM Chinese proprietary medicine
§ Glucose level measured by blood glucose meter

collected during their hypoglycaemic episodes. It was considered likely that both patients mistakenly took gliclazide from drugs that they had stockpiled in the past. Taking unknown tablets bought from a retail pharmacy was the likely source of the OHA in case 18. Consumption of Chinese proprietary medicine (CPM) adulterated with glimepiride, nateglinide and rosiglitazone was the likely responsible source in case 19. In four patients (cases 20 to 23), the source of the OHA remained unknown.

Discussion

Hypoglycaemia is a common complication in patients with diabetes and is mostly related to drugs.[11] However, its occurrence and possible aetiology in non-diabetics is less well described. A study carried out in a Philadelphia teaching hospital identified 88 patients without diabetes who presented with hypoglycaemia requiring admission over 9 years. Common causes included chronic renal failure (25%), alcohol intoxication (15%), liver failure (12%),

sepsis (12%), cancer (12%), endocrine disorders (12%), and OHA (3%). However, only 16 of 88 patients underwent OHA screening.[12] Another study carried out in a teaching hospital in Turkey found 72 non-diabetic patients admitted with hypoglycaemia over 8.5 years; identified common aetiologies included: endocrine deficiencies (35%), malignancies (21%), insulinoma (10%), chronic renal failure (8%) and liver failure (4%).[13] Nevertheless, drug-induced hypoglycaemia in non-diabetics was not listed and whether OHA screening had been specifically sought was not mentioned. For non-diabetic patients with hypoglycaemia, without OHA screening the frequency of inadvertent or deliberate OHA use may be grossly underestimated.

Klonoff et al[14] reviewed the world literature from 1961 to 1992 and summarised a total of 43 case histories of patients with hypoglycaemia who had inadvertently taken OHAs and 23 others who had factitiously self-administered them. A study screening for OHAs by radioimmunoassay in patients with low glucose levels with inappropriately high insulin and C-peptide concentrations, found that they were present in 34/93 (37%) of such patients seen over 2 years; presence of OHAs were unexpected in 20 of these 34 cases.[15] Compared to these previous reports, the TRL has identified a total of 23 cases of inadvertent OHA use leading to hypoglycaemia within 10 months. The large number of cases identified within such a short period of time suggests that this situation might be particularly common in Hong Kong. Moreover, the cases reported in this study may represent just the tip of the iceberg. Though hypoglycaemia could be ascribed to OHAs in 45%, referrals to our TRL constituted a highly selected group. Thus, it might be inappropriate to estimate the number of undetected cases in the wider population, based on the relatively small cohort of 51 cases encountered in this study. Nevertheless, the index of awareness about this phenomenon is variable among clinicians and cases may well be under-recognised 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 hospitalisation as well as considerable morbidity and even mortality. There can be a considerable financial impact from hypoglycaemia caused by medication dispensing errors.[16] This was also evident in our patient who was initially treated as having an insulinoma based on CT findings.

Although glibenclamide is known to have a higher risk of hypoglycaemia than gliclazide and other sulphonylureas,[17,18] in our series gliclazide was more commonly responsible. Gliclazide was also the OHA detected in the two patients who died, although the latter outcome appeared to be unrelated to the hypoglycaemic episodes. We postulate that gliclazide was implicated more frequently than alternative OHAs owing to its greater popularity among local prescribers.

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. Conventional toxicology screening may not be sufficient. To meet this challenge, our TRL developed a two-tier analysis system. The first involved the HPLC-based broad-spectrum screening, which was designed in-house to identify 13 OHA parent compounds and six OHA metabolites. The inclusion of OHA metabolites was particularly important for patients whose sampling was delayed. The second tier was the target analysis based on a LC/MS/MS method. This was superior to the HPLC-DAD broad-spectrum screening due to enhanced sensitivity and specificity. Evidently in 12 of our cases, an OHA was detected only by target analysis, and not by broad-spectrum screening.

We have explored the possible sources of OHAs in our cases. Taking family members' medications by mistake is one of the most common, 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.

For the nine RCHE residents, drug administration error 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[19] provide evidence of insufficiencies in several areas of drug management in these facilities, namely: physical storage, quality of storage, drug administration systems (including documentation), and the staff's knowledge about relevant drugs. Under these circumstances, possible drug administration error merits serious consideration, especially in patients with multiple morbidities and in receipt of multiple medications. We therefore recommend that every RCHE should regularly review and if necessary rectify drug management procedures. Training of RCHE staff about drugs should be enhanced and include information about proper drug storage as well as administration and documentation procedures. The prevention of hypoglycaemic events from erroneous OHA use will serve dual benefits, safeguarding RCHE residents' health, and avoiding unnecessary, inconvenient and costly hospitalisations.

Imbibing of CPM adulterated with OHAs (including glimepiride, nateglinide and rosiglitazone) was identified as the cause of hypoglycaemia in one patient. Three similar cases (none of whom developed hypoglycaemia) have

previously been identified by the TRL.[20] Similar cases have also been reported in Australia,[21] United States,[22] and Taiwan.[23]

Hypoglycaemia due to inadvertent use of OHAs is recognised 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 explored and if necessary remedial/preventive measures should be implemented. The importance of targeted toxicological investigation cannot be overemphasised.

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