

Anti-Diabetic Drugs as a Cause of Hypoglycaemia Among Acute Medical Admissions in Hong Kong and Singapore – Relationship to the Prescribing Patterns in Diabetic Patients

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ABSTRACT

Severe hypoglycaemia due to anti-diabetic drugs is a more important cause of medical admissions in Hong Kong (1.5%) than in Singapore (0.4% – 0.8%), although the prevalence and pattern of diabetes mellitus in the two Chinese populations are similar. Review of the available drug utilisation data indicated that glibenclamide and tolbutamide are the most frequently used sulphonylurea in Hong Kong and Singapore, respectively. These drugs also predominate among diabetic patients admitted with hypoglycaemia in the respective population. Since the risk of hypoglycaemia is greater for glibenclamide than other sulphonylureas, the increased incidence of anti-diabetic drug-induced hypoglycaemia in Hong Kong may, at least in part, be related to the frequent use of glibenclamide.

Keywords: hypoglycaemia, sulphonylureas, diabetes, Hong Kong, Singapore

INTRODUCTION

As in Singapore, diabetes mellitus in Hong Kong is predominantly of the non-insulin-dependent type (type II diabetes mellitus)⁽¹⁾. Its crude prevalence rate is 4.5%, which is similar to that of Singapore Chinese (4%)⁽²⁾. The truncated aged-adjusted prevalence (30 – 64 years) is also similar among Chinese living in Hong Kong and Singapore (men 9% vs 6.9%, women 6.3% vs 7.8%)⁽²⁾.

Possibly because of the common occurrence of NIDDM, severe hypoglycaemia due to anti-diabetic drugs is an important cause of acute medical admissions in Hong Kong (1.5%)⁽³⁻⁴⁾ and Singapore (0.4% – 0.8%)^(5, 6). Since hypoglycaemia may cause permanent brain damage and even deaths, identifying possible reasons for the increased frequency of this drug-related complication in Hong Kong is of obvious importance. In this review, variations in the pattern of drug use and other factors were therefore considered.

Anti-diabetic drug induced hypoglycaemia as a cause of medical admissions

Four studies of drug-related admissions⁽³⁻⁵⁾ or epidemiology of diabetes mellitus⁽⁶⁾ have provided

information on the importance of anti-diabetic drug-induced hypoglycaemia as a cause of medical admissions and the drugs involved (Table I). Three patients on metformin alone in one of the Singapore study⁽⁵⁾ were excluded from the present analysis because hypoglycaemia does not occur during metformin monotherapy⁽⁷⁾. In both the Singapore studies^(5, 6), it is not clear if only NIDDM patients admitted with hypoglycaemia were studied.

As already described, anti-diabetic induced hypoglycaemia is seen more often among medical admissions in Hong Kong than in Singapore. It is obvious from Table I, that the relative importance of insulin and sulphonylureas as an aetiological agent also differs considerably between Hong Kong and Singapore. Overall, insulin and sulphonylureas account for 22% and 78% of the study cases in Hong Kong, compared to figures of 42% and 58% in Singapore.

In countries with predominantly IDDM, the incidence of sulphonylurea and insulin induced severe hypoglycaemia requiring hospital treatment is 4.2 and 100 per 1,000 patients/year, respectively⁽⁸⁾. Decreased use of insulin in Hong Kong (or increased use of insulin in Singapore) cannot be the explanation for the observed variations in aetiological agents for two reasons. The relative use of insulin should be much the same since the pattern of diabetes mellitus is similar in both patient populations. Since insulin treatment carries a 20-fold increase in risk of hypoglycaemia compared to sulphonylurea therapy, decreased use in Hong Kong (or increased use in Singapore) of insulin would have been associated with a lower incidence (a higher incidence in Singapore) of anti-diabetic drug-induced hypoglycaemia among acute medical admissions.

Utilisation of anti-drugs

As can be seen in Table I, glibenclamide and chlorpropamide feature more prominently among the sulphonylurea cases in Hong Kong (77%) than in Singapore (31%, excluding two cases involving unknown drugs). This finding may suggest that the relative use of different sulphonylureas differs considerably between Hong Kong and Singapore.

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Table I – Anti-diabetic drugs induced hypoglycaemia in diabetic patients as a cause of acute medical admissions

	Period	NIDDM/ Chinese only		Anti-diabetic drugs responsible	Rate of admission
Hong Kong Chan et al ⁽³⁾	Jan-Nov 1990	Yes/Yes	9	glibenclamide 18 glipizide 6 chlorpropamide 3	1.5% (36/2404)
Chan and Critchley ⁽⁴⁾	Nov 1992 – Feb 1993	Yes/Yes	2	glibenclamide 7 gliclazide 3	1.5% (14/925)
Singapore Lee et al ⁽⁵⁾	Sept 1982 – April 1993	No?/No?	7	tolbutamide 7 glibenclamide 2 gliclazide 1 chlorpropamide 1	0.4% (20/4562)
Lee et al ⁽⁶⁾	Sept – Oct 1990	?/No	4	glibenclamide 1 glipizide 1 unknown oral hypoglycaemic 2	0.8% (8/1033)

Table II – Treatment of diabetic patients

	Settings	Patients	Diet only	Metformin only	Metformin + sulphonylureas	Sulphonylureas only	Insulins only
Hong Kong Chan et al ⁽¹⁰⁾	Hospital-based specialist general medical clinic	98 Chinese 100% all NIDDM	16	11	20 (metformin 20, glibenclamide 16, gliclazide 2, glipizide 1, tolbutamide 1)	48 (glibenclamide 31, glipizide 14 gliclazide 3)	3
Singapore Lee et al ⁽⁶⁾	Hospital-based medical admissions	135 Chinese 64.4% Indians 18.5% Malays 17.1% mostly NIDDM	24	----- 84 on metformin and/or sulphonylureas ----- (tolbutamide 56, glibenclamide 24, chlorpropamide 1, others 13, mainly metformin)			27
Lee et al ⁽¹¹⁾	Primary health care	187 mostly NIDDM	13	----- 156 on metformin and/or sulphonylureas ----- (metformin 65, tolbutamide 114, glibenclamide 33, chlorpropamide 11)			18*

Ideally, national utilisation of anti-diabetic drugs should be analysed. In Hong Kong, the 1994 data from the public sector, where the great majority of diabetic patients receive treatment, have been analysed⁽¹⁰⁾. The proportion of patients treated by different anti-diabetic drugs were then estimated to be as follows: sulphonylureas 70.24% (glibenclamide 58.80%, gliclazide 10.20%, tolbutamide 1.29%, chlorpropamide 0.62%, acetohexamide 0.33%), metformin 20.22%, insulin 9.53%. Glipizide was not included in the analysis because its sales data were not available.

National sales data from Singapore were not available. Findings from three small studies of drug use in hospital, clinic or primary care settings in Hong Kong or Singapore are summarised in Table II. It is worth noting that in Singapore, tolbutamide was the most frequently used sulphonylurea (66.6% – 72.2%), followed by glibenclamide (20.8% – 28.6%) and chlorpropamide (1.2% – 7.0%). In Hong Kong, glibenclamide was the most frequently used sulphonylurea (69.1%) in hospital-based general medical clinic.

Since the risk of sulphonylurea induced hypoglycaemia is known to be greater for chlorpropamide (taking the incidence as 100) and glibenclamide (111) than for glipizide (46) and tolbutamide (21)⁽⁹⁾, it is likely that the higher

incidence of anti-diabetic drug induced hypoglycaemia in Hong Kong may be related, at least in part, to the increased use of glibenclamide. Not surprisingly, this drug predominates among cases admitted to hospital with hypoglycaemia (Table I).

Other factors

The health care system through which patient care is delivered, may also be of importance. Old age and renal impairment are important risk factors for insulin and sulphonylurea induced hypoglycaemia⁽³⁾. It will be useful to find out if, in the presence of such risk factors, dose is reduced and long-acting sulphonylureas are avoided. Elderly diabetic patients are particularly prone to develop hypoglycaemia partly because of their lack of knowledge of warning symptoms. When 126 NIDDM patients attending a general medical clinic in Hong Kong were asked to answer 13 questions designed to test their knowledge of hypoglycaemic symptoms⁽¹²⁾, the overall score (maximum = 13) was low (mean \pm SD = 4.2 \pm 0.4) and there was an age-related decline in the scores (aged \leq 55 years 6.0 \pm 0.7, 56-65 years 4.4 \pm 0.7, 66 – 75 years 3.8 \pm 0.5, \geq 76 years 1.9 \pm 0.9). However, there have been no comparative studies of knowledge of hypoglycaemic symptoms and diabetes mellitus among patients in Hong Kong and Singapore.

CONCLUSION

Glibenclamide and tolbutamide are the most frequently used sulphonylurea in Hong Kong and Singapore respectively. These drugs also predominate among diabetic patients admitted with hypoglycaemia in the respective population. Since the risk of hypoglycaemia is greater for glibenclamide than other drugs, the increased incidence of anti-diabetic drug induced hypoglycaemia in Hong Kong compared with Singapore (1.5% vs 0.4% – 0.8%) may, at least in part, be related to the frequent use of glibenclamide. Longer-acting sulphonylureas (chlorpropamide and glibenclamide) are particularly hazardous in the elderly, in whom it is advisable to use shorter-acting sulphonylureas^(13, 14).

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