

ANTI-DIABETIC DRUG USE AND THE RISK OF MOTOR VEHICLE CRASH IN THE ELDERLY

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ABSTRACT

Background

Studies of the risk of motor vehicle crash associated with diabetes have produced conflicting results.

Objectives

To assess whether the use of anti-diabetic drugs among the elderly increases the risk of motor vehicle crash.

Methods

The computerized databases of the various universal insurance programs of Québec were linked to form a cohort of all 224,734 elderly drivers that was followed from 1990-1993. Using a nested case-control approach, all 5,579 drivers involved in an injurious crash (cases) and a random sample of 13,300 control subjects were identified. Exposure to anti-diabetic drugs was assessed in the year preceding the index date, namely the date of the crash for the cases and a randomly selected date during follow-up for the controls.

Results

The adjusted rate ratio of an injurious crash was 1.4 (95% CI: 1.0-2.0) for current users of insulin monotherapy relative to non-users and 1.3 (95% CI: 1.0-1.7) for sulfonylurea and metformin combined. Monotherapy, using either a sulfonylurea or metformin, was not associated with an increased risk. There was a dose-response effect in subjects using high doses of combined oral therapy (RR 1.4; 95% CI: 1.0-2.0). For users of insulin monotherapy or of high doses of combined oral therapy, the increase corresponds to an excess rate of 32 crashes per 10,000 elderly drivers per year.

Conclusions

Elderly drivers treated with insulin monotherapy or a combination of sulfonylurea and metformin, especially at high doses, have a small increased risk of injurious crashes. There is no increased risk associated with any regimen of oral monotherapy.

Key Words: Cohort study, case-control analysis, diabetes, elderly, injurious motor vehicle crash, pharmacoepidemiology

Elderly persons with diabetes may have more frequent motor vehicle crashes because of the complications associated with advanced disease, such as retinopathy and neuropathy, or from hypoglycaemia, a common side effect of some anti-diabetic drugs.^{1,2} This side effect, which

results in cognitive-motor slowing and loss of consciousness, could handicap driving performance particularly in the elderly.^{3,4} While some epidemiologic studies have found an increased risk of motor vehicle crash for individuals with diabetes⁵⁻⁷, others have not.⁸⁻¹⁰

Most studies published to date have focused on insulin or insulin-dependent diabetes, while evidence suggests that sulfonylureas, oral hypoglycaemic agents used by a majority of those with type 2 diabetes, are also likely to produce hypoglycaemia, particularly among seniors.^{2,11,12} Only two epidemiological studies have investigated the risk for individuals with diabetes using these oral agents. The first did not have sufficient power to assess with precision the relative risk for the use of oral hypoglycaemic drugs in general and sulfonylureas in particular.⁷ The second found no association with the use of oral agents, but also had insufficient power to obtain precise estimates of the risk.¹⁰ In the present study, we assess whether the use of insulin, sulfonylureas and biguanides is associated with an increased risk of motor vehicle crash in a large population-based cohort of elderly drivers.

METHODS

The study cohort was the object of a prior report on benzodiazepines, where the methods are described in detail.¹³ Briefly, we formed a cohort of all eligible drivers in the Province of Québec, Canada, identified from the province's automobile insurance agency's (*Société de l'assurance automobile du Québec* - SAAQ) driver's license file, who, between June 1 1990 and May 31 1993, were 67-84 years old. Given the restriction of the universal drug program to residents 65 years of age and older, sixty-seven was chosen as the age of entry to ensure that study subjects had at least 2 years of health coverage prior to cohort entry. An upper age of 84 was chosen because individuals are less likely to be driving beyond this age. Other inclusion criteria included possession of a valid driver's license and residence in Québec for at least 2 years preceding cohort entry. The date of cohort entry was June 1, 1990, and the exit date was the earliest of May 31, 1993 (end of study), the date of the event, age of 85 years, date of death, or the date of termination of health coverage due to emigration from the province.

The study outcome, identified from the SAAQ accident report file, was defined as involvement of a cohort member as the driver in a motor vehicle crash in which at least one victim, not necessarily the driver, sustained bodily injury. Crashes with property damage only were not

included because, from a public health perspective, they are of less relevance and importance than those with bodily injury, and they are also more likely to be underreported. In the case of multiple crashes during the study period, only the first eligible event was used. Prescription drug use and other covariate information were identified from the files of the *Régie de l'assurance maladie du Québec* (RAMQ), the agency responsible for administering universally insured health-care services for the province. The prescription drug database includes information on all out-patient prescription medications dispensed to individuals 65 years of age and older, and to recipients of social assistance. The accuracy and comprehensiveness of these files have been assessed, with < 1% of information contained in the records out of range or missing.¹⁴ Further assessment of accuracy, based on 723 prescriptions provided to 306 elderly patients attending an Internal Medicine clinic, revealed that 83% of these were present in the RAMQ database and correctly identified the patient and drug dispensed. Because of the large size of the cohort and the time-dependent nature of the exposure, a nested case-control approach was employed, which is a valid and efficient method of analyzing cohort data.¹⁵ All cases occurring during cohort follow-up were identified and assigned the date of a first injurious motor vehicle crash as their event date (i.e., index date). A random sample of 6% of the subjects from the cohort formed the control group and each control was assigned as an index date a date randomly selected from its follow-up time.

The following exclusion criteria were applied equally to all cases and controls: residence in a long-term care setting during the study period (defined as at least 1 physician visit in a long-term care setting) and previous hospitalization (defined as a hospitalization in the 60 days preceding the index date, regardless of length, or a hospital admission in the year before the index date with a duration of 30 days or more).

Anti-diabetic drug exposure

All anti-diabetic drugs available on the Québec formulary during the study period were identified. Insulins were regrouped into one category, and oral hypoglycaemic drugs were divided into sulfonylureas and biguanides, as these were the

only two classes of oral agents available at that time. There being only one biguanide available in Canada during the study period (i.e., metformin), this drug class is herein referred to as metformin. Prescriptions of oral hypoglycaemic agents dispensed in the year preceding the index date were also classified according to their recommended defined daily dose (DDD) at the time of the study, namely 10 mg for glyburide, 250 mg for chlorpropamide, 1500 mg for tolbutamide, 1000 mg for acetohexamide, and 1500 mg for metformin.¹⁶ The DDD is the assumed average maintenance dose for the main indication of a particular drug and is a well-established method for comparing equipotent doses of various drugs.¹⁷⁻¹⁹ The cumulative DDD was computed over the one-year period preceding the index date and the average daily DDD was then determined.

Data analysis

Anti-diabetic drug use was assessed during the one-year time window preceding the index date, namely the date of the crash for the cases and a randomly selected date during follow-up for the controls, as well as during the 30 days prior to the index date to reflect current exposure. For each of these time windows, exposure was defined as the dispensing of at least one prescription for an anti-diabetic agent. In all analyses, the reference group was defined as no use of any anti-diabetic agent in the year preceding the index date.

The rate ratio of injurious motor vehicle crash for all anti-diabetic drug groups was estimated using logistic regression.²⁰ To assess the dose-response relationship, the rate ratio was estimated by categorising the mean DDD as above or below 1 unit per day, except for the group receiving combined oral therapy for which the mean DDD was categorised as above or below 2 units per day to reflect dual drug therapy. All rate ratios were adjusted for the potentially confounding effects of age (within 1 year), sex, previous motor vehicle crash (dichotomized), and place of residence (urban or rural). In addition, the use of agents with central nervous system (CNS) effects and the chronic disease score (excluding diabetes) were evaluated as possible confounders using the change-in-estimate method.²¹ Rate ratios were adjusted for these factors only if the resulting estimate changed by more than 10%.

Use of CNS agents was defined as receipt of a prescription for any of the following medications in the 60 days preceding the index date: sedatives/hypnotics; analgesics; antidepressants; tranquilizers/anti-psychotics; lithium; centrally acting muscle relaxants. These agents were considered as they may increase the risk of motor vehicle crashes. The chronic disease score (CDS), shown to be a valid indicator of morbidity, is based on patterns of use of selected medications in the year preceding the index date and includes medications used to treat such chronic conditions such as heart disease, hypertension, and respiratory disease.²² Scoring rules are applied on the basis of the medication class or classes used in the treatment of each condition.

RESULTS

The cohort of eligible elderly drivers included 224,734 subjects from which 5,579 eligible cases were identified and the control group randomly selected from the cohort comprised 13,300 drivers. The characteristics of cases and controls are outlined in Table 1. Cases were similar to controls with respect to age, place of residence, and chronic disease score, but were considerably more likely to be male and have had a previous crash. In addition, cases were somewhat more likely to have been exposed to CNS drugs.

TABLE 1 Characteristics of cases and controls

Characteristic	Cases (N = 5,579)	Controls (N = 13,300)
Age, years (mean ± SD)	73.9 ± 4.3	73.4 ± 4.2
Male (%)	80.0	73.0
Rural residence (%)	48.0	46.0
CNS drug use (%) *	78.0	76.0
Previous motor vehicle crash (%)	3.4	1.9
Chronic disease score (mean ± SD)	2.8 ± 2.8	2.6 ± 2.7

CNS = central nervous system drugs.

*Exposure to any of the following drugs in the 60 days prior to the index date: benzodiazepines and other sedatives/hypnotics; opioids, partial opioids or other

analgesics; antidepressants; tranquilizers/antipsychotics; lithium; centrally acting skeletal muscle relaxants.

The prevalence of use of any anti-diabetic drug in the year preceding the index date was 8.4% among the cases and 8.2% among the controls (Table 2). Users of insulin in the one-year period preceding the index date represented 1.3% of the cases and 1.1% of the controls for an adjusted rate ratio of 1.2 (95% CI: 0.9-1.6). For the subsets of users of insulin alone and insulin in combination

with oral hypoglycaemic drugs, the rate ratios were 1.3 (95% CI: 0.9-1.7) and 1.0 (95% CI: 0.5-1.7) respectively. Oral hypoglycaemic drugs were used by 7.1% of the cases and 7.0% of the controls for an adjusted rate ratio of 1.0 (95% CI: 0.9-1.1). The adjusted rate ratio for the combined use of sulfonylureas and metformin was 1.2 (95% CI: 0.9-1.5).

TABLE 2 Crude and adjusted rate ratios of injurious motor vehicle crash according to the anti-diabetic therapy dispensed in the year preceding the index date

Anti-diabetic therapy	Cases (n=5,579)	Controls (n=13,300)	Crude rate ratio	Adjusted* rate ratio	95% confidence interval
No use [†] (reference)	5,111	12,214	1.0	1.0	Reference
Any insulin use	73	148	1.2	1.2	0.9 – 1.6
Insulin only	57	110	1.2	1.3	0.9 – 1.7
Insulin and oral agents	16	38	1.0	1.0	0.5 – 1.7
Oral hypoglycemics only	395	938	1.0	1.0	0.9 – 1.1
Sulfonylureas only	238	614	0.9	0.9	0.7 – 1.0
Metformin only	35	78	1.1	1.1	0.8 – 1.6
Both agents	122	246	1.2	1.2	0.9 – 1.5

*Adjusted for age, sex, previous motor vehicle crashes and place of residence.

[†]No use in the year preceding the index date

Table 3 indicates that the risk of injurious crashes was somewhat higher for current use of these drugs (in the month prior to the event) than for any use in the year preceding the index date. The adjusted rate ratio for the current use of insulin monotherapy was 1.4 (95% CI: 1.0-2.0), while

that for sulfonylureas and metformin combined was 1.30 (95% CI: 1.0-1.7).

On the other hand, use of either sulfonylurea or metformin monotherapy was not associated with an increased risk (RR 1.0; 95% CI: 0.8-1.1 and RR 1.0; 95% CI: 0.7-1.6 respectively).

TABLE 3 Crude and adjusted rate ratios of injurious motor vehicle crash according to current use of anti-diabetic therapy dispensed in the month prior to the index date

Anti-diabetic therapy	Cases [†] (n=5,579)	Controls [†] (n=13,300)	Crude rate ratio	Adjusted* rate ratio	95% Confidence interval
No use [‡] (reference)	5,111	12,214	1.0	1.0	Reference
Any insulin use	65	117	1.3	1.3	1.0 – 1.8
Insulin only	64	115	1.4	1.4	1.0 – 2.0
Insulin and oral agents	1	2	1.1	1.0	0.5 – 2.0
Oral hypoglycemics only	329	734	1.1	1.0	0.9 – 1.2
Sulfonylureas only	206	491	1.0	1.0	0.8 – 1.1
Metformin only	35	81	1.0	1.0	0.7 – 1.6
Both agents	88	162	1.3	1.3	1.0 – 1.7

*Adjusted for age, sex, previous motor vehicle crashes and place of residence.

[†]This analysis excludes 74 cases and 235 controls that received an anti-diabetic agent in the year preceding the event but are non users in the 30 days preceding the event.

[‡]No use in the year preceding the index date.

A dose-response effect was observed for the use of the oral hypoglycaemic drugs (Table 4). Among individuals receiving these agents, the risk of an injurious crash was greatest for those managed with high doses of combined therapy using sulfonylurea and metformin for an adjusted rate ratio of 1.4 (95% CI: 1.0-1.2) per two DDD.

Users of high doses of sulfonylurea monotherapy appeared to be at a slightly greater risk with adjusted rate ratio of 1.1 (95% CI: 0.8-1.5) per DDD but this estimate was associated with uncertainty due to the small number of individuals receiving high doses of these agents. There were too few users of metformin monotherapy to clearly determine if a dose-

response effect exists for this treatment modality (RR 2.0; 95% CI: 0.6-6.5).

Considering a baseline rate of injurious crash of 80 per 10,000 drivers per year in the non-diabetic elderly population (data not shown), we estimate 112 injurious motor vehicle crashes per year among individuals with diabetes treated strictly with insulin or high doses of combined oral therapy. The latter corresponds to an excess of 32 crashes per 10,000 elderly drivers treated with either modality per year. In our study population, the prevalence of use of these treatments was 2% and therefore accounted for 15 additional crashes per year.

TABLE 4 Crude and adjusted rate ratios of injurious motor vehicle crash according to the mean defined daily dose (DDD) of oral hypoglycaemic agents dispensed in the year preceding the index date

Oral hypoglycaemic drugs	Cases (n=5,579)	Controls (n=13,300)	Crude rate ratio	Adjusted* rate ratio	95% Confidence interval
No use [†] (reference)	5,111	12,214	1.0	1.0	Reference
Sulfonylureas only[‡]					
DDD > 1	62	128	1.2	1.1	0.8 – 1.5
DDD ≤ 1	182	507	0.9	0.8	0.7 – 1.0
Metformin only[‡]					
DDD > 1	5	6	2.0	2.0	0.6 – 6.5
DDD ≤ 1	32	75	1.1	1.0	0.7 – 1.6
Both agents combined[‡]					
DDD > 2	63	105	1.4	1.4	1.0 – 2.0
DDD ≤ 2	67	155	1.0	1.0	0.8 – 1.3

*Adjusted for age, sex, previous motor vehicle crashes place of residence and the use of insulin.

[†]No use in the year preceding the index date.

[‡]Adjusted for the concurrent use of insulin among: 6 cases and 21 controls for sulfonylureas; 2 cases and 3 controls for metformin; 8 cases and 14 controls for both oral agents combined.

DISCUSSION

In this population-based case-control study of elderly drivers aged 67 to 84, we found that the use of insulin alone or a combination of sulfonylurea and metformin, particularly at high doses, is associated with an increase in the rate of involvement in injurious motor vehicle crash (MVC) of approximately 30-40%. However, there was no increased risk with the use of either sulfonylurea or metformin used alone. The risk was somewhat higher among current users of insulin and combined oral therapy compared to use anytime in the year before the event, possibly reflecting the acute nature of drug induced hypoglycaemia. The increased risk of motor

vehicle crash with insulin and the combined use of sulfonylureas and metformin, particularly at high doses, are consistent with both elevated rates of hypoglycaemia associated with these forms of therapy and the complications associated with more advanced disease, such as retinopathy and neuropathy. We did not have information on the type and duration of diabetes, treatment history, or the presence of diabetes-related complications to assess the relative contributions of disease progression and drug-induced hypoglycaemia on this risk. Although metformin monotherapy does not usually cause hypoglycaemia, except in association with inadequate caloric intake, it does in combined use with a sulfonylurea.^{23,24} On the other hand, the lack of an association with

sulfonylurea monotherapy, oral hypoglycaemics with a longer duration of action known to induce serious hypoglycaemia, together with the increased risk observed for combined oral therapy and insulin monotherapy, both markers of disease progression, contradict the hypoglycaemia hypothesis.^{1,12,24,25} Moreover, the gradual increase in risk consistent with the stepped-care approach to the treatment of type 2 diabetes in Québec (from monotherapy using either a sulfonylurea or metformin, to combined therapy using both of these agents, to insulin) is more indicative of the effects of disease progression and associated complications than the hypoglycaemic effects of these drugs. The effect of advanced disease and related complications is further supported by a recent cohort study of almost 10,000 elderly females, where it was reported that older women with diabetes, particularly those treated with insulin, had a higher risk of falls than non-diabetics.²⁴ The risk factors for falls identified in this study population included poor balance, poor vision, and loss of pressure sensitivity (a measure of peripheral neuropathy), all factors associated with more advanced disease which may also contribute to an increased risk of MVCs. Further studies with data on disease severity and duration may aid in resolving this question.

Our results can in part explain the conflicting findings of previous studies associating diabetes with motor vehicle crashes.^{5,6,8,9} Clearly, the fact that the risk varies with the type and pattern of drug treatment suggests that different population mixes of these regimens may have produced the apparently conflicting results from other studies. A previous crash is known to be an important determinant of subsequent crashes, as demonstrated in our study and others.^{5,6,8,9} Yet, adjusting for this factor in the analyses produced little or no change in the risk estimates. This indicates that, despite the prognostic importance of this factor, a previous crash did not influence use or non-use of the agents assessed and consequently, was not a confounding factor for the association under study.

Our study had several limitations. First of all, anti-diabetic drug exposure was assessed from records of prescriptions dispensed on an outpatient basis. Because of the nature of the disease, we expect non-compliance to be low among insulin users. On the other hand, the use of

oral hypoglycaemic medications may be more irregular, which would tend to overestimate the true exposure classification of these agents.

Secondly, the data sources did not contain information on alcohol use or driving frequency but the potential confounding effects of these factors is likely minimal as previous studies in this area indicate.⁷ Specifically, the extent of potential confounding by alcohol use is believed to be minimal among the elderly because alcohol is not a major risk factor for MVCs for this age group as it is for younger drivers.^{26,27} The frequency and amount of alcohol use decreases with age, as does the decision to drive after having consumed alcohol^{28,29}, and previous studies in this area also provide evidence for lack of confounding by alcohol use.³⁰ Driving frequency would be a confounder if frequency of driving varied according to use or non-use of anti-diabetic drugs. Using data from the 1987 Québec Health Survey, we found that elderly diabetics drove only 130 kilometres less per year than others, who drove on average 8160 kilometres per year.³¹ Such a small difference is unlikely to be an important source of bias. In addition, if driving frequency varied by anti-diabetic drug treatment, we would expect users of insulin to be most likely to be warned against driving, given the known high rate of hypoglycaemia associated with this agent. If this had happened in our study, the use of insulin would have appeared to be protective since these individuals would not have been at risk of a MVC. However, we found the risk of MVCs to be highest for users of insulin monotherapy.

Thus, if at all, the reported risks are likely underestimates of the true risks. Finally, while we cannot rule out the possibility that some users of insulin alone had long-standing type 1 diabetes, such individuals are unlikely to represent a large proportion of insulin users in our study given the considerably older age of our population and the higher rate of diabetes-related mortality in those with type 1 disease^{32,33}, as well as treatment recommendations encouraging the use of insulin monotherapy over that of combined therapy during the study period.^{34,35}

Despite these limitations, our findings lead us to conclude that elderly persons treated with insulin or a combined regimen of sulfonylureas and metformin, particularly at high doses, have a small increased risk of MVCs. This would be true

whether the effect is drug-induced, due to the presence of diabetes related complications or a combination of these two factors given that the type and pattern of treatment is strongly correlated with disease progression. What is unclear at this time is whether those with diabetes-related retinopathy and neuropathy who are not receiving such treatments are also at increased risk.

The problem of motor vehicle crashes among elderly drivers is growing due to higher crash rates and increasing numbers of licensed drivers.^{36,37} In addition, prevalence data indicate that diabetes has reached epidemic proportions worldwide.^{38,39} Although the risk increases observed in our study are small, MVCs in this age group are associated with significant psychological consequences and loss of autonomy, as well as with considerably higher morbidity and mortality.^{40,41} For individuals treated with insulin alone or high doses of combined oral therapy, efforts should be made to reduce their risk of injury, including, among other things, an assessment of vision and peripheral neuropathy and education on approaches to minimize this risk, such as measuring blood glucose levels prior to driving. These groups of elderly diabetics with an elevated risk of injurious motor vehicle crash must be informed about this risk, while those treated with a sulfonylurea or metformin as monotherapy can be reassured.

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