

# Incidence of Lactic Acidosis in Metformin Users

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**OBJECTIVE** — The purpose of this study was to determine the incidence of lactic acidosis in a geographically defined population of metformin users.

**RESEARCH DESIGN AND METHODS** — The study was based on a historical cohort from the Saskatchewan Health administrative databases. Individuals with a metformin prescription dispensed between 1980 and 1995 inclusive were eligible for the cohort. Person-years of exposure were calculated. Cases were defined by hospital discharge with a diagnosis of acidosis (*International Classification of Diseases, Ninth Revision* code: 276.2) and confirmation by chart review of a blood lactate level  $\geq 5$  mmol/l. Death registrations of individuals dying within 120 days of a metformin prescription were also reviewed.

**RESULTS** — During the study period, 11,797 residents received one or more metformin prescriptions, resulting in 22,296 person-years of exposure. There were 10 subjects who had hospital discharges with a diagnosis of acidosis. However, primary record review revealed only two cases with laboratory findings of elevated blood lactate levels, for an incidence rate of 9 cases per 100,000 person-years of metformin exposure. In both cases, other factors besides metformin could have contributed to the lactic acidosis. No additional cases were found on review of death registrations.

**CONCLUSIONS** — From 1980 through 1995, the incidence rate of lactic acidosis was 9 per 100,000 person-years (95% CI 0–21) in patients dispensed metformin in Saskatchewan, Canada. This incidence rate was derived from a population with complete ascertainment of hospitalizations and deaths associated with lactic acidosis in metformin users. It is similar to previously published rates based on passive reporting of cases, and it is well below the lactic acidosis rate of 40–64 per 100,000 patient-years in patients prescribed phenformin.

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Metformin is a biguanide oral antihyperglycemic agent typically used to treat type 2 diabetes. Although marketed in Europe, Canada, and other countries in the 1970s, it was approved in the U.S. by the Food and Drug Administration (FDA) relatively recently—in 1995. Approval was delayed primarily because of the risk of lactic acidosis associated with the use of an earlier biguanide, phenformin. Biguanides decrease gluconeogenesis from alanine, pyruvate, and lactate,

and the accumulation of lactic acid may intensify under certain circumstances (1). The exact mechanism is complex, and Misbin has postulated that diabetes itself predisposes to lactic acidosis (2). In 1977, phenformin was banned as an “imminent hazard” by the FDA because it caused hundreds of cases of lactic acidosis, which has a 50% fatality rate. The estimated rate of phenformin-associated lactic acidosis ranged from 40 to 64 cases per 100,000 person-years (3,4).

The lactic acidosis rate in metformin users has been reported to be much lower: 0–8.4 cases per 100,000 person-years (4–6). However, rates have been based on passive reporting of cases. The FDA identified the need for a population-based incidence rate of lactic acidosis in metformin users because of concern about the serious underreporting that often accompanies passive reporting (7,8). Through the mechanism of a cooperative agreement, the FDA asked Saskatchewan Health to conduct a study; Saskatchewan Health is a government department of the Canadian province of Saskatchewan with complete ascertainment of outpatient prescriptions, hospitalizations, and deaths of the ~1 million people of the province.

## RESEARCH DESIGN AND METHODS

Saskatchewan Health is a provincial government department that funds a wide range of health services provided to the 1 million residents of the province. In almost all of its health programs, residents of the province enjoy universal coverage (i.e., 99% of the province's population is covered). There is no eligibility distinction based on socioeconomic status, and data collection is complete for the entire covered population. As a byproduct of funding these health services, Saskatchewan Health has a large volume of health data that exist centrally in computerized form. These data and their application in epidemiologic research have been described in detail elsewhere (9). The databases of different programs can be linked using a unique number assigned to each resident, allowing longitudinal exposure-outcome research.

The Cross Agency Study Committee (CASC) of Saskatchewan Health reviews all linkage studies to ensure that appropriate measures are taken to protect the confidentiality of the province's health beneficiaries and providers. After linkage was accomplished, all personal identifiers and fields of information irrelevant to the analysis of the study question were removed from the study data set. Each resident's unique health number was replaced with a study-specific identification number that bears no resemblance

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**Abbreviations:** CASC, Cross Agency Study Committee; FDA, Food and Drug Administration; ICD-9, *International Classification of Diseases, Ninth Revision*; SPDP, Saskatchewan Prescription Drug Plan.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

to the health number. The study was approved by the CASC.

The Saskatchewan Prescription Drug Plan (SPDP) covers the drug costs of every beneficiary, except for a small proportion of the covered population (~9%) whose prescription drug benefits are provided by the federal government. These federal beneficiaries were not included in this study. The outpatient prescription drug database captures data from pharmacy claims for formulary drugs dispensed to eligible beneficiaries. Drug data are accessible electronically from September 1975 to the present. Data are incomplete, however, for the 18-month period from July 1987 through December 1988 because of a program change that resulted in claims being submitted by patients after reaching a deductible (claims are now submitted by pharmacists at point-of-sale), and this time period was excluded from the study.

Metformin has been on the market in Canada since 1972 and has been listed in the Saskatchewan Formulary since 1981. The outpatient prescription drug database was searched for all beneficiaries with a metformin prescription dispensed between 1 January 1980 and 31 December 1995.

Person-years of exposure were calculated by summing the number of days between each prescription. Some 5% of prescriptions were exceptions to the usual length of time between prescriptions (e.g., same-day prescriptions and those for extended absences). For these exceptions, the quantity dispensed was used to calculate the number of days of exposure per prescription.

Using the unique number assigned to each resident, the hospital database was searched for any inpatient stays with a discharge diagnosis (primary, secondary, or other) of acidosis (*International Classification of Diseases, Ninth Revision* [ICD-9] code: 276.2) and an admission date occurring within 120 days after a metformin prescription. Because the ICD-9 code 276.2 is not specific for lactic acidosis, but also includes metabolic, respiratory, and NOS (not otherwise specified) acidosis, medical record review was essential to verify lactic acidosis, establish temporality between metformin exposure and lactic acidosis, and evaluate other possible risk factors for lactic acidosis. Lactic acidosis was defined as acidosis in which the blood lactate is  $\geq 5$  mmol/l (10,11).

To identify possible deaths from lactic acidosis without hospitalization, informa-

tion on cause of death (i.e., ICD-9 codes 276.2) was reviewed from death registrations (similar to death certificates in the U.S.) for all individuals who died within 120 days after filling a metformin prescription.

Hospital admissions and deaths had to occur within 120 days of a prescription being dispensed because metformin patients were considered at risk of lactic acidosis while they were taking the medication. Oral hypoglycemic agents may be dispensed in 100-day quantities under the SPDP (although many are dispensed in the more usual 34-day quantities). Therefore, patients were considered at risk for 120 days after a dispensed prescription to allow for consumption of the prescription (given a 100-day quantity), subsequent early fills (i.e., not beginning prescription immediately upon filling because the previous prescription was not finished), and possible noncompliance (i.e., prescription lasting longer than intended).

**RESULTS** — During the study period, 11,797 drug plan beneficiaries received one or more prescriptions for metformin, for 22,296 person-years of exposure. There were 10 subjects with a hospital discharge diagnosis code of 276.2 within 120 days after the dispensing of a metformin prescription. Six patients were excluded for the following reasons: two were no longer taking metformin at admission, one patient was diagnosed with ketoacidosis, and three patients had metabolic acidosis, including one with intentional formaldehyde poisoning.

Four patients were considered to present potential cases of metformin-associated lactic acidosis based on discharge diagnosis and laboratory findings or clinical notation. For two patients, physician notes in the medical record indicated the possibility of metformin-associated lactic acidosis, but blood lactate levels were not ordered. One of these, a 72-year-old woman who had been taking 1 g of metformin twice a day for ~16 months, had metformin discontinued on admission, but it was resumed 9 days later and then discontinued again in 2 days because of nausea. She died 2 weeks later of congestive heart failure. The other was an 85-year-old woman who had been taking 500 mg twice a day for ~3.5 years. The physician noted that lactic acidosis may have been due to sepsis and that metformin should be discontinued because of renal failure.

Only two patients had lactate levels ordered, and they were elevated in both. However, the reported lactate level of 12

mmol/l in a 60-year-old man with hepatic encephalopathy and a 20-year history of liver disease and alcoholism may have been spurious because the second lactate level of 1.9 ~24 h later was so much lower. During his hospital stay, he experienced sepsis, a gastrointestinal bleed, and a focal seizure. He had been taking 500 mg metformin twice daily for ~10 months.

The second patient, an 83-year-old woman who had been taking metformin 500 mg twice a day for ~3 months and had an elevated blood lactate of 13.2 mmol/l died on the day of admission; cause of death was reported as acidosis likely associated with a necrotic gut.

Of the 995 deaths occurring within 120 days of filling a metformin prescription, 969 death registrations were available for review. No additional cases of lactic acidosis were discovered.

An incidence rate of 9 cases per 100,000 person-years (95% CI 0–21) (12) was calculated based on the calculated person-years of exposure and two cases of lactic acidosis with substantiating lactate levels in metformin users. If the case with a possible spurious laboratory value is discounted, the incidence is reduced to 4.5 cases per 100,000 person-years (0–13).

**CONCLUSIONS** — This is the first known population-based longitudinal (16-year) postmarketing study with complete ascertainment of patients dispensed metformin, hospitalizations for lactic acidosis, and deaths with an ICD-9 code of 276.2. Because the rate of lactic acidosis in metformin users is low, this study has the advantage of having enough accumulated person-time of metformin exposure for detection of cases. While it could be argued that the rate of 9 per 100,000 person-years in Saskatchewan, Canada, is not generalizable to other populations, it is only slightly higher than previously published rates based on passive reporting of 0–8.4 cases per 100,000 person-years in other countries. From 1995 to 1996, the first year of metformin marketing in the U.S., the rate of lactic acidosis in metformin users was estimated to be 5 per 100,000 person-years based on the reporting to the FDA of 47 confirmed cases in ~1 million users (13). However, this rate is probably underestimated because there is usually underreporting of cases to the FDA.

Our study is consistent with other information concerning the importance of one or more risk factors in the develop-

ment of lactic acidosis in metformin users. The two Canadian metformin users with confirmed diagnosis of lactic acidosis had sepsis. Of the 47 American patients with confirmed diagnoses of lactic acidosis, 43 had risk factors, including preexisting cardiac disease and congestive heart failure, renal insufficiency, chronic pulmonary disease with hypoxia, and age >80 years (13). To determine the independent effect of metformin on the development of lactic acidosis, a very large study would be required to compare rates of lactic acidosis in metformin users with rates in users of other oral hypoglycemic agents while controlling for confounders. We believe the present study indicates that lactic acidosis is a relatively rare event in metformin users, most of whom appear to have concomitant predisposing risk factors.

In conclusion, from 1980 through 1995, the rate of lactic acidosis in metformin users of Saskatchewan, Canada, was 9 per 100,000 person-years (95% CI 0–21). This rate is similar to those reported earlier, and it is well below the rates of 40–64 cases per 100,000 person-years associated with phenformin use.

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