Frequency of Liver Disease in Type 2 Diabetic Patients Treated With Oral Antidiabetic Agents

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OBJECTIVE — We evaluated liver disease in conventionally treated type 2 diabetic patients to provide a reference against which reports of liver disease related to novel oral antidiabetic treatments could be compared.

RESEARCH DESIGN AND METHODS — In this follow-up study, patients with type 2 diabetes who were treated with oral antidiabetic agents were identified from the U.K.-based General Practice Research Database and were followed to determine whether they developed liver disease. The specific types and etiologies of liver disorders were determined. Incidence rates were calculated based on the accumulated exposure time to oral antidiabetic agents.

RESULTS — Among 44,406 type 2 diabetic patients, 605 had a computer diagnosis of liver disease with an incidence rate of 53.2/10,000 person-years (95% CI 49.2–57.6). Of the 605 subjects, 186 had nonsymptomatic, mild, and transient liver disorders; 249 had a predisposing condition; and 113 had another cause for the disease. A total of 57 cases were possibly drug induced with an incidence rate of 5.0/10,000 person-years (3.9–6.5). Of the cases, 11 were attributed to other drugs, 8 were attributed to fatty liver disease of diabetes, and the remaining cases were attributed to uncertain causes. Oral antidiabetic agents were continued in 51 of these 57 cases, and we could not rule out oral antidiabetic agents as a cause of liver disease in 2 cases with an incidence rate of 0.2/10,000 person-years (<0.1–0.6).

CONCLUSIONS — In this population, the background incidence of liver disease was high. Most cases involved other systemic diseases that may cause liver disease.

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A series of spontaneous reports on hepatotoxicity related to the new oral antidiabetic treatment troglitazone (1) has prompted this investigation of the baseline risk of liver disease in type 2 diabetic patients who are treated with conventional oral antidiabetic agents. Spontaneous reports provide only limited information about the incidence of adverse events related to a drug. Because not all events are reported, the information on reported cases is often incomplete, and the total number of drug users (i.e., the denominator to which the cases relate) is either unknown or unreliable when estimated from drug sales data (2,3). Therefore, we conducted a follow-up study of a defined population of type 2 diabetic patients treated with conventional oral antidiabetic agents to provide a baseline estimate of liver disease frequency for this particular population, who could be potential users of the new treatment. Furthermore, we determined the most likely cause of liver disease for all cases, particularly whether one of the conventional hypoglycemic treatments induced liver disease.

RESEARCH DESIGN AND METHODS

— More than 4 million residents in the U.K. (primarily in England and Wales) are enrolled with selected general practitioners who use office computers provided by Value Added Medical Products (London) and who have agreed to provide data for research purposes. This database is currently owned by the U.K. Department of Health and is known as the General Practice Research Database (GPRD). The GPRD is generally representative of the population in England and Wales (4). General practitioners have been trained to record medical information in a standard manner and supply the data anonymously on an ongoing basis. Among other items, the recorded information includes the patient's characteristics, medical conditions, and details of hospital stays. In addition, the general practitioners generate prescriptions directly from the computer, and these medications are automatically transcribed into the patient's computer record. A modification of the Oxford Medical Information System (OXMIS) classification is used to enter medical conditions, and a coded drug dictionary based on the Prescription Pricing Authority's dictionary is used to record prescriptions (5,6).

Study population

In this follow-up study, we used the GPRD to identify all patients with type 2 diabetes (*International Classification of Diseases* codes 250.0, 250.1, 250.2) who were exposed to an oral antidiabetic agent during the period 1989–1996.

A subject was defined as exposed to an oral antidiabetic agent from the date of the first prescription. We determined person-time for each exposed subject from the date of the first oral antidiabetic agent prescription until the last prescription plus 90 days, until the subject left the practice or died, or

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Abbreviations: GPRD, General Practice Research Database; LFT, liver function test; OXMIS, Oxford Medical Information System.

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

Table 1—*Diagnoses reviewed according to the OXMIS code*

OXMIS codes	Diagnosis
070	Infectious hepatitis
070 F	Fulminant hepatitis
070 N	Non-A and non-B hepatitis
K 501	Liver biopsy
570 XX	Acute hepatitis, acute massive hepatic necrosis, subacute massive hepatic necrosis
573 XX	Other liver disorders
574 XX	Gall bladder disorders
575 XX	Other gall bladder disorders
576 A	Obstructive jaundice
785 CP	Pale stools
L 3260	LFT
L 3260 AB	Abnormal LFT
L 3262 AB	Biochemical liver dysfunction
L 3263 AB	Abnormal liver enzymes
L 3263 H	Raised liver enzymes
L 3264 AB	Abnormal hepatic function
K 5091	Hepatostomy
5710 HA	Alcoholic hepatitis
5730 D	Hepatocellular damage
7516 JA	Familial intrahepatic cholestasis
7852 XX	Jaundice
5719 CH	Drug-induced jaundice

XX, category includes a range of diagnoses.

until the study period ended. If a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) was received in combination with an oral antidiabetic agent, the person-time was the time from the use of an oral antidiabetic agent with a statin. The person-times for oral antidiabetic agent exposure comprised the denominators from which rates of disease were calculated.

Case ascertainment

We identified all patients with a first-time computer-recorded diagnosis of a liver disorder that occurred within 90 days after receiving a prescription for an oral antidiabetic agent by using 22 OXMIS codes used in previous studies of drug-related liver disease (Table 1) (7–9). The computerized patient profiles of all such subjects were reviewed by a physician, and the subjects were classified as having one of the following: *1*) presence of predisposing conditions before the first prescription of an oral antidiabetic agent (e.g., congestive heart failure, cancer, alcoholism, or previous liver disease); 2) presence of predisposing conditions after receiving the first oral antidiabetic prescription but before receiving the liver disease diagnosis; *3*) mild, transient, and asymptomatic elevation of liver enzymes (the disease was considered mild and transient when the patient was not hospitalized or referred to a consultant, the oral antidiabetic agent was continued, and the computer record did not include further mention of a liver abnormality); *4*) the presence of another possible cause of the liver disease, such as viral or bacterial infections or autoimmune disease; and 5) the etiology of the liver disease was uncertain, and further case review was performed. The original medical records were requested for patients who were hospitalized or referred to a specialist.

For subjects who were not hospitalized, were not referred to a specialist, or whose medical records were not available, a determination of case status was based solely on the clinical diagnosis and laboratory values recorded in the computer profile.

If values of liver function tests (LFTs) were available, the following criteria were used to confirm liver disorders: *1*) an increase of at least twice the upper limit of normal range in alanine aminotransferase or conjugated bilirubin or 2) a combination of increases in aspartate aminotransferase, alkaline phosphatase, and total bilirubin with an increase in one of the levels of at least twice the upper limit of normal range (10).

RESULTS

Study population

We identified 44,406 patients with type 2 diabetes who were exposed to one or more oral antidiabetic agents alone or in combination with a statin. The age and sex distribution of these subjects is shown in Table 2. Most of the population was aged between 50 and 79 years (76%). The subjects received a total of 1,562,401 prescriptions for oral antidiabetic agents. Most subjects (63%) received ≥15 prescriptions for an oral antidiabetic agent (Table 3).

Subjects with predisposing conditions

Of the 44,406 study subjects, 4,216 had a condition that predisposed them to liver disease before they received a study drug. Among these subjects, 21% had a history of liver disease, 29% had cancer, 3% had a diagnosis of alcoholism, 36% had congestive heart failure, and 12% had some combination of these conditions. Among the subjects with predisposing conditions, 131 (3.0%) subsequently had a computer-recorded diagnosis of a liver disorder. These subjects were not examined further because they had an apparent predisposing condition before they received an oral antidiabetic agent. The remaining 40,190 subjects were free of a computer-recorded predisposing condition at the time of the first oral antidiabetic agent prescription.

Identification and evaluation of liver disease cases

We identified 605 subjects of the 40,190 subjects (1.5%) who had a first-time computer diagnosis of a liver disorder during exposure to an oral antidiabetic agent. Among these subjects, 43% were female, 11% of the subjects were aged <50 years, 20% were aged 50–59 years, 32% were aged 60–69 years, and 37% were aged >70 years. Of the 605 subjects, 249 (41.2%) developed a predisposing condition after receiving an oral antidiabetic agent but before receiving the diagnosis of a liver disorder. A total of 186 (31.0%) subjects had mild asymptomatic liver enzyme abnormalities that were not clinically relevant, and 113 (18.7%) subjects had a specified nondrug cause for the liver disorder on the computer record. A total of 57 subjects remained as possible drug-induced liver disorder cases. For the 37 patients who had been hospitalized or referred to a consultant, medical records

Table 2—*Age and sex distribution of the study population*

Age (years)	Men	Women	Total
<50	3,022	2,114	5,136 (12)
50–59	5,029	3,572	8,601 (19)
60–69	7,072	5,757	12,829 (29)
70+	7,640	10,200	17,840 (40)
Total	22,763 (51)	21,643 (49)	44,406

Data are *n* (%).

Table 3—*Number of users and number of prescriptions according to exposure cohort*

Exposure cohort	Number of users	Number of prescriptions
Sulfonylureas*	22,691 (51)	507,991 (33)
Metformin	4,890 (11)	100,351 (6)
Other oral antidiabetic agents†	175 (<1)	1,370 (<1)
More than one oral antidiabetic agent	15,440 (35)	899,970 (58)
With a lipid-lowering drug‡	1,210 (3)	52,719 (3)
Total	44,406 (100)	1,562,401 (100)

Data are *n* (%). *Sulfonylureas include glibenclamide, chlorpropamide, gliclazide, glipizide, gliquidone, and tolbutamide; †other agents include guar gum and acarbose; ‡lipid-lowering drugs include simvastatin, fluvastatin, and pravastatin.

were requested for further case evaluation, and 26 records were received. All other cases were evaluated based on the information in the computer record. Table 4 shows the age and sex distribution of these 57 subjects. Details on patients and their categorization according to the type of liver disease are shown in Table 5.

Two patients had disorders that were possibly causally related to an oral antidiabetic agent. One of these patients was a woman aged 58 years who had substantial elevation of alanine aminotransferase and alkaline phosphatase. After two prescriptions, metformin was discontinued, and elevated liver enzymes returned to normal within 8 weeks. The other patient was a debilitated woman aged 86 years who had received one prescription for metformin and one for glyburide. She developed jaundice shortly thereafter and died 1 month later. The cause of death was noted as "liver failure."

A total of 29 patients had transient asymptomatic jaundice, mild transient elevated liver enzymes, or mild transient hepatitis. The oral antidiabetic agent was continued in all of these cases, and these subjects were not considered to be of clinical importance. Eight had fatty liver disease secondary to diabetes, eleven had liver disease attributed to the use of a nonstudy drug, and one had insufficient information to determine the etiology of the liver disease. In 4 of these 20 cases, oral antidiabetic therapy was discontinued because of poor diabetes control or weight gain.

Six patients were diagnosed for the first time with persistent liver function abnormalities after taking an oral antidiabetic agent. In each of these cases, oral antidiabetic treatment was continued. Of these six patients, one had asymptomatic mild elevations that were noted during a 2-year period that subsequently returned to normal. Two subjects had mild chronic asymptomatic elevations of LFTs for which follow-up ceased after 9 and 19 months, respectively. Another patient had chronic asymptomatic elevations of alkaline phosphatase of uncertain origin; monitoring of LFTs was stopped after 2 years, and no further mention was made of the problem. One patient presented with ascites and subsequently died; the clinical diagnosis was nonspecific chronic hepatitis. Finally, one subject presented with jaundice that led to a liver transplant, and the clinical diagnosis was again nonspecific hepatitis. We had no clinical suspicion that antidiabetic agent therapy was causally related to the disease in any of these six subjects.

Frequency of liver disease

The overall frequency of newly diagnosed liver disorders was 605 out of 40,190 subjects with an incidence rate of 53.2/10,000 person-years of exposure (95% CI 49.2–57.6) to an oral antidiabetic agent. When subjects with mild and transient liver disorders (not clinically significant) were excluded from the numerator, the frequency was 492 out of 40,190 or 43.2/10,000 person-years (39.6–47.3).

The incidence rates of clinically relevant liver disease in the 57 subjects without predisposing conditions or other causes for the disease are shown in Table 5. The rate for all 57 cases of liver disorders was 5.0/10,000 person-years (3.9–6.5). The rate of liver disorders attributed to an oral antidiabetic agent was 0.2/10,000 person-years (<0.1–0.6), and the rate of liver disorders attributed to a nonstudy drug was 1.0/10,000 person-years (0.5–1.7). Among the cases attributed to a nonstudy drug were four cases attributed to the use of a statin with a rate of 4/1,191 or 33.6/10,000 person-years (13.1–86.0) (Table 5). In the remaining seven subjects in which another drug was implicated, the drugs were fluoxetine, chlorpromazine, itraconazole, thioridazine, amoxicillin with clavulanic acid, amoxicillin, and thioxanthene.

CONCLUSIONS — This study describes the underlying frequency of liver disease in patients treated with conventional oral antidiabetic medications. We studied this population to estimate the background rate of liver disease in subjects who are likely to be treated with new alternative oral antidiabetic medications. This rate provides a reference against which spontaneous reports of liver injuries associated with the novel oral antidiabetic agents can be evaluated. We categorized every case of liver disease according to the specific diagnosis and evaluated the etiology, particularly regarding whether and how often the liver disease cases were attributed to oral antidiabetic treatments.

Cases may be clearly attributable to causes such as viral or bacterial infections or less clearly to pharmacological treatments, to underlying or predisposing conditions, or even to diabetes itself. An association between diabetes and liver disease has been described (11). For example, higher frequencies of elevated liver enzymes, especially of alanine aminotransferase or γ-glutamyl transpeptidase, have been found in 20–30% of type 2 diabetic patients and in 5% of type 1 diabetic patients (12), and diabetes has been described as a predictor for elevated levels of alanine aminotransferase (13). Furthermore, liver diseases histologically categorized as steatosis, steatohepatitis, fibrosis, or cirrhosis with similarities to alcoholic liver diseases have been described in diabetic patients (14). Moreover, diabetic patients may be at higher risk for developing primary liver cancer (15). Few population-based studies on specific types of liver injuries have been performed because of the need to examine the liver tissue of people who do not have an indication for liver biopsy. Most studies have been performed

Table 4—*Age and sex distribution of the 57 cases of liver disorder with an unknown etiology*

Age (years)	Men	Women	Total
<50	0	4	4
50–59	10	5	15
60–69	8	11	19
70+	6	13	19
Total	24	33	57

Data are *n*.

Table 5—*Rates of liver disease according to category of liver disease*

Category of liver disease	*n*	Person-years at risk	Incidence rate per 10,000 person-years (95% CI)
Oral antidiabetic-agent associated	2	113,644	0.2 (<0.1–0.6)
Attributed to a nonstudy drug*	11	113,644	1.0 (0.5–1.7)
Transient illness	29	113,644	2.6 (1.8–3.7)
Chronic illness	6	113,644	0.5 (0.2–1.2)
Attributed to a fatty liver disease	8	113,644	0.7 (0.4–1.4)
Total	57†	113,644	5.0 (3.9–6.5)

*Four cases were attributed to a lipid-lowering drug with a rate of 33.6/10,000 (95% CI 13.1–86.0); †in one subject, the category of disease was uncertain.

in specialized diabetic populations, such as obese patients or patients undergoing gastric surgery (16,17), so the results from those studies may be too confounded to provide an estimate for the general population. We are not aware of any study that specifically addressed the frequency of liver disease among patients with type 2 diabetes treated with oral antidiabetic agents.

In studying type 2 diabetic patients who received oral antidiabetic medications, we did not evaluate people with mild diabetes controlled by diet and exercise, or severe diabetes requiring insulin treatment only. However, these groups were not pertinent to this study.

A total of 6,865 patients among the 44,406 (15.5%) oral antidiabetic users had additionally been treated with insulin at some time. Among the 57 cases of liver disease of uncertain cause, only 1 patient had received insulin before the event, and in that case the liver disorder was attributed to another nonstudy drug. Thus, liver disease was not related to insulin use in patients who were also taking oral antidiabetic agents.

The clinical information available from the computer records of the GPRD has been validated against additional information kept on manual records and has satisfactory validity for clinical studies (5). Therefore, we are confident that the information on the computer was sufficient for the determination of the final diagnosis.

The strategy we followed during case evaluation was to establish the most likely cause for the liver disease, including any predisposing and underlying conditions associated with the development of liver disorders that occurred before drug exposure (18). If these conditions occurred after the drug exposure, then we considered them to be the most likely cause for the liver disease because they may have masked any other possible cause. Therefore, we did not further evaluate the extent to which other conditions, the diabetes itself, or drug treatment were possibly involved (19).

We found a high overall liver disease incidence rate of 53.2/10,000 person-years (49.2–57.6) among type 2 diabetic patients during oral antidiabetic agent exposure but a very low incidence rate of 0.2/10,000 person-years (<0.1–0.6) for cases that possibly resulted from the use of oral antidiabetic agents. Two-thirds of all liver disease cases were most likely due to predisposing conditions (see RESEARCHDESIGN AND METHODS). For the 57 cases without predisposing conditions, we reviewed the patients' records to determine whether the physicians had designated an oral antidiabetic agent as the most likely cause of the liver disease. Most cases were attributed to other causes or to nonstudy drugs and were thus not regarded as causally related to oral antidiabetic treatment, a judgment that is supported by the continuation of treatment with oral antidiabetic agents in these patients. The number of prescriptions (a surrogate for duration of treatment) varied in these patients between 1 and 40. Both of the cases with liver disease possibly induced by an oral antidiabetic agent had short treatment periods.

Four cases of liver disease were attributed to treatment with statins with an incidence rate of 33.6/10,000 person-years (13.1–86.0). The risk of hepatic injury attributable to statin use has been described previously (20,21), and therefore one must consider statin use as a possible cause when evaluating spontaneous reports of liver disease.

The liver disorders reported in this study, except in rare instances, were not serious acute liver injury but were more mild forms of liver disorders that resolved without further complications. Three cases of liver failure occurred, two resulting in death and one involving liver transplantation. One case was possibly induced by an oral antidiabetic agent, but we had no clinical suspicion that an oral antidiabetic agent was causally related to liver failure in the other two cases. Thus, these data suggest that newly diagnosed acute liver failure among users of oral antidiabetic agents occurs but is uncommon in the absence of serious predisposing illness. We further conclude that the background rate of relatively mild liver disease (not due to oral antidiabetic treatment) in a population of type 2 diabetic patients is not uncommon and should be considered when evaluating spontaneous reports of liver disease in patients treated with novel oral antidiabetic agents.

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