Incidence of Drug-Induced Hepatic Injuries: A French Population-Based Study

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The incidence of hepatic adverse drug reactions (ADRs) remains unknown in the general population. The goal of this population-based study was to assess the incidence and seriousness of hepatic ADRs. All new cases of symptomatic drug-induced hepatic injuries were collected by 139 trained physicians (general practitioners [GPs] and specialists) between November 1997 and November 2000 in an area containing 81,301 inhabitants who could not go elsewhere for medical care. Over 3 years, 34 cases of hepatic ADRs were collected, 82% of them in outpatients. Global crude annual incidence rate was 13.9 ± 2.4 per 100,000 inhabitants; corresponding standardized annual global rate was 8.1 ± 1.5. There was no difference between urban and rural areas. Standardized incidence female/male ratio was 0.86 (0.26-2.90) until 49 years of age and 2.62 (1.00-6.92) after this age. Diagnosis was carried out by GPs in half of the cases. The outcome was recovery for 32 patients and death for 2. The main drugs implicated were anti-infectious, psychotropic, hypolipidemic agents, and nonsteroidal anti-inflammatory drugs (NSAIDs). Our results suggest that the number of hepatic ADRs in the French population would be 16 times greater than the number noted by spontaneous reporting to French regulatory authorities. In conclusion, the incidence and seriousness of drug-induced hepatitis are largely underestimated in the general population. These results may be useful for further evaluation of drug-induced hepatotoxicity. (HEPATOLOGY 2002;36:451-455.)

Liver damage is a frequent adverse drug reaction (ADR). Several methods can be used to assess this risk in postmarketing surveillance. Spontaneous reporting is one of the surveillance systems routinely used to identify hepatic ADRs associated with the use of drugs. This method, however, has often failed to quantify them in the general population. Some studies have been performed in France, but have only assessed incidence of ADR-induced hospitalizations.[1] The incidence of ADRs, especially hepatic ones, remains unknown in the general population. This knowledge would be useful in evaluating the risk/benefit ratio of hepatotoxic drugs. The goal of this study was to assess the incidence and seriousness of drug-induced hepatic injury in a general population.

Patients and Methods

Population Studied. This study was performed over 3 years, from November 5, 1997, to November 4, 2000, in the population living in the area around Nevers, a regional capital located in the rural French administrative department of Nievre. This area was chosen because the population could hardly go elsewhere for medical care: annual population mobility rate is below 1% and Nevers is more than 200 kilometers from the 3 nearest university hospitals. The residents of this isolated area are therefore mostly treated locally, and only a few patients are treated outside the local health care network. The 5 gastroenterologists practicing in this department in private and public medical hospitals supported and participated in the study. This favorable situation leads us to believe it is highly unlikely that we missed any serious cases of hepatic injury.

Abbreviations: ADR, adverse drug reaction; GP, general practitioner; NSAID, nonsteroidal anti-inflammatory drug.

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The 670 km^2 area defined by postcode numbers included 81,301 inhabitants over age 15, with a male/female sex ratio of 0.9 according to the most recent census taken in 1999; 81% of these (78,311) were urban dwellers, and 19% (18,871) were rural dwellers.

Data Collection. The 3 biologists and the 139 physicians received general information about the study: 75 general practitioners (GPs), 5 gastroenterologists, and 59 specialists who were usually directly consulted by patients whether in private or public practice (rheumatologists, psychiatrists, gynecologists, dermatologists, internists, and anesthesiologists). One hundred thirty-four physicians gave their support to the study; of these, 94 were trained by the scientific committee for the diagnosis of hepatic drug injuries in usual practice. Physicians were to continue their current practice, and in particular would not have to systematically use hepatic screening tests in treated patients unless specifically required by drug use guidelines. Each physician received a written protocol with notification forms and a biannual information letter produced by the scientific committee to encourage participation.

Physicians who suspected an adverse hepatic effect in outpatients or hospitalized patients over age 15 and residing in the area had to fill in a standardized notification form to report the case.

The main indicated items were physician characteristics (name, address, GP or specialist, private or public consultation), patient characteristics (first 3 letters of surname, age, sex, medical history), hepatic symptoms, and drug characteristics.

The French definition of adverse effects[2] was used: harmful and unwanted reaction occurring after prescribed or unprescribed drug intake at therapeutic dosage including treatments taken without respect for guidelines but excluding suicide attempts.

According to the proposal of an International Consensus Meeting,[3] hepatic injury was defined by an increase of alanine aminotransferase (ALT) or conjugated bilirubin over 2 N (upper limit of the normal range) or combined increase in aspartate aminotransferase, alkaline phosphatase (AP), and total bilirubin, provided that one of them is above 2 N. Cytolytic type was defined as ALT/AP ratio ≥ 5, cholestatic type as ratio ≤ 2, and mixed type as $2 <$ ratio < 5. Patients with isolated increased γ glutamyl transpeptidase were excluded.

Diagnosis of hepatic ADRs required at least hepatitis A, B, C serology and hepatobiliary ultrasonography. The results of all other investigations performed to assess the etiology of hepatic symptoms had to be indicated. Outcome (recovery or not, death) and seriousness (hospitalization, death related to adverse effect, invalidity or incapacity) had to be reported.

Table 1. Global Imputability: Chronological and Semiological Scores Crossing Table

	S_1: Dubious	S_2: Possible	S_3: Suggestive
C_0: incompatible	I_0 unlikely	I_0 unlikely	I_0 unlikely
C_1: dubious	I_1 questionable	I_1 questionable	I_2 possible
C_2: possible	I_1 questionable	I_2 possible	I_3 likely
C_3: suggestive	I_3 likely	I_3 likely	I_4 very likely

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The characteristics gathered for all drugs taken by the patient during the 2 months before the initial hepatic abnormality were commercial name, date of intake (beginning and end or ongoing), dosage, and method of administration. The drugs involved in the cases were assessed with regard to chronological and semiological criteria.[3] To establish the score of the possible relationship between each drug taken by the patient and the case, we used the method defined by the French regulatory authorities.[4] This method establishes the score of the possible relationship between each drug taken by the patient and the case. A global imputability score I (I_0, unlikely; I_1, questionable; I_2, possible; I_3, likely) is the result of crossing the chronological and semiological criteria scores (Table 1). Chronological score (C_0, incompatible; C_1, dubious; C_2, possible; C_3, suggestive) combines positive, negative, or unknown compatibility of time of onset, course of reaction, and potential reactivation in case of drug readministration. Semiological score (S_1, dubious; S_2, possible; S_3, suggestive) combines positive, negative, or unknown compatibility of previous knowledge of the considered adverse event with the suspected drug, exclusion of non–drug-related causes, and positivity of potential validated laboratory tests. Cases in which all drugs taken by the patient had I_0 or I_1 scores were excluded.

Physicians had to report suspected cases as soon as possible to the research fellow, who further investigated these cases on line and on site if necessary. The scientific committee reviewed all of the data every 3 months and chose patients included in the cases.

Statistical Analysis. Population data were provided by the National Institute for Statistics and Economics Studies. Population data and incident cases were tabulated by 5-year age groups. This enabled the calculation of crude and standardized incidence rates by sex. For the purposes of international comparison, standardized incidence rates were calculated by direct method using the World Standard Population as a reference population. Computations were performed using Stata Statistical Software (Stata Corporation, College Station, TX).

Results

During the 3 years of the study, 95 cases were recorded. Sixty-one were excluded: 19 cases occurred out of the study period or received an incorrect postal code, 1 was an intoxication after suicide attempt, 11 were diagnosis mistakes (1 isolated increase of γ glutamyl transferase, 1 rhabdomyolysis, 3 cardiac failures, 1 chronic alcoholism, 1 steatosis, 1 end-stage human immunodeficiency virus disease, 1 metastatic bladder cancer, and 2 Oddi spasms), 19 had incompatible chronological criteria for drugs (I_0, 7 cases; I_1, 12 cases) and 11 were nonsignificant biological abnormalities. In the end, 34 cases of drug-induced injuries were included: 12 men (mean age, 50.9; range, 27-77) and 22 women (mean age, 57.8; range, 25-80; $P = .24$).

Incidence Rates. Global crude annual incidence rate was 13.9 ± 2.4 per 100,000 inhabitants: 10.4 ± 3.0 per 100,000 in men and 17.1 ± 3.6 in women (NS), 13.7 ± 2.6 in the urban area and 15.0 ± 5.7 in the rural area (NS). Corresponding standardized annual global rates were 8.1 ± 1.5: 6.3 ± 1.9 in men and 9.8 ± 2.3 in women (NS), 7.9 ± 1.6 in the urban area and 9.9 ± 4.3 in the rural area (NS). Standardized female/male incidence ratio was 0.86 (0.26-2.90) until age 49 and 2.62 (1.00-6.92) after that age. No significant difference in use of medication was found between the 2 sexes (3.0 ± 1.7 in men and 4.5 ± 2.7 in women; $P = .09$) even if the mean number of drugs taken at the time of diagnosis was higher after 50 years old, with mean value 4.7 ± 2.6 (3.3 ± 2.0 in men and 5.2 ± 2.6 in women; $P = .13$) than before this age, mean 2.4 ± 1.4; $P = .01$ (2.7 ± 1.6 in men and 2.2 ± 1.1 in women; $P = .60$). Diagnosis (Table 2) was made by GPs in 17 cases (50.0%) and by gastroenterologists in 10 cases (29.4%).

Description of Drug-Induced Hepatic Injuries. All 34 cases (Table 3) of drug-induced hepatic injuries were acute hepatitis: 18 cytolytic hepatitis (among them, 2 fulminant hepatitis), and 16 cholestatic or mixed hepatitis. Ten patients had jaundice. Forty drugs were involved: 29 of 34 cases of hepatic injury were caused by a single drug; in each of the last 5 cases, 2 to 3 drugs were suspected. No case was induced by drug-drug interaction.

The drugs most often implicated were anti-infectious (10 cases: 25.0%), psychotropic (9 cases: 22.5%), hypolipidemic (5 cases: 12.5%), and nonsteroidal anti-inflammatory drugs [NSAIDs] 10.0%). Two cases were caused by antiandrogenic drugs for prostatic carcinoma treatment.

Four of the 34 patients (11.8%) needed hospitalization; all patients recovered after stopping the suspected drugs except 2, who died of fulminant hepatitis (5.9%). In these latter cases, drugs respectively suspected were nilutamide in a 62-year-old patient treated for prostatic carcinoma and prolonged acetaminophen treatment in a 72-year-old woman living alone, in a poor state of nutrition, who has taken the drug for chronic rheumatic pain for a few years at an increasing dosage evaluated by the family as from 4 to 5 g daily during the last month preceding the fulminant hepatitis.

Table 2. Distribution of the 34 Cases in the 2 Genders According to Age, Residence Status, Source of Diagnosis, and Liver Injury

	Male		Female		Total		
	n	%	n	%	n	%	P
Geographic location							
Urban area	9	75.0	18	81.8	27	79.4	
Rural area	3	25.0	4	18.2	7	20.6	.638
Age							
<35	2	16.7	2	9.1	4	11.8	
35-49	4	33.3	3	13.6	7	20.6	
≥50	6	50.0	17	77.3	23	67.6	.260
Type of hepatitis							
Cytolytic	7	58.3	9	40.9	16	47.1	
Cholestatic or mixed	4	33.3	12	54.5	16	47.1	
Fulminant	1	8.4	1	4.6	2	5.8	.611
Source of diagnosis							
GPs	8	66.7	9	40.9	17	50.0	
Gastroenterologists	1	8.3	9	40.9	10	29.4	
Other specialists	3	25.0	4	18.2	7	20.6	.135
Status of the patients*							
Outpatient	11	91.7	17	77.3	28	82.4	
Hospitalized	1	8.3	5	22.7	6	17.6	.293
Severity of hepatic injury							
Absence	10	83	20	90.9	30	88.2	
Hospitalized	2	16.7	2	9.1	4	11.8	
Death	1	8	1	4.5	2	5.9	.807

*At the time of diagnosis.

Discussion

Drug-induced hepatic injuries are well-known ADRs, usually recorded by spontaneous reporting in postmarketing surveillance. Although this information is important in alerting National Health Systems on the type and severity of hepatic ADRs, especially for new drugs, epidemiologic studies are essential for establishing the incidence of ADRs in the general population. Most studies have been performed in a population treated by a particular class of drugs, but there are no overall population-based data on hepatotoxic ADRs. Perez Guthann et al.[5] conducted a nested case-control study to estimate and compare the relative risk of hospitalization for newly diagnosed acute liver injury associated with the use of NSAIDs and other hepatotoxic drugs and their interaction in 228,392 members of the Saskatchewan Health Plan from 1982 to 1986. Crude risks ranged from 1 case for 100,000 prescriptions of methyldopa, ampicillin, or

Table 3. Characteristics of the 34 Drug-Induced Hepatitis Injuries

Number	Gender	Age	Presentation	ALT Peak (N)	AP Peak (N)	Bilirubin Peak (μmole)	Type	Drugs	Treatment Duration (d)	Time to Resolution (d)
1	M	38	Asthenia	6	1.1		Cytol	Paroxetine	120	30
2	M	67	Jaundice	7	2.5	57	Mixt	Valpromide	1,095	90
3	F	25	Hepatomegaly	6	1.3		Mixt	Amoxicilline + clavulanic acid	10	12
4	F	57	Asthenia	3	1		Cytol	Sertraline	150	25
5	F	66	No	4	1		Cytol	Methotrexate	360	30
6	F	52	Anorexia	4	1		Cytol	Amoxicilline + clavulanic acid	15	18
7	F	52	Jaundice	20	2	74	Cytol	Amoxicilline + clavulanic acid	6	30
8	M	77	Jaundice	48	2	152	Cytol	Flutamide	41	30
9	F	52	Anorexia	5.5	1.6		Mixt	Cloxacilline	5	15
10	M	68	Asthenia	3.5	1		Cytol	Atorvastatine	60	15
11	F	74	Asthenia, nausea	60	1.2		Cytol	Carbamazepine	730	21
12	F	54	Dark urine	10	2		Cytol	Halothane	1	30
13	M	27	Eruption	2	2		Chol	Amoxicilline	6	60
14	M	36	Abdominal pain	3	1.5		Chol	Ibuprofen	4	30
15	F	72	Jaundice	100	1	125	Fulmin	Paracetamol	730	Death
16	F	59	Nausea/anorexia	3	4		Chol	Venlafaxine	100	45
17	F	80	Abdominal pain	2	2		Chol	Ibuprofen	10	15
18	F	34	Jaundice	8	2.5	112	Mixt	Cyamemaz/desogestrel + ethinylest	300	90
19	F	73	Asthenia	13	1.5		Cytol	Fenofibrate	1,825	15
20	M	62	Jaundice	53	3	574	Fulmin	Nilutamide	60	Death
21	F	67	Jaundice	7	3	36	Mixt	Amoxicilline + clavulanic acid	7	15
22	M	36	Asthenia	3	1		Cytol	Fluvoxamine/lortazepam/zopiclone	45	30
23	M	51	Jaundice	4.5	3.5	47	Chol	Atorvastatine	300	30
24	F	40	Vomiting	5	1		Cytol	Interferon	60	30
25	M	73	Nausea/anorexia	74	1		Cytol	Pirilene	53	60
26	F	55	Asthenia	5	2		Mixt	Nevirapine	30	21
27	F	41	Jaundice	4	2	102	Chol	Nevirapine	21	30
28	M	32	Asthenia	8	1		Cytol	Nevirapine	30	30
29	F	74	Vomiting	9	2		Mixt	Fenofibrate	75	10
30	F	61	Anorexia	21	5.5		Mixt	Sulfazalasine/diclofenac	30/16	21
31	M	44	Asthenia	23	1		Cytol	Atorvastatine/ticlopidine	30/30	21
32	F	70	Abdominal pain	2.2	3		Chol	Ketoprofen/propoxyfen	3	30
33	F	38	Eruption	2.5	1		Cytol	Sulfasalazine	20	8
34	F	75	Jaundice	8	2	113	Mixt	Clopidogrel	46	30

NOTE. ALT and AP peak: maximal dosage (n = upper limit of the normal range)—Bilirubin peak: bilirubin dosages within normal range were not indicated; treatment duration: time between onset of treatment and first biological abnormal hepatic tests; time to resolution: time between stopping treatment and biological normalization.

NSAIDs to 14 cases per 100,000 prescriptions in current users of erythromycin estolate. Lanza et al.[6] studied 68,000 NSAID users belonging to a health maintenance organization to ascertain the frequency of liver abnormalities. The crude incidence was 0.51 per 1,000 person-years. In their review, Dossing et al.[7] estimated that 1 of 600 to 1 of 3,500 hospital admissions are linked to a hepatotoxic reaction, amounting to 2% to 3% of all admissions caused by ADRs. Bagheri et al.[8] conducted a prospective study in 1997. They selected patients from a computerized hospital process using biochemistry laboratory data based on abnormal serum enzyme values. Among the 147 selected patients, 8.8% cases of drug-induced hepatic injuries were suspected. Whatever the methods used, we failed to find published studies assessing the incidence of drug-induced hepatic injuries in the general population, either in France or abroad.

Our study was based on clinical and not on systematic biological detection. In that case, detection was performed by trained practitioners for outpatients as well as for hospitalized patients; this method was chosen to avoid overnotification of nonclinical linked biological abnormalities. Therefore, all cases were detected in symptomatic patients, and our results are more likely to underestimate than overestimate the real ADR incidence rate by missing some cases, despite the rigor of the investigators.

Our results showed a crude incidence rate of 13.9 of 100,000 inhabitants per year, which represents the first estimation of drug-induced hepatic injury in a general population. For comparison, hepatitis C annual detection rate is on the order of 30.0 in 100,000 in our region.[9]

This result suggests that more than 8,000 cases of hepatic ADR could occur annually in France, leading to 500 deaths. With regard to the 400 to 500 hepatic ADRs spontaneously notified per year by physicians to French Regulatory Authorities (Banque Française de Pharmacovigilance, Agence Française de Sécurité Sanitaire des

Produits de Santé, Paris), hepatic ADRs would be at least 16 times more frequent than is notified by spontaneous reporting.

In published literature, we failed to find studies assessing the rate of ADRs detected systematically in outpatients compared with hospitalized patients. In our study, diagnosis of drug-induced hepatic injuries was mainly carried out in outpatients. GPs detected and reported almost half of the cases. This result differs from those of the Lemozit et al. study[10] based on spontaneous ADR reporting, which found that hospital-based physicians reported more adverse reactions (89%) than nonhospital physicians (11%).

The difference found for the standardized annual incidence rates between the sexes was not globally significant, but our results do not go against the generally accepted idea that hepatic ADRs occur more often in women than in men.[11] Specific incidences rates, which were similar in the 2 sexes until age 49, became more than twice as high in women as in men after this age. It suggests that contrary to in men, the risk of drug adverse effects could vary during the life of women with a dramatic increase after menopause. In spite of a mean number of drugs slightly higher in women than in men, the role of multiple medications seemed insufficient to explain differences between the 2 sexes after age 50. Other factors might explain a role of female sex in ADRs: differences in pharmacokinetics; level of circulating hormones (endogenous and exogenous), which might change drug metabolism in the liver; and a difference in reporting rates between the 2 sexes.[12]

Our results emphasize the usefulness of prospective population-based studies in evaluating the real incidence of a drug-induced pathology compared with spontaneous reporting. This methodology particularly shows the benefits of involving and training GPs and private physicians in symptomatic ADR detection in outpatients, which often escapes spontaneous notification. These results may be useful as a reference for further studies of drug-induced hepatotoxicity.

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References

1. Pouyanne P, Haramburu F, Imbs JL, Begaud B for the French Pharmacovigilance Centers. Admissions to hospital caused by adverse drug reactions: cross sectional incidence study. BMJ 2000;320:1036.
2. Décret du 13 mars 1995, n° 95-278, article 5144-4. In Journal Officiel de la République Française. Lois et decrets. Paris, 14 mars 1995, 3935-3938.
3. Benichou C. Criteria of drug-induced hepatic disorders. Report of an international consensus meeting. J Hepatol 1990;11:272-276.
4. Begaud B, Evreux JC, Jouglard J, Lagier G. Unexpected or toxic drug reaction assessment (imputation): actualization of the method used in France. Therapie 1985;40:111-114.
5. Perez Guthann S, Garcia Rodriguez LA. The increased risk of hospitalizations for acute liver injury in a population with exposure to multiple drugs. Epidemiology 1993;4:496-501.
6. Lanza LL, Walker AM, Bortchinak EA, Gause DO, Dreyer NA. Incidence of symptomatic liver function abnormalities in a cohort of NSAID users. Pharmacoepidemiology and Drug Safety 1995;4:231-237.
7. Dossing M, Anderson PB. Drug-induced liver disease in Denmark. Scand J Gastroenterol 1982;17:205-211.
8. Bagheri H, Michel F, Lapeyre-Mestre M, Lagier E, Cambus JP, Valdiguie P, Montastruc JL. Detection and incidence of drug-induced liver injuries in hospital: a prospective analysis from laboratory signals. Br J Clin Pharmacol 2000;50:479-484.
9. Minello A, Boschi F, Harb M, Milan C, Faivre J, Hillon P. Mise en place d'un registre des hépatites virales B et C dans le département de la Côte d'Or. Methodologie, premiers résultats. Gastroenterol Clin Biol 1998;22: 766-771.
10. Lemozit JP, Petit de la Rhodière G, Lapeyre-Mestre M, Bagheri H, Montastruc JL. A comparative study of adverse drug reactions reported through hospital and private medicine. Br J Clin Pharmacol 1996;41:166-168.
11. Conforti A, Leone R, Ghiotto E, Velo G, Moretti U, Venegoni M, Bissoli F. Spontaneous reporting of drug-related hepatic reactions from two Italian regions (Lombardy and Veneto). Digest Liver Dis 2000;32:716-723.
12. Kando JC, Yonkers KA, Cole JO. Gender as a risk factor for adverse events to medications. Drugs 1995;1:1-6.