

Hepatic adverse drug reactions: a case/non-case study in Italy

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Abstract

Objective Adverse drug reactions (ADRs) can involve all tissues and organs. Liver injuries are considered among the most serious and are a cause for concern among physicians and patients. To assess the extent of drug-induced liver injuries in Italy we compared the number of cases of hepatic ADRs with reports of all other drug-related reactions present in the same database.

Methods Spontaneous reports from six Italian Regions collected from January 1990 to May 2005 were analysed. Adverse reactions were classified according to WHO Adverse Reaction Terminology for causality assessment,

and only those with “certain”, “probable” or “possible” causality assessment were included. Association between drugs and hepatic ADRs was assessed using the case/non case method, calculating the ADR reporting odds ratio (ROR) as a measure of disproportionality.

Results On May 2005, the database contained 35,767 ADR reports, of which 11,829 were excluded because they were unclassifiable or unlikely in terms of causality assessment. Therefore, the analysis was carried out on 23,938 reports, of which 1,069 concerned hepatic ADRs (cases) and 22,869 concerned non-cases. The proportion of serious ADRs was about 40% in the overall database, and about 74% among cases. The drug classes with the highest number of cases were statins (ROR=2.9, 95% CI 2.4–3.5), antiplatelet agents (ROR=3.5; 95% CI 2.6–4.6), NSAIDs (ROR=2.9; 95% CI 2.1–3.9) and macrolides (ROR=1.7; 95% CI 1.2–2.3).

Conclusion Hepatic adverse drug reactions remain a serious concern for several drugs widely used in clinical practice. Monitoring hepatic enzymes on a monthly basis for the first 6 months of treatment has been suggested for patients taking medications known to be hepatotoxic. A better knowledge of the epidemiology and mechanisms of hepatic ADRs may contribute to minimising their occurrence.

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Introduction

Adverse drug reactions (ADRs) are a partially avoidable cause of comorbidity and mortality. A meta-analysis published in 1998 showed that the incidence of serious ADRs in hospitalised patients is extremely high, with

ADRs being between the fourth and sixth leading cause of death in the United States [1]. ADRs can involve all tissues and organs; drug-induced liver injuries are considered among the most serious and are a matter of concern among physicians and patients. Moreover, hepatic ADRs remain the leading cause of drug-induced death and have often caused withdrawal of drugs from the market [2].

Liver damage is a potential complication for most drugs due to the anatomical and physiological features of the liver, which represents a primary target of drug toxicity. Drug-induced liver injuries may range from asymptomatic and non-serious increases in hepatic enzymes to life-threatening events such as fulminate hepatitis or hepatocellular necrosis [3]. The hepatotoxic mechanism of most drugs remains unknown; however, two possible types of reaction have been proposed: (1) predictable, dose-related, high-incidence reactions (e.g. acetaminophen overdose hepatotoxicity mediated by the formation of a reactive metabolite), and (2) non-predictable, low-incidence idiosyncratic drug reactions (e.g. immunoallergic reaction to halothane or autoimmune cytotoxicity of nitrofurantoin) [3].

Few epidemiological studies on this topic have been published to date [4]. Pre-marketing studies are unable to detect all possible types of hepatic ADR, in particular rare events; therefore, post-marketing surveillance systems, and, primarily, spontaneous reporting, are valuable tools in the identification of hepatic ADRs associated with the use of drugs in real-life practice. The aim of this study was to assess the extent of drug-induced liver injuries in Italy by comparing the number of cases of hepatic ADRs with reports of all other drug-related reactions.

Methods

The present study was based on data from spontaneous reporting in six Italian Regions (Veneto, Provincia Autonoma di Trento, Lombardia, Emilia Romagna, Sicilia, Friuli Venezia Giulia—these regions joined the database in the order given) that maintain a pooled ADR database. These regions have a total of about 23,700,000 inhabitants (42% of the Italian general population; see web site: <http://www.gruppogif.org>). To date, these regions contribute more than 60% of the national spontaneous reporting system. Spontaneous reports collected from January 1990 to May 2005 were analysed. In each regional centre, the reports were reviewed by medically qualified personnel (clinicians, pharmacologists and pharmacists) before being loaded into the database. Adverse reactions were classified according to the WHO Adverse Reaction Terminology (WHO-ART) for causality assessment, and only those with “certain”, “probable” or “possible” causality assessment were included [5].

Association between drugs and hepatic ADRs was analysed using a case/non case method [6–8]. Cases were defined as reports of hepatic adverse reactions classified under organ-system class code 700 of the WHO-ART classification [9]. Non-cases were all reports of reactions other than those being studied. Association between liver damage and the suspected drug was calculated using the ADR reporting odds ratio (ROR) as a measure of disproportionality. Calculation of ROR is identical to that of finding the odds ratio (OR) in a case-control study, and each drug was compared in turn to all the other drugs. RORs and 95% confidence intervals (CIs) were calculated using the statistical package Epi Info, version 3.3.2–2005 (<http://www.cdc.gov/epiinfo/>).

Results

On May 2005, the database contained 35,767 reports of ADRs, of which 11,829 were excluded because they were unclassifiable or unlikely according to the WHO-ART for causality assessment. Therefore, the analysis was carried out on 23,938 reports, of which 1,069 (4.5%) concerned hepatic ADRs (cases) and 22,869 concerned non-cases. The percentage of the serious ADRs was about 40% in the overall database, and much higher (about 74%) among the cases. A similar trend was observed for the proportion of lethal ADRs, 184 among non-cases (0.8%) and 16 among cases (1.5%). Among the 23,938 reports, the causality assessment was certain in 4.5% (1.3% among cases and 4.7% among non-cases), probable in 47.2% (60.0% and 46.6%) and possible in 48.3% (38.6% and 48.7%). Female/male ratios within cases (1.2) and non-cases (1.4) were not significantly different (chi-square=3.432, $P=0.064$).

Table 1 shows the drug classes (ATC IV level) with at least ten reports of hepatic ADRs, ranked by number of cases, with the corresponding ROR values and 95% CI. Table 2 shows the ROR for the most relevant drug classes and related agents. Table 3 shows examples of reported serious ADRs for selected agents, i.e., fluvastatin, ticlopidine, and interferon beta 1-a.

HMG-CoA reductase inhibitors [ATC code: C10AA] were the drug class with the highest number of hepatic reactions: 137 cases compared to 1,117 non-cases (ROR 2.9; 95% CI 2.4–3.5). In particular, fluvastatin, atorvastatin and simvastatin showed significant RORs. The relatively low number of cases for rosuvastatin and cerivastatin was probably due to the recent introduction of the former and the withdrawal from the market (in 2001) of the latter.

A significant ROR was also found for platelet aggregation inhibitors [B01AC] with 62 cases vs 399 non-cases (ROR 3.5; 95% CI 2.6–4.6). These cases were primarily due to ticlopidine (58 cases, ROR 4.6; 95% CI 3.4–6.2),

Table 1 Cases and non-cases and corresponding reporting odds ratio (ROR) of the drug classes with at least ten reports of hepatic adverse drug reactions (ADRs)

ATC IV	Drug categories	Cases	Non-cases	ROR (95% CI)
C10AA	Hydroxymethylglutaryl-CoA reductase Inhibitors	137	1,117	2.9 (2.4, 3.5)*
B01AC	Platelet aggregation inhibitors excluding heparin	62	399	3.5 (2.6, 4.6)*
M01AX	Other anti-inflammatory and antirheumatic agents, non-steroidal	52	394	2.9 (2.1, 3.9)*
J01FA	Macrolides	46	587	1.7 (1.2, 2.3)*
J01MA	Fluoroquinolones	34	865	0.8 (0.6, 1.2)
J04AC	Hydrazides	28	7	87.6 (36.4, 220.3)*
L03AB	Interferons	27	131	4.5 (2.9, 6.9)*
C01BD	Antiarrhythmics, class III	26	89	6.4 (4.0, 10.1)*
J05AF	Nucleoside and nucleotide reverse transcriptase inhibitors	22	112	4.3 (2.6, 6.9)*
J04AB	Antibiotics	20	24	18.1 (9.6, 34.1)*
N02BE	Anilides	19	177	2.3 (1.4, 3.8)*
J04AK	Other drugs for treatment of tuberculosis	18	7	55.8 (22.0, 147.2)*
C09AA	ACE inhibitors, plain	16	471	0.7 (0.4–1.2)
C10AB	Fibrates	16	65	5.3 (3.0, 9.5)*
J05AG	Non-nucleoside reverse transcriptase inhibitors	16	49	7.1 (3.8, 12.8)*
J01EE	Combinations of sulfonamides and trimethoprim	15	233	1.4 (0.8, 2.4)
M01AH	Coxibs	14	630	0.5 (0.3, 0.8)
N06AB	Selective serotonin reuptake inhibitors	14	255	1.2 (0.7, 2.1)
A02BC	Proton pump inhibitors	13	273	1.0 (0.6, 1.8)
L02BB	Antiandrogens	13	38	7.4 (3.7, 14.4)*
M01AB	Acetic acid derivatives and related substances	12	336	0.8 (0.4, 1.4)
N03AB	Hydantoin derivatives	11	23	10.3 (4.7, 22.2)*
N03AF	Carboxamide derivatives	11	139	1.7 (0.9, 3.2)
N03AG	Fatty acid derivatives	11	33	7.2 (3.4, 14.8)*
N05AH	Diazepines, oxazepines and thiazepines	11	67	3.5 (1.8, 6.9)*
J02AC	Triazole derivatives	10	86	2.5 (1.2, 5.0)*
L04AA	Selective immunosuppressive agents	10	138	1.6 (0.8, 3.0)
N02AA	Natural opium alkaloids	10	45	4.8 (2.3, 9.9)*

*Significant ROR

whereas clopidogrel and acetylsalicylic acid had non-significant RORs.

Among all NSAIDs [M01AA to M01AX], a significant disproportionality was found only for nimesulide, with 52 cases vs 394 non-cases (ROR 2.9; 95% CI 2.1–3.9). This overall finding was due mainly to a dramatic increase in the number of reports on hepatic ADRs for nimesulide after the news of the withdrawal of the drug from the Finnish market in 2002 (from 1–2 reports per year to 14–15 in 2002 and later).

Macrolide antibiotics [J01FA] showed a significant association with hepatic ADRs (ROR 1.7; 95% CI 1.2–2.3), due mainly to erythromycin (ROR 6.8; 95% CI 2.7–16.8) and clarithromycin (ROR 1.8; 95% CI 1.2–2.8).

Among interferons [L03AB], a significant ROR was found only for interferon beta-1a (ROR 18.1; 95% CI 9.6–34.1).

Didanosine and stavudine among nucleoside reverse transcriptase inhibitors (NRTI) [J05AF] and nevirapine

among non-nucleoside reverse transcriptase inhibitors (NNRTI) [J05AG] showed significant RORs.

Among selective immunomodulating agents [L04AA], only leflunomide showed a high disproportionality (ROR 6.4; CI 95% 2.3–16.9).

As expected, all groups of drugs for treatment of tuberculosis were significantly associated with hepatic reactions: examples are hydrazides [J04AC], with isoniazid showing 28 cases and 7 non-cases (ROR 87.6; 95% CI 36.4–220.0); antibiotics [J04AB], with rifampicin showing 18 cases and 19 non-cases (ROR 20.5; 95% CI 10.3–41); others [J04AK], with pyrazinamide showing 12 cases and 3 non-cases (ROR 86.2; 95% CI 22.7–384.5).

On the other hand, as shown in Table 1, several drug classes showed no statistical association with hepatic drug reactions. For example, for COXIBs [M01AH], 14 cases and 630 non-cases were reported (ROR 0.5; 95% CI 0.3–0.8).

Table 2 Cases and non-cases and corresponding ROR for the most relevant drug classes and related agents

Drug categories	Cases	Non-cases	ROR (95% CI)
<i>Hydroxymethylglutaryl-CoA reductase Inhibitors</i>	137	1,117	2.9 (2.4, 3.5)*
Fluvastatin	57	117	10.9 (7.8, 15.4)*
Atorvastatin	27	303	1.9 (1.3, 2.9)*
Simvastatin	31	302	2.2 (1.5, 3.3)*
Cerivastatin	6	212	0.6 (0.2, 1.4)
Pravastatin	10	129	1.7 (0.8, 3.3)
Rosuvastatin	6	54	2.4 (0.9, 5.8)
<i>Platelet aggregation inhibitors excluding heparin</i>	62	399	3.5 (2.6, 4.6)*
Ticlopidine	58	281	4.6 (3.4, 6.2)*
Clopidogrel	3	39	1.6 (0.4, 5.5)
Acetylsalicylic acid	1	79	0.3 (0, 1.8)
<i>Macrolides</i>	46	587	1.7 (1.2, 2.3)*
Clarithromycin	24	286	1.8 (1.2, 2.8)*
Azithromycin	8	112	1.5 (0.7, 3.2)
Roxithromycin	2	32	1.3 (0.3, 5.0)
Erythromycin	7	22	6.8 (2.7, 16.8)*
Telithromycin	1	56	0.4 (0, 2.5)
Spiramycin	1	46	0.5 (0, 3.1)
Flurithromycin	1	14	1.5 (0.2, 9.9)
Josamycin	1	7	3.1 (0.5, 17.5)
Miocamycin	1	12	1.8 (0.3, 11.3)
<i>Interferons</i>	27	131	4.5 (2.9, 6.9)*
Interferon beta-1a	20	24	18.1 (9.6, 34.1)*
Interferon alfa-2b	3	48	1.3 (0.3, 4.5)
Interferon beta-1b	3	15	4.3 (1, 15.7)
Peginterferon alfa-2b	1	44	0.5 (0, 3.3)
<i>Nucleoside and nucleotide reverse transcriptase inhibitors</i>	22	112	4.3 (2.6, 6.9)*
Didanosine	4	11	7.8 (2.1, 26.4)*
Lamivudine	3	21	3.1 (0.7, 10.8)
Lamivudine+zidovudine	1	17	1.3 (0.2, 8.3)
Abacavir	2	20	2.1 (0.5, 7.6)
Stavudine	9	29	6.7 (2.9, 14.7)*
Tenofovir	2	8	5.3 (0, 27)
Zalcitabine	1	6	3.6 (0.5, 20)
<i>Non-nucleoside reverse transcriptase inhibitors</i>	16	49	7.1 (3.8, 12.8)*
Nevirapine	15	29	11.2 (5.7, 21.7)*
Efavirenz	1	20	1.1 (0.2, 7.2)
<i>Selective immunosuppressive agents</i>	10	138	1.6 (0.8, 3.0)
Cyclosporine	2	14	3.1 (0.8, 10.2)
Infliximab	1	95	0.2 (0, 1.5)
Leflunomide	6	20	6.4 (2.3, 16.9)*

*Significant ROR

Discussion

Our study was based on the spontaneous reporting of suspected ADRs and therefore the results should be interpreted in this context. The advantages of this system include its inexpensiveness and the possibility of monitoring all marketed drugs in the entire population. The primary aim of a post-marketing pharmacovigilance system is to detect previously unknown adverse drug-related reactions or those occurring in a quantitatively or qualitatively different manner from that expected [10]. On the other

hand, a well-known limit of this approach is under-reporting, with the risk of underestimating the real burden of important ADRs. However, according to Van der Heijden et al. [11], if under-reporting concerns all ADRs, it would not bias the analysis of a large database. Another possible flaw is that the reports originate from different sources (physicians, pharmacists) and this may affect the quality of data. Despite these limitations, the role of this type of post-marketing surveillance should not be disregarded. Our analysis focused on hepatic adverse reactions, which are the leading cause of drug-induced death and have lead to withdrawal of some drugs from the market.

Table 3 Examples of reported serious ADRs for selected agents

Description	Fluvastatin	Ticlopidine	Interferon beta 1-a
Cholestasis intrahepatic	1	1	–
Gall bladder disorder	–	1	–
Hepatic dysfunction nonicteric	–	–	1
Hepatic enzymes increased	23	13	11
Hepatic function abnormal	4	4	1
Hepatitis	13	3	1
Hepatitis acute	6	5	2
Hepatitis cholestatic	4	16	–
Hepatitis toxic	4	2	3
Hepatocellular damage	1	3	1
Icterus	1	5	–
Icterus cholestatic	–	5	–
Total	57	58	20

We found significant RORs for widely used drug classes such as statins, antiplatelet agents, antimicrobial agents, NSAIDs, etc. An intrinsic limit of our analysis is related to the large number of tests performed, which affects the nominal level of significance. Apart from their significance, the ROR values obtained by us were in most cases quite large. Within each drug class, we found differences between individual agents deserving of detailed comment. It is known that statins can induce hepatic adverse reactions and this is considered a class-effect. Generally, they are represented by an asymptomatic and reversible increase in hepatic enzymes and, rarely, by serious liver damage [12]. In our database, out of the 1,254 ADR reports for statins, 137 concerned hepatic reactions (10.9%). As far as the individual drugs are concerned, an extremely high disproportionality was observed for fluvastatin (ROR 10.9, 95% CI 7.8–15.4). As suggested by Chong et al. [13], a possible explanation is that fluvastatin is the only statin metabolised by cytochrome P450 CYP2C9. Our finding is supported by the results of a recent meta-analysis [14], which showed that fluvastatin is more associated with liver function test abnormalities in comparison to other statins. This difference in the profile of hepatic safety of different statins should be taken into account when prescribing these drugs to individual patients, particularly patients with liver disease.

As far as NSAIDs are concerned, the only agent with a significant ROR was nimesulide. A systematic review showed that nimesulide [15, 16] and sulindac [16] are more probably associated with liver toxicity. In our analysis, sulindac did not appear significantly associated with hepatic injuries. It is important to highlight that nimesulide, which is not available in the United States market and in some European countries, was withdrawn from the Finnish market in 2002 due to some cases of lethal

fulminate hepatotoxicity. On May 2004, the European Medicines Agency (EMA) stated that, on the basis of the evaluation of world-wide spontaneous reporting systems and published data [17], the frequency of serious hepatic ADRs with nimesulide appears to be similar to that of other NSAIDs [18]. At the same time the EMA recommended restricted use of products containing nimesulide. We cannot exclude that the high number of reports of hepatic ADRs with nimesulide in our database could have been influenced by the alarm over this drug that was occurring in other countries. This is an example of the influence of press news or regulatory actions on the rate of ADR spontaneous reporting. The incidence of serious hepatic ADRs with nimesulide is considered low [15]. However, considering the wide use of this drug in Italy [19], the number of subjects affected by liver reactions to this drug would be not negligible.

Another drug with a significant ROR was ticlopidine. In the database we found 58 cases out of 339 reports, corresponding to 17.1%. This figure is comparable to the value of 21.1% reported in a Spanish study based on a spontaneous reporting system [20]. The liver toxicity of ticlopidine is known and appears to be due to an idiosyncratic mechanism [21]. Therefore the use of a lower dose of the drug would not protect the patient from potential hepatic damage. The choice of clopidogrel could be a valid therapeutic alternative in patients at increased risk of hepatotoxicity.

Among interferons, the only agent with a significant ROR was interferon beta-1a (ROR 18.1; 95% CI 9.6–34.1). In fact, 20 out of 24 cases of hepatic ADRs with interferons have been ascribed to interferon beta-1a. Although hepatic ADRs are relatively frequent with interferons alpha, such reactions with interferon beta are less well documented [22]. This potential “signal” arising from our data needs to be further investigated.

In our database we found 26 cases out of 115 reports (ROR 6.4; 95% CI 4.0–10.1) concerning amiodarone. The risk of liver injuries with this antiarrhythmic agent is stated in the summary of product characteristics (SPC). Among our 26 cases, 13 were serious non-lethal hepatic ADRs (acute hepatitis, toxic hepatitis, etc.) occurring with intravenous amiodarone. A recent case-series also indicates some fatal cases after intravenous administration [23]. Although this adverse reaction is rare, the authors’ conclusion was that clinicians should be aware of these symptoms and their possible management.

Among macrolides, we found significant RORs only for clarithromycin and erythromycin. It should be highlighted that the new ketolide telithromycin did not show any association with liver toxicity (1 case and 56 non-cases); however, three serious cases of hepatotoxicity due to telithromycin have been recently documented [24]. In the

SPC of telithromycin, hepatitis and cholestatic hepatitis are said to be rare or very rare events [25]. These data should be kept in mind in prescribing this drug, awaiting other post-marketing safety data [26].

Among drugs used to treat HIV infection, we found a significant ROR for two NRTIs, didanosine and stavudine, and for the NNRTI nevirapine. Some evidence for hepatic toxicity with nevirapine is available [27]. However, it is difficult to assess a causal relationship among these drugs and hepatic ADRs, considering that HIV patients can show multiple aetiologies for such abnormalities (drug toxicity, viral hepatitis, opportunistic infections, substance abuse, etc.). Close monitoring of all HIV patients treated with anti-HIV drugs (in particular NNRTIs) is recommended [28].

Another important finding arising from our data concerns the immunomodulating agent leflunomide, used in the treatment of rheumatoid arthritis. We found a significant disproportionality with 6 cases (4 classified as serious) out of 26 reports, whereas other immunomodulating agents, such as cyclosporin and infliximab, did not show any association with liver injury. Our data are consistent with the statement of the EMEA, which, on the basis of 296 reports of hepatic ADRs with leflunomide, recommended higher attention by physicians in the use of this drug [29]. However, an observational study published in 2004, conducted on 101 consecutive rheumatoid arthritis patients taking leflunomide followed for an average duration of 10 months, did not support this concern [30].

The hepatic adverse effects of drugs such as acetaminophen and the antiepileptics carbamazepine, phenitoin and valproic acid [31, 32] are well recognised. Anti-tuberculosis agents showed a significant ROR in terms of hepatic toxicity and this is a well-known occurrence. Our data are consistent with this evidence. There is a growing body of evidence that amoxicillin-clavulanic acid may induce serious hepatic adverse effects [33–35]. In our database, we found 31 cases (26 serious) out of 723 reports of ADR concerning amoxicillin-clavulanic acid. However the association did not appear statistically significant (ROR=1; 95% CI 0.6–1.4) and this may be due to the “diluting effect” of a higher reported number of ADRs other than hepatic reactions. As a matter of fact, our database contains 31/723 (4.3%) hepatic ADR for amoxicillin/clavulanic acid and only 4/616 (0.6%) for amoxicillin alone.

A particular finding arising from our analysis concerns COXIBs, which showed an inverse association with the reported hepatic adverse reactions, probably due to the much greater attention of doctors in reporting cardiovascular and gastro-intestinal adverse reactions than hepatic ones. Our analysis did not yield any signal of liver injury with COXIBs. This assumption is in part supported by two publications [36, 37] on the hepatic safety and tolerability of celecoxib, which showed an overall incidence of hepatic

reactions similar to that for placebo but significantly lower than other NSAIDs.

In conclusion, hepatic adverse drug reactions remain a matter of concern in the prescription of several drugs widely used in clinical practice. Our study, like other studies based on spontaneous reporting, cannot provide the true incidence of any ADR and its causal relationship. However, it may be helpful in an educational capacity to better assess drug risk/benefit profiles. The growing availability of information about the hepatotoxic profile of many drugs could avoid unwanted and noxious hepatic ADRs. Monitoring hepatic enzymes on a monthly basis for the first 6 months of treatment has been suggested for patients taking medications known to be hepatotoxic. A better knowledge of the epidemiology and mechanisms of hepatic ADRs may thus contribute to minimising their occurrence.

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