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Drug-induced hepatic injury in children: a case/non-case study of suspected adverse drug reactions in VigiBase

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Drug-induced hepatic injury is one of the most important reasons for drug withdrawal in adults.
- Very little is known about drug-induced hepatic injury in children and adolescents.

WHAT THIS STUDY ADDS

- The rate of hepatic injury as suspected adverse drug reactions in the paediatric population is low.
- Drugs associated with hepatotoxicity in children and adolescents were mostly known to be associated with hepatotoxicity in adults as well.

AIM

To identify which drugs are associated with reports of suspected hepatic injury in children and adolescents.

METHODS

Using a worldwide pharmacovigilance database, VigiBase, we conducted a case/non-case study on suspected adverse drug reactions (ADRs) occurring in the population <18 years old. Cases were all the records with hepatic ADRs and non-cases were all the other ADR records. Records regarding topically administered drugs were excluded from both groups. The association between drug and suspected hepatic ADRs was calculated using the reporting odds ratio (ROR) as a measure of disproportionality while adjusting for gender, country, reporter and calendar year. Sub-analyses were performed within therapeutic class and by excluding vaccination-related reports to reduce confounding.

RESULTS

Overall, 6595 (1%) out of 624 673 ADR records in children and adolescents concerned hepatic injury. Most of the reported hepatic injuries concerned children 12–17 years of age. Drugs that were most frequently reported as suspected cause and were associated with hepatic injury comprised paracetamol, valproic acid, carbamazepine, methotrexate, minocycline, zidovudine, pemoline, ceftriaxone, bosentan, ciclosporin, atomoxetine, olanzapine, basiliximab, erythromycin and voriconazole. The association between hepatotoxicity and all these drugs, except for basiliximab, is already known.

CONCLUSIONS

Drug-induced hepatic injury is infrequently reported (only 1% of total) as a suspected ADR in children and adolescents. The drugs associated with reported hepatotoxicity (paracetamol, antiepileptic and anti-tuberculosis agents) are known to be hepatotoxic in adults as well, but age related changes in associations were observed. VigiBase is useful as a start to plan further drug safety studies in children.

Introduction

Drug-induced hepatic injury is one of the most important reasons for drug withdrawal [1], but very little is known about drug-induced hepatic injury in the paediatric population. Most of the evidence comes from small case series [2].

Although pharmacovigilance activities were boosted after the thalidomide disaster in children, pharmacovigilance and pharmacoepidemiology studies in children are still infrequent. There is not enough systematic monitoring of drug safety (i.e. signal generation) in children and adolescents separately. On the contrary, signal generation is generally performed considering the entire population. Children are not just small adults and the pharmacologic effects (both therapeutic and adverse ones) of drugs in these patients cannot be extrapolated from the observed effects in adults. Susceptibility to drug toxicity changes with age and can differ largely between newborns, toddlers, adolescents and adults, because of age-dependent maturation of pharmacokinetic processes. This is particularly so for the liver which is the main organism for drug metabolism [3–5]. Most drugs are metabolized through the cytochrome P450 (CYP 450) isoenzymes. The change in maturation and activity of CYP 450 occurring with age may have a strong influence on the capacity to eliminate the drugs between newborns and adults. For instance, at birth, the CYP 450 isoenzymes are only 50% of the adult values, but their expression quickly changes during the first months [6].

Considering the lack of comprehensive information about drug-induced hepatic injury in children and adolescents, the aim of this study was to assess which drugs are associated with hepatic injury in the paediatric population, in a worldwide spontaneous reporting database.

Methods

Data source and selection of cases and non-cases

For this study we analyzed the reports of suspected ADRs in VigiBase, the World Health Organization (WHO) global individual case safety report (ICSR) database which was established in 1968 and is maintained by the Uppsala Monitoring Centre (UMC) [7]. VigiBase is the largest database worldwide with >4 million ICSRs covering more than 40 years. The suspected ADRs are sent to UMC from the national centres participating in the WHO Programme for International Drug Monitoring. Currently, 95 countries submit ICSRs to VigiBase. The origin of reports is heterogeneous as some of these countries have voluntary reporting and others more mandatory systems. Healthcare professionals, consumers and marketing authorization holders may fill the reports. A significant proportion of the WHO-UMC database comprises data from the US Food and Drug Administration spontaneous reporting database (AERS) [8, 9]. Due to the multiple entry modes and duplicate reporting of national reports to both WHO and AERS, removal of the duplicates is an important quality procedure at UMC. Duplicate detection in VigiBase is not only limited to the simple check of case identifiers and manual inspection of given case series, but includes also specific statistical algorithms [10]. The suspected ADRs are coded by using the WHO-Adverse Reactions Terminology (WHO-ART) and MedDRA (Medical Dictionary for Regulatory Activities) [11]. Drugs are coded by the WHO Drug Dictionary, which offers indexing and retrieval of drugs by the hierarchical Anatomical Therapeutic Chemical (ATC) classification [11].

Data analysis

For the evaluation of drug-induced hepatic injury in children and adolescents, we used all the records of suspected ADRs occurring in people <18 years old, as registered in VigiBase during the period January 2000 until December 2006. We excluded all the records in which the suspected drug was a topically administered medication (assuming that these would not cause liver injury and would lead to underestimation of risk). For signal detection, we used the records as unit of analysis, which is the normal routine in the WHO-UMC [12]. An ICSR can contain more than one suspected drug and/or more than one ADR, whereas a record is a unique combination of a drug and an ADR. Hence, an ICSR containing two ADRs with one suspected drug will count for two records and an ICSR containing two ADRs with two suspected drugs will count for four records. Information on these records include country of origin, reporter, age at onset, year of onset, gender, reported drug, reported ADR, start and stop date of the drug, start and stop date of the ADR, dosing regimen of the drug, administration route and causality assessment of the event.

Associations between specific drugs and hepatic ADRs were analyzed using the case/non-case method [13, 14], a technique which was introduced in 1991 in a study with WHO data on serum sickness to cefaclor [15]. Cases of hepatic injury were records of suspected ADRs in which one of the following preferred terms was indicated: abnormal hepatic function, active chronic hepatitis, biliary tract disorder, bilirubinaemia, bilirubinaemia aggravated, bilirubinuria, cholangitis, cholecystitis, cholelithiasis, cholestatic hepatitis, fatty liver, gallbladder disorder, gamma-GT increased, hepatic cirrhosis, hepatic coma, hepatic enzymes increased, hepatic failure, hepatic necrosis, hepatitis, hepatocellular damage, hepatomegaly, hepatorenal syndrome, hepatosplenomegaly, jaundice, sGOT increased and sGPT increased. These are all the preferred terms listed in the system-organ class 'liver and biliary diseases' from the WHO-ART [12, 16]. Records with Budd-Chiari syndrome, infectious and viral hepatitis and veno-occlusive liver disease were excluded as these hepatic injuries are not drug-related [16]. Non-cases were all non-hepatic suspected ADR records in children and adolescents. The sus-

pected ADR reporting odds ratio (ROR) was calculated as measure of disproportionality for all the drugs that had at least four records of hepatic injury [17].

In a first crude approach, we compared the odds of exposure to a specific drug in hepatic injury cases with the odds of exposure to the specific drug in all non-hepatic ADR records. Second, the crude RORs were adjusted for calendar year, gender, country of reporting and type of reporter by using multivariate logistic regression analysis. Third, the analysis was restricted to the drugs belonging to the same therapeutic class (ATC-based, II level). This sensitivity analysis was carried out to limit confounding by indication and by severity and to investigate whether the effect of a specific drug was greater than its class effect. An additional analysis was conducted in which all the records associated with vaccines were excluded, since vaccines may distort reporting odds ratios due to the large number of records of vaccine-related ADRs, and the low probability of vaccine-induced hepatic injury. A fourth analysis was conducted which limited the records to those with a reported causality assessment ('certain', 'probable' or 'possible'). As the last step, we looked at effect modification by age stratifying the analysis in the following age categories: 0–1 month, 0–2, 3–11 and 12–17 years. Due to the low number of reports for neonates, these were combined in the category 0–2 for all main analyses.

The statistical package SPSS (version 15.0) was used for all statistical analyses. MICROMEDEX(c) was used as the drug information source to verify whether hepatotoxicity was mentioned as a potential adverse drug reaction for those medications which were found to be associated in our study [18].

Results

In the period 2000–06, VigiBase comprised 226 087 suspected spontaneous ICSRs in the population aged <18 years, corresponding to a total of 867 405 records. The FDA-AERS contributed most of these records ($n = 569\,701$). Stratification by country showed that the highest rate of reporting of hepatic injury was observed in Germany (5% of total German records) (Table 1).

After exclusion of all records related to topically administered drugs, 624 673 records of suspected ADRs remained and these were the basis of our analysis. Most suspected ADR records regarded children aged <3 years (47.8% of total records), but vaccine-related reports accounted for a large proportion of reports in this age category (Table 2).

Among 624 673 records, only 1.1% (number of cases = 6595) concerned hepatic injury. The rate of hepatic injury reporting in the paediatric population increased with age (from 0.5% of total records among the youngest children up to 2.2% of total records among the oldest) and was highest for children aged 12–17 years. Upon exclusion of vaccine-related ADR records, the age related increase in the rate of reported hepatic injury was less pronounced (Table 2).

Table 1

Distribution of suspected ADR records by country from VigiBase*

Country	Total records† $n = 867\,405$ (%)	Hepatic injury records† $n = 9036$ (% of total records per country)
United States of America	569 701 (65.7)	5363 (0.9)
France	24 005 (2.8)	968 (4.0)
Germany	16 431 (1.9)	827 (5.0)
United Kingdom	44 004 (5.1)	352 (0.8)
Canada	86 555 (10)	300 (0.4)
Australia	27 727 (3.2)	262 (0.9)
Spain	7 309 (0.8)	143 (2.0)
Sweden	7 919 (0.9)	95 (1.2)
Netherlands	4 289 (0.5)	64 (1.5)
Ireland	5 798 (0.7)	46 (0.8)
Thailand	17 058 (2.0)	44 (0.3)
New Zealand	18 833 (2.2)	28 (0.2)
Italy	4 600 (0.5)	18 (0.4)

*Data from 2000 until 2006. †Only the countries with more than 4000 reports have been listed in the table.

Ranked by the absolute number of cases (Table 3), the top 10 most frequently suspected drugs for hepatic injury were isotretinoin (6.4% of total number of cases), followed by paracetamol (5.3%), valproic acid (3.2%), carbamazepine (2.1%), methotrexate (2.0%), hepatitis B vaccine (1.9%), minocycline (1.8%), lamotrigine (1.7%), zidovudine, pemoline and ceftriaxone (1.6%). The reporting odds ratio for hepatic injury was statistically significant for all drugs mentioned above, except for hepatitis B vaccine. After adjustment for calendar year, gender, country of reporting and type of reporter, significant associations remained for all these drugs (Table 3).

Ranked by the strength of the crude ROR, the top 10 drugs with associations higher than 10 included oxymetholone, norethisterone/ethinyloestradiol combination, milrinone, retinol, atazanavir, pemoline, pyrazinamide, isoniazid, naltrexone and troglitazone (Table S1).

When restricting the analysis to the drugs belonging to the same therapeutic class, in most of the cases RORs decreased, pointing to confounding by indication or class effects (Table 4). Within the therapeutic groups that were most frequently involved in hepatic ADRs (with at least 100 cases), the following drugs were standing out from their class: sultiame, ethosuximide, phenobarbital, valproic acid and carbamazepine among the antiepileptics (N03), aztreonam, loracarbef, erythromycin, ceftriaxone, josamycin, minocycline among antibacterial agents (J01), paracetamol among analgesics (N02), pemoline, nefazodone, atomoxetine among psycho-analeptic drugs (N06) and mercaptopurine, gemtuzumab, tioguanine and methotrexate among antineoplastic drugs (L01).

Table 2

Age and gender distribution of suspected ADR records* from VigiBase

	Total records		Hepatic injury records	
	With vaccines $n = 624\,673$ (%)	Without vaccines $n = 226\,266$ (%)	With vaccines $n = 6595$ (% of total records per category)	Without vaccines $n = 6147$ (% of total records per category)
Age groups (years)				
<3	298 718 (47.8)	43 465 (19.2)	1360 (0.5)	1104 (2.5)
3 to 11	177 029 (28.3)	75 345 (33.3)	1962 (1.1)	1882 (2.5)
12 to 17	148 926 (23.8)	107 456 (47.5)	3273 (2.2)	3161 (2.9)
Gender				
Girls	298 209 (47,7)	108 431 (47.9)	3136 (1.1)	2947 (2.7)
Boys	316 280 (50.6)	113 264 (50.1)	3328 (1.1)	3072 (2.7)
Unknown	10 184 (1.6)	4 571 (2.0)	131 (1.3)	128 (2.1)

*Excluding topical drugs.

After exclusion of records involving vaccines we retained a total of 226 266 records of suspected ADRs in children and adolescents and 6147 of these (2.7%) concerned hepatic injury. Exclusion of vaccine-related records from the analysis resulted in a strong decrease in the association between individual drugs and hepatic injury (Table 3 and Table S1).

Drugs that were consistently associated with hepatic injury, upon all sensitivity analyses and adjustments, with the highest number of absolute cases (number of cases ≥50) were paracetamol, valproic acid, carbamazepine, methotrexate, minocycline, zidovudine, pemoline, ceftriaxone, bosentan, ciclosporin, atomoxetine, olanzapine, erythromycin and voriconazole. Hepatic injury is already listed in the SPC for all these drugs, except for basiliximab [17]. Basiliximab is indicated for prophylaxis of acute rejection in patients receiving renal transplantation, as part of an immunosuppressive regimen that also includes ciclosporin, a known hepatotoxic drug. In all the basiliximab cases ciclosporin was reported as the concomitant drug. In order to assess whether basiliximab adds to the hepatic injury risk a sensitivity analysis was done to compare whether the association between hepatic injury and ciclosporin plus basiliximab *vs.* ciclosporin alone (ROR 4.1, 95% CI 0.9, 18.1; $P = 0.06$) was different from the association between hepatic injury and ciclosporin plus other immunosuppressant drugs *vs.* ciclosporin alone (ROR 1.1, 95% CI 0.2, 5.3, $P = 0.94$).

Finally, we looked at the records in which the causality assessment was completed (number of cases = 1224). Causality was considered as 'certain' in 75 cases, 'probable' in 897 and 'possible' in 252. Calculation of the RORs for hepatic injury based on all ADRs with certain, probable or possible causality confirmed our main findings (data not shown).

To inspect effect modification by age, age-specific RORs were calculated for all drugs with at least 30 cases. For each drug, a trend towards a reduction in strength of ROR was observed with increasing age, except for atomoxetine, olanzapine, infliximab, isoniazid and gemtuzumab. Exclusion of vaccine-related records had great impact. The age trend in RORs disappeared mostly with some exceptions. With increasing age, the association between hepatic injury and ciclosporin, phenytoin, topiramate and vincristine gradually decreased, while the association between hepatic injury and erythromycin, gemtuzumab and mercaptopurine progressively increased (Table S2). Among 6595 cases in the study population, 287 cases (4.3%) concerned newborns (until 1 month of age). In this specific population, the strongest association with hepatic injury was observed for rifampicin (number of cases = 6, ROR 22.4, 95% CI 12.0, 41.7), paracetamol (number of cases = 9, ROR 10.8, 95% CI 6.2, 19.0), erythromycin (number of cases = 4, ROR 5.4, 95% CI 2.2, 13.3) and HIV medications (zidovudine, stavudine, didanosine, nelfinavir, lamivudine, nevirapine).

Discussion

This is the first study that has explored drug-induced hepatic injury in children and adolescents based on the international WHO-UMC database of suspected ADR reports. There are several important findings from this study. First, hepatic injury is infrequently reported as a suspected ADR in children and adolescents (1% of total records). Although we cannot accurately evaluate the absolute risk of hepatic injury from this type of data, it is generally perceived that drug-induced hepatic injury is seldom seen in the paediatric population. Children use less of the drugs that are known to induce hepatotoxicity and often for a much shorter duration [19].

Second, the reporting rate and associations with hepatic injury seemed to change with age, although this trend attenuated once vaccine-related reports were excluded. The absolute number of reports may increase with age due to fact that at an older age children are more likely to be exposed for a longer time to well-known hepatotoxic drugs, such as retinol and isotretinoin for the treatment of acne, or oestrogens as oral contraceptive pills [11].

Table 3

ROR for hepatic injury of individual drugs ranked by absolute number of cases (with at least 30 cases) in population <18 years old

Drug	Number of cases	Number of non-cases	ROR (95% CI) With vaccines Number of cases = 6595 Crude	ROR (95% CI) With vaccines Number of cases = 6595 Adjusted*	ROR (95% CI) Without vaccines Number of cases = 6147 Adjusted*
Isotretinoin	420	12 051	3.4 (3.1, 3.8)	1.9 (1.7, 2.1)	1.3 (1.1, 1.5)
Paracetamol	347	4 049	8.4 (7.7, 9.3)	6.0 (5.4, 6.8)	3.4 (3.1, 3.8)
Valproic acid	208	3 065	6.5 (5.8, 7.4)	4.0 (3.5, 4.7)	2.2 (1.9, 2.6)
Carbamazepine	140	2 271	5.9 (5.1, 6.8)	3.6 (3.0, 4.3)	2.1 (1.8, 2.5)
Methotrexate	134	1 873	6.8 (5.9, 7.9)	4.2 (3.5, 5.1)	2.5 (2.1, 3.0)
Minocycline	117	959	11.6 (10.0, 13.5)	4.3 (3.5, 5.3)	3.5 (2.9, 4.3)
Lamotrigine	112	3 005	3.5 (3.0, 4.2)	2.2 (1.8, 2.7)	1.3 (1.1, 1.6)
Zidovudine	106	2 446	4.1 (3.4, 4.9)	4.5 (3.7, 5.5)	1.2 (1.0, 1.5)
Pemoline†	104	282	35.1 (30.5, 40.4)	31.6 (25.0, 40.0)	14.4 (11.5, 18.2)
Ceftriaxone	104	1 695	5.8 (4.9, 6.9)	5.0 (4.0, 6.1)	2.6 (2.1, 3.2)
Methylphenidate	96	4 199	2.2 (1.8, 2.6)	1.3 (1.0, 1.6)	0.7 (0.6, 0.9)‡
Bosentan	85	353	22.8 (19.4, 26.9)	15.0 (11.8, 19.2)	7.3 (5.7, 9.2)
Ciclosporin	71	117	5.7 (4.6, 7.1)	3.0 (2.4, 3.9)	1.6 (1.3, 2.1)
Atomoxetine	64	1 624	3.7 (2.9, 4.7)	2.0 (1.5, 2.6)	1.3 (1.0, 1.6)
Azithromycin	63	2 932	2.0 (1.6, 2.6)	1.8 (1.4, 2.3)	0.8 (0.6, 1.0)‡
Olanzapine	62	845	6.9 (5.5, 8.7)	3.1 (2.4, 4.0)	2.3 (1.7, 2.9)
Erythromycin	60	1 196	4.7 (3.7, 6.0)	4.2 (3.2, 5.5)	2.3 (1.8, 3.1)
Infliximab	60	2 083	2.7 (2.1, 3.5)	1.3 (1.0, 1.7)	0.9 (0.7, 1.1)‡
Risperidone	59	2 611	2.1 (1.7, 2.7)	1.0 (0.8, 1.4)‡	0.7 (0.5, 0.9‡)
Phenytoin	57	1 222	4.4 (3.4, 5.6)	3.0 (2.3, 4.0)	2.0 (1.5, 2.6)
Voriconazole	52	270	18.2 (14.7, 22.5)	10.7 (7.9, 14.6)	6.7 (5.0, 9.1)
Topiramate	51	1 356	3.5 (2.7, 4.6)	2.1 (1.6, 2.8)	1.1 (0.9, 1.5)‡
Sulfamethoxazole/trimethoprim	48	3 064	1.5 (1.1, 2.0)	1.3 (1.0, 1.7)	0.9 (0.7, 1.2)‡
Isoniazid	47	140	31.7 (25.7, 39.1)	23.8 (16.7, 33.7)	14.0 (9.9, 19.7)
Vincristine	46	1 119	3.9 (2.9, 5.1)	2.7 (2.0, 3.7)	1.5 (1.1, 2.0)
Lamivudine	45	764	5.6 (4.2, 7.3)	4.9 (3.6, 6.6)	1.7 (1.3, 2.3)
Ethinylestradiol/levonorgestrel	43	928	4.4 (3.3, 5.8)	1.9 (1.4, 2.6)	1.5 (1.1, 2.1)
Oxcarbazepine	43	1 205	3.4 (2.5, 4.5)	1.9 (1.4, 2.6)	1.1 (0.8, 1.5)‡
Gemtuzumab	42	241	16.4 (12.9, 20.9)	17.1 (12.3, 24.0)	6.7 (4.8, 9.4)
Fluconazole	42	409	9.7 (7.5, 12.5)	8.6 (6.2, 12.0)	3.6 (2.6, 5.0)
Mercaptopurine	41	252	15.3 (12.0, 19.6)	11.4 (8.1, 16.0)	6.0 (4.3, 8.4)
Phenobarbital	41	594	6.5 (4.9, 8.6)	6.6 (4.8, 9.2)	3.9 (2.8, 5.4)
Amoxicillin/clavulanate potassium	38	1 309	2.7 (2.0, 3.7)	1.7 (1.2, 2.3)	0.8 (0.6, 1.2)‡
Tioguanine	37	240	14.5 (11.2, 18.9)	14.5 (11.2, 18.9)	6.2 (4.4, 8.8)
Rifampicin	37	243	14.3 (11.0, 18.6)	8.3 (5.8, 12.0)	5.1 (3.6, 7.3)
Nevirapine	37	1 487	2.3 (1.7, 3.2)	2.8 (2.0, 3.9)	0.8 (0.6, 1.1)‡
Cytarabine	36	885	3.8 (2.8, 5.2)	2.9 (2.1, 4.1)	1.5 (1.1, 2.2)
Clozapine	36	1 646	2.1 (1.5, 2.8)	0.8 (0.6, 1.1)‡	0.7 (0.5, 0.9)‡
Clarithromycin	35	1 081	3.0 (2.2, 4.2)	1.8 (1.3, 2.5)	1.0 (0.7, 1.4)‡
Interferon beta	30	497	5.7 (4.1, 7.9)	4.4 (3.0, 6.5)	2.3 (1.6, 3.3)
Acetylsalicylic acid	30	1 070	2.6 (1.9, 3.7)	1.3 (0.9, 1.9)‡	0.9 (0.6, 1.3)‡

The following drugs had more than 30 cases but were not associated with hepatic injury: Hepatitis B vaccine, ibuprofen, poliovirus vaccine live oral, measles, mumps and rubella vaccine, diphtheria and tetanus toxoids and pertussis, sertraline, haemophilus B conjugate vaccine. *Adjusted for gender, age, country, and type of reporter. †Drugs withdrawn from the market due to hepatotoxicity. ‡Adjusted RORs not statistically significant.

After stratifying the analyses by three different age categories, we observed some effect modification by age which could be expected based on changes in hepatic maturation, drug pharmacokinetics and pharmacodynamics during childhood [3, 6, 20]. The general trend was that the RORs decreased with increasing age and clear patterns were seen for paracetamol and valproic acid. Paracetamol had a higher ROR in younger children, which is contrary to our expectations since in young children the toxic metabolite of paracetamol is produced much less [1, 20, 21]. An explanation could be that, among toddlers, intoxication from paracetamol is mainly due to unintentional therapeutic error by inappropriate dosing, unintentional multiple overdosing, ingestion of paracetamol along with another hepatotoxic drug and use of adult rather than paediatric preparations [22]. The finding of a decreasing association with age for valproic acid is consistent with previous data [20, 23]. Also for ciclosporin and vincristine the associations with hepatic injury decreased. This can be explained by the fact that the isoenzyme CYP 3A4, which plays a fundamen-

Table 4

ROR for hepatic injury by therapeutic class*

Therapeutic classes	ATC code (II level)	Number of cases (% on 6595)	Drug	Adjusted† RORs within therapeutic class (95% CI)
Antiepileptics	N03	762 (12)	Sulthiame	3.6 (1.6, 7.9)
			Ethosuximide	2.8 (1.6, 4.9)
			Phenobarbital	2.0 (1.4, 2.9)
			Valproic acid	1.5 (1.3, 1.8)
			Carbamazepine	1.3 (1.0, 1.5)
Antibacterials	J01	742 (11)	Aztreonam	5.9 (2.2, 15.4)
			Loracarbef	3.9 (1.5, 10.1)
			Erythromycin	3.4 (1.2, 10.0)
			Ceftriaxone	3.1 (2.5, 3.8)
			Josamycin	2.9 (1.5, 5.7)
			Minocycline	2.7 (2.1, 3.6)
Analgesics	N02	472 (7)	Paracetamol	5.6 (4.5, 6.9)
			Paracetamol/hydrocodone	1.8 (1.1, 3.0)
Psychoanaleptics	N06	457 (7)	Pemoline‡	30.7 (23.3, 40.6)
			Nefazodone	7.3 (4.3, 12.4)
			Atomoxetine	1.7 (1.3, 2.3)
Antineoplastics	L01	421 (6)	Mercaptopurine	4.2 (3.0, 6.0)
			Gemtuzumab	4.2 (2.9, 5.9)
			Tioguanine	3.9 (2.7, 5.7)
			Methotrexate	3.2 (2.0, 5.3)
Antivirals	J05	397 (6)	Atazanavir	21.5 (11.3, 41.0)
			Emtricitabine	6.4 (2.0, 21.0)
			Lamivudine	1.7 (1.3, 2.4)
			Zidovudine	1.5 (1.1, 1.9)
Psycholeptics	N05	287 (4)	Chlorprothixene	4.8 (1.6, 14.2)
			Olanzapine	3.5 (2.6, 4.7)
Immunosuppressants	L04	251 (4)	Basiliximab	2.6 (1.6, 4.2)
			Ciclosporin	1.4 (1.0, 1.9)
Antimycobacterials	J04	120 (2)	Pyrazinamide	2.3 (1.2, 4.4)
			Isoniazid	2.1 (1.3, 3.2)
Sex hormones	G03	115 (2)	Norethisterone/ethinylestradiol	24.5 (6.4, 93.6)
			Estradiol	6.7 (2.0, 22.1)
			Norethisterone	5.8 (2.5, 13.5)
			Ethinylestradiol/levonorgestrel	2.1 (1.4, 3.2)
Antimycotics	J02	107 (2)	Voriconazole	1.9 (1.2, 3.0)

For each therapeutic class, only those drugs with statistically significant adjusted RORs for hepatic injury have been reported. *Only therapeutic classes with at least 100 cases have been considered in this analysis. †Adjusted for age, gender, country of reporting and type of reporter. ‡Drug withdrawal from the market because of hepatotoxicity.

tal role in the metabolism of these drugs, is expressed less in newborns and infants than in adolescents. This may lead to a reduced capacity in younger children to eliminate these drugs.

The third important, but not surprising, finding was that the drugs associated with hepatotoxicity in children have also been associated with hepatotoxicity in adults. Interestingly, pemoline and troglitazone, drugs with the highest ROR in our analysis, have already been withdrawn from the market due to their hepatotoxicity [1]. The fact that no (except one) new hepatotoxic drugs were identified in children is reassuring, especially since metabolism and enzyme maturation changes quickly in children and could have impact on toxicity.

Fourth, basiliximab was associated with hepatic injury in this study, and this drug has never been associated with adverse hepatic reactions in adults [18]. Basiliximab is, however, always combined with ciclosporin, a well-known hepatotoxic drug, which makes it difficult to investigate whether it is basiliximab or ciclosporin or some interaction. Indirect comparisons of basiliximab/ciclosporin combination *vs*. single use of ciclosporin still showed an increase in risk of hepatic injury for the combination ciclosporin/basiliximab but this may also be caused by severity of disease. It will be important to monitor the hepatic safety of basiliximab in the future.

Both strengths and limitations of this study are related to the data source we used in the study, a large database of suspected ADR records. Advantages are that the system covers all drugs and patients from most countries worldwide. The system is sensitive and capable of detecting side effects quickly after market launch [24]. The spontaneous reporting system reflects both real-life events and real-life prescribing, and therefore may comprise drug use patterns that cannot be studied in clinical trials for ethical reasons, such as overdoses and inappropriate co-medication [24]. The use of these data also has limitations. Firstly, drug-related hepatic injury cannot be viewed as a single disease,

and many different mechanisms and factors lead to hepatotoxicity. On top of that, there is no standardized definition of drug-induced hepatic injury, and collection of spontaneous reports of hepatotoxicity may differ between countries. Also, the frequency with which countries report to the WHO-UMC database varies considerably due to several technical issues: extent of drug use, drug marketing year, general knowledge on the adverse drug effects, public attention to specific safety issues (i.e. specific monitoring programmes), and health professionals' attitudes to reporting ADRs [24]. To address confounding due to these factors, we adjusted the main analyses for country of reporting and type of reporter. Secondly, the spontaneous reporting systems contain limited clinical information [24]. Thirdly, these systems may be very vulnerable to selective reporting and its extent is both variable and hard to measure. Selective reporting may lead to distortions in comparisons between drugs [24]. Moreover, only a minority of ADRs are identified and reported, which is a phenomenon known as under-reporting [25]. Under-reporting leads to two main limitations: (i) underestimation of the frequency of ADRs and, consequently, of the extent of a problem and (ii) no cases or very few cases of a true adverse drug reaction might be received from spontaneous reporting system, thus requiring a sensitive and specific methodology for signal detection [24]. Fourthly, causality assessment is frequently not reported, which means that the risk of confounding (especially by indication) is even higher. A sensitivity analysis, conducted on the drugs with causality assessment, showed that those with strongest associations remained, which strengthens our conclusion that these drugs may be hepatotoxic in children.

Finally, the high number of vaccine-related reports in specific age categories constitutes a strong confounding effect in signal generation in children. Part of this confounding effect could be removed by age adjustment. Exclusion of vaccine-related reports was more effective since the change in estimates upon exclusion went far beyond the effects observed after age adjustment alone. Although the strength of the associations was attenuated, the main findings still remained statistically significant.

In conclusion, hepatotoxicity is infrequently reported as a suspected ADR in children and adolescents. Our analysis showed that well-known hepatotoxic drugs in adults, such as paracetamol, anti-epileptic drugs, and anti-tuberculosis agents, are also associated with hepatotoxicity in children. Further pharmacoepidemiological investigations are needed to quantify the risk of drug-induced hepatic injury in the paediatric population.

Competing interests

AC received a fee for speaking at educational programmes on pharmacovigilance and funds for research from the Italian Drug Regulatory Agency (AIFA).

KV has been involved as project leader contracted by various pharmaceutical companies and received unconditional research grants from Pfizer, Yamanouchi and Boehringer-Ingelheim, none are related to the subject of this study. FR received funds for research from AIFA – Campania region. MCJMS is scientific coordinator of the Integrated Primary Care Information (IPCI) group which is partially funded through unconditional research grants from the pharmaceutical industry namely: Pfizer, Merck, Astra Zeneca, Eli Lilly, GSK and Altana. None of the research projects for these companies is related to this study. MCJMS has been a consultant to Pfizer, Novartis Consumer Health, Servier, Celgene and Lundbeck.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1 ROR for hepatic injury of individual drugs ranked according to the strength of the crude association in the population <18 years old.
Table S2 Crude ROR for hepatic injury of individual drugs (with ≥30 cases from the main analysis) stratified by age groups.

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