Pharmacologie médicale

Bordeaux PharmacoEpi
CIC Bordeaux CIC1401

Drug-induced acute liver injury (ALI) in the French claims database: individual and population risks

A. Grolleau[1], V. Barbet[1], N. Thurin[2], R. Lassalle[1], M. Duong[1], C. Droz-Perroteau[1], N. Moore[2]

[1]Bordeaux PharmacoEpi, INSERM CIC1401, Université de Bordeaux, Bordeaux, France – [2]Bordeaux PharmacoEpi, INSERM CIC1401, INSERM U1219, Université de Bordeaux, Bordeaux, France

Abstract

Background: ALI is a major source of drug-induced regulatory and healthcare activity: The former may be more concerned by relative risks, the latter by total population burden of disease.
Objectives: To identify individual and population risks of drug-induced admission for ALI.
Methods: Case-population study of adults with a 1st hospital admission for non-overdose ALI from 2010 to 2014, identified in SNIIRAM, the French nationwide claims system database of 66.6 million persons (99% of the French population). ALI was identified by discharge summaries ICD-10-codes K71.1, 71.2, 71.6, 71.9 (acute toxic liver injury) and 72.0 (hepatic failure). Exposure was defined as a dispensing between 7-60 days before admission. Exposure was number of patients dispensed the drug at least once over the study timeframe in EGB, the 1/97th sample of SNIIRAM, extrapolated to the whole population.
Results: Of 4807 cases of ALI, 80.7% were exposed to at least one drug between 7-60 days before admission. Of the 280 drugs with at least one dispensing within 7-60 days before admission for ALI, the highest ranked drugs for individual risk were antituberculosis agents such as rifampicin, pyrazinamide, isoniazide, ethambutol and their associations, with one case of ALI for about 1000 exposed patients or fewer. Other high-risk drugs were colestyramine (1/5312 pts), erythromycin (1/5374 pts), cibenzoline (1/6452 pts). However, these drugs are not much used and were among those with the fewest absolute number of cases (fewer than 60 cases in 5 years). On the other hand, drugs with the largest numbers of cases such as non-overdose paracetamol (1495 cases), esomeprazole/omeprazole (910 cases) or coamoxiclav (293 cases) had event risks around 1/30000 to 1/60000 pts. Some drugs like furosemide and atorvastatin had both high numbers of events (284 and 263) and high event rates (1/15000). They may merit further exploration. Comparisons within drug classes (e.g., antibiotics or NSAIDs) may also reveal unexpected findings.
Conclusions: A nationwide population based data-source can provide information on both relative and absolute risks, that can help to inform individual and collective decision-making.

Conflict of Interest Statement

This study was supported by an unconditional public joint help *from Direction Générale de la Santé* (DGS), from *Mission recherche de la Direction de la Recherche, des Etudes, de l'Evaluation et des Statistiques* (MiRe-DREES) of *Caisse Nationale d'Assurance Maladie des Travailleurs Salariés* (CNAMTS), *Régime Social des Indépendants* (RSI) and *Caisse Nationale de Solidarité pour l'Autonomie* (CNSA), as part of the general call for projects by IReSP (*Appel à Projets, Institut de Recherche en Santé Publique*) in 2013. It was conducted by Bordeaux PharmacoEpi Platform, CIC Bordeaux CIC1401 of the Bordeaux University. All authors, none other relationships to disclose for this study.

Background

- ALI is a major source of drug-induced regulatory and healthcare activity: the former may be more concerned by relative risks, the latter by total population burden of disease.
- To our knowledge, hepatotoxicity studies were based on identification of individual cases and concerned a few hundred cases.
- A previous field study (SALT) exhaustively explored the acute liver failure leading to liver transplantation in 7 countries[1]. The EPIHAM study was conducted in order to identify drugs with less severe hepatotoxicity, still resulting in hospital admission using the French nationwide claims database.

1. Gulmez SE, Larrey D, Pageaux GP, Lignot S, Lassalle R, Jove J, et al. Transplantation for acute liver failure in patients exposed to NSAIDs or paracetamol (acetaminophen): the multinational case-population SALT study. Drug Saf. 2013;36(2):135-44.

Objectives

To identify individual and population risks of drug-induced admission for ALI in France using the nationwide claims database.

Methods

- **Design:** Case-population study of adults with a 1st hospital admission for non-overdose ALI from 2010 to 2014.
- **Data sources**
  - ✓ Study performed using the French nationwide claims database (*Système National d'Information Inter-Régimes de l'Assurance Maladie*, SNIIRAM) of 66.6 million persons (99% of the French population) and of the 1/97th representative sample of SNIIRAM *(Echantillon Généraliste de Bénéficiaires*, EGB).
  - ✓ These databases contain anonymised data on: general characteristics (gender, year of birth, month and year of death), long term diseases (LTD), outpatient reimbursed healthcare expenditure (visits, medical procedures, lab tests, drugs, medical devices), hospital discharge summaries (ICD-10 diagnostic codes for hospitalization, medical acts, date of entry and exit of hospitalization and length of stay).
- **Study populations**
  - ✓ **Cases** identified in SNIIRAM among adult patients with a 1st hospital admission from January 1st, 2010 to December 31st, 2014 with main diagnosis of acute toxic liver injury (ICD-10-codes K71.1, K71.2, K71.6, K71.9) or hepatic failure (ICD-10-code K72.0) (Figure 1).
  - ✓ **Reference population** identified in EGB among adult patients affiliated at least one day for each year considered to the national healthcare insurance system for salaried workers, extrapolated to the whole French population.
- **Exposure**
  - ✓ **Cases**: drug dispensation between 7 and 60 preceding date of the 1st hospital admission for ALI.
  - ✓ **Exposed population**: number of patients dispensed the drug at least once over the study timeframe in EGB (01/01/2010 - 31/12/2014) among reference population, extrapolated to the whole French population.
- **Statistical analysis**
  - ✓ Index date: date of 1st hospitalization for ALI (with aggregation of concomitant stays for patients hospitalized in several medical units).
  - ✓ Population risk estimated with the number of exposed cases over 5 years.
  - ✓ Individual risk estimated with the ratio between the number of exposed patients of the reference population and the number of exposed cases over 5 years.

Results

- **Study population**
  - ✓ 4 807 cases with a 1st hospital admission for non-overdose ALI from 2010 to 2014 were identified.
  - ✓ The main diagnosis of 1st hospitalization at index date was acute toxic liver injury for 61.4% of cases and hepatic failure for 38.6% of cases.
  - ✓ Identification procedure of ALI cases in SNIIRAM from the population source and ALI cases characteristics are described in an other poster presentation[2].

2. Grolleau A, Barbet V, Thurin N, Lassalle R, Duong M, Droz-Perroteau C, Moore N. Drug-induced acute liver injury (ALI) in the French claims database: description of cases. Poster. 33rd ICPE, August 26-30, 2017, Montréal, Canada.

- **Population risk**
  - ✓ Over 7-60 days preceding the date of the 1st hospital admission for ALI, 3 877 cases (80.7%) were exposed to at least one drug.
  - ✓ Drugs with the largest numbers of cases were: non-overdose paracetamol, esomeprazole, omeprazole, phloroglucinol, domperidone and amoxicillin associated with enzyme inhibitors with number of cases ranging from 1 495 to 293 (Table 1).
  - ✓ These drugs had event risks of ALI around one case of ALI for about 30 000 exposed patients (paracetamol, esomeprazole) to one case of ALI for about 60 000 exposed patients (phloroglucinol, amoxicillin associated with enzyme inhibitors).
  - ✓ Furosemide and atorvastatin had both high numbers of events (284 and 263) and high event rates (one case for about 15 000 patients).

Table 1. Top 10 of dispensed drugs over 7-60 days before the 1st hospital admission with the largest number of ALI cases identified between 2010 and 2014.

Drug dispensations over 7 - 60 days before the index date	Cases n = 4 807	Patients n = 65 375 384	Ratio patients / cases
N02BE01 - Paracetamol	1 495	52 020 957	34 797
A02BC05 - Esomeprazole	502	14 161 092	28 209
A02BC01 - Omeprazole	408	17 494 549	42 879
A03AX12 - Phloroglucinol	311	20 033 756	64 417
A03FA03 - Domperidone	298	13 555 192	45 487
J01CR02 - Amoxicillin and enz. inhib.	293	19 059 269	65 049
C03CA01 - Furosemide	284	4 284 346	15 086
C10AA05 - Atorvastatin	263	4 140 201	15 742
A02BC02 - Pantoprazole	245	8 622 136	35 192
N05CF02 - Zolpidem	244	6 741 764	27 630

- **Individual risk**
  - ✓ Antituberculosis agents (mainly in association) were the therapeutic drug family with the highest ranked drugs for individual risk: rifampicin, pyrazinamide, ethambutol and isoniazide.
    For these drugs, the event risks ranged from one case of ALI for 578 exposed patients to one case of ALI for 6 332 exposed patients (Table 2).
  - ✓ Other high-risk drugs were colestyramine (one case for 5 312 patients), erythromycin (one case for 5 374 patients), cibenzoline (one case for 6 452 patients) and methyldopa (one case for 6 719 patients).
  - ✓ These drugs are not much used and were among those with the lowest absolute number of cases (fewer than 60 cases in 5 years for erythromycin).

Table 2. Top 10 of dispensed drugs over 7-60 days before the 1st hospital admission with the highest rank for ALI individual risk, identified between 2010 and 2014.

Drug dispensations over 7 - 60 days before the index date	Cases n = 4 807	Patients n = 65 375 384	Ratio patients / cases
J04AM05 - Rifampicin, pyrazinamide and isoniazide	35	20 247	578
J04AK01 - Pyrazinamide	10	7 702	770
J04AK02 - Ethambutol	27	22 268	825
J04AC01 - Isoniazide	14	17 940	1 281
J04AM02 - Rifampicin and isoniazide	31	59 782	1 928
C10AC01 - Colestyramine	30	159 373	5 312
J01FA01 - Erythromycin	56	300 937	5 374
J04AB02 - Rifampicin	22	139 309	6 332
C01BG07 - Cibenzoline	5	32 261	6 452
C02AB02 - Methyldopa (racemic)	10	67 189	6 719

Conclusions

- Many drugs are dispensed before 1st hospital admission for acute liver injury.
- Population risk and individual risk, taking into account actual exposure, can be estimated with information contained in the French nationwide claims database.
- Further analyses on associated drugs with high individual or high population risk are needed, in order to identify risk of each drug among its therapeutic drug family (for NSAID for example) to determine if a safe alternative drug exists in this family.