Drugs-induced acute liver injury (ALI) in the French claims database: description of cases

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Abstract

Background: ALI is a major source of drug-induced regulatory action, hospital admissions and burden of care. More studies only concern a few hundred cases. Objectives: To identify drugs that most commonly lead to hospital admission for ALI. Methods: Case-population study of adults with a 1st hospital admission for non-overdose ALI from 2010 to 2014, identified in SNIRAM, the French nationwide claims system database of 66.6 million persons (98% of the French population). ALI was identified by discharge summary codes (ICD-10 codes K71.1, K71.2, K72.0, K72.1; section toxic liver injury) and K72.0 (hepatitis). Exposure was defined as a dispensation between 0-7 days and 7-40 days before admission, to allow for potential protopathic bias identification. Population exposure was conditioned to dispensed the drug at least once within the study timeframe, in EGB, the 10th sample of SNIRAM, extrapolated to the whole population. Results of hospital admission for ALI were estimated using the population exposure in the 10 countries included in the study. Results: Mean (SD) age was 54.5 (19.6) years, 58.7% were women, and 47.6% had at least one long-term disease. Data on exposure is presented on 250 different drugs.

Within 7 days preadmission, the 10 most frequent drugs were paracetamol (17.8%), phosphatidyl (6.0%), diclofenac (2.7%), acetaminophen (2.4%), ibuprofen (2.4%), metamizol (2.3%), amoxicillin (2.3%), association (2.6% or alone (2.2%), and codeine in association (2.8%). Many drugs were associated with treatment of hepatic symptoms. Over 7-40 days, the 10 most frequent drugs were ibuprofen (31.1%), paracetamol (10.5%), acetaminophen (8.0%), phosphatidyl (5.6%), diclofenac (2.5%), association, ibuprofen (2.5%), amoxicillin (in association with 8.1%), fosinopril (2.0%), atorvastatin (3.5%), paracetamol (3.1%), and aspirin (3.1%). Among these, rates per million users were highest for metopimazine 20.8 (17.7), 24.4 and dopamine 31.3 (18.5 - 24.0 days, and within 7 days, or over 40 days for abreviation 0.3 (5.5 - 7.2) and fenofibrate 65.3 (3.7 - 7.8)

Conclusions: This large study provides information on drugs associated with hospital admission for ALI. It confirms known associations such as paracetamol. Protopathic bias is probably for GI active or analgesic drugs found within 7 days during the period 7-40 days. The 10 most frequent drugs were paracetamol (17.8%), phosphatidyl (6.0%), diclofenac (2.7%), acetaminophen (2.4%), ibuprofen (2.4%), metamizol (2.3%), amoxicillin (2.3%), association (2.6% or alone (2.2%), and codeine in association (2.8%).

Methods

- **Design:** Case-population study of adults with a 1st hospital admission for non-overdose ALI from 2010 to 2014.
- **Data sources:** Used performed using the French nationwide claims database (Systeme National d’Information Inter-Régements de l’Assurance Maladie, SNIRAM) of 66.6 million persons (98% of the French population) and of the 10th representative sample of SNIRAM (Echantillon Généraliste de Bénéficiaires, EGB).
- **Case identification:** These databases contain anonymized data on: general characteristics (gender, year of birth, month and year of death), long term diseases (LTD), outpatient reimbursed healthcare expenditure (visits, medical procedure, 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 SNIRAM 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 health insurance system for salaried workers, extrapolated to the whole French population.
- **Exposure:** Cases: drug dispensing between 7 and 60 days or 0 days and 0 days preceding date of the index hospital admission for ALI. Exposed population: number of patients among the reference population dispensed the drug at least once over the study timeframe in EGB (01/01/2010 - 31/12/2014), 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). Risk of hospital admission for ALI: expressed as the rate (95% CI) of number of drug-exposed cases over the study timeframe by million of drug-exposed patients among the representative sample of SNIIRAM (66.6 million persons). Veterinary and mainly outside hospital. Drug use outside hospital is not accounted for in this study.

Results

**Exposure of adult ALI cases**

- Over 7-60 days: 80.7% of ALI cases were exposed to at least one drug.
- Within 7 days, 52.7% of ALI cases were exposed to at least one drug.

**Risk of hospital admission for ALI:** Among the 10 most frequent dispensed drugs, rates per million users were highest for:

- Furosemide and atorvastatin over 7-60 days (Figure 2a).
- Domperidone and metronidazole within 7 days (Figure 2b).

Conclusions

- Many drugs are dispensed before 1st hospital admission for acute liver injury.
- Known associations such as paracetamol were confirmed.
- Gastro-intestinal active or analgesic drugs were frequently found within 7 days preadmission, suggesting that protopathic bias is probable. Further sensitive analyses are needed to confirm this hypothesis.

**Figure 1:** Identification procedure of ALI cases in SNIRAM between 2010 and 2014.

**Figure 2a:** Risk of hospital admission for ALI among the top 10 most dispensed drugs per million users dispensed between 2010 and 2014.

**Figure 2b:** Risk of hospital admission for ALI (Figure 2a) and 9-7 days (Figure 2b) before the index date among the 10 most dispensed drugs.