Background: Hepatic injury is a major safety issue. Most drugs and drug classes have been associated with liver toxicity. Objectives: To quantify exposure to different drug classes prior to hospital admission for acute liver injury (ALI) in the French national healthcare systems database, SNDS. Methods: All hospital admissions for acute liver injury (K71.1, K7.2, K7.02) over 2009–2014 were identified in SNDS (86 million persons). Previous diagnoses of liver disease and/or cirrhosis were excluded. Exposures of interest were all drug classes at the highest AIC level, dispensed from 7 to 60 days before hospital admission. Reference populations were the French population over the study period, stratified at the 1.5th percentile (K71.1, K7.2, K7.02) or 95% confidence interval (K7.0). Results: 5 controls per case from EGB, matched on age, gender, and index date, for case-control analysis. Results are provided as a) number of hospitalizations for ALI between 2010 and 2014 with main diagnosis of acute toxic liver injury (ICD-10 codes K71.1, K71.2, K71.6, K71.9) or any chronic disease associated with ALI (SNDS between 2010 and 2014), 11/MPY, OR 1.8[1.66-1.94]. Analgesics including paracetamol and ibuprofen were associated with a significantly increased risk of hospitalization for ALI (ATC level 5) (Table 1). Atorvastatin was associated with an increased risk of hospitalization for ALI (OR 2.0, 95%CI 1.6-2.5), with a higher risk of hospitalization for ALI in the 60 days before the hospital admission (OR 2.2, 95%CI 1.66-2.96). Furosemide was associated with a significantly increased risk of hospitalization for ALI (OR 1.8, 95%CI 1.3-2.6). A previous study (SALT) exhaustively explored the acute liver failure leading to liver transplantation in 7 countries. The EPHAM study was conducted in order to identify drugs with less severe hepatotoxicity, still resulting in hospital admission using the French nationwide claims database. Conclusion: The hospitalization risk for ALI with previous exposures to drugs was probably increased by the ICC-10 codes chosen, which selected for toxic liver injury, with a three times higher exposure to any drugs in cases than in controls. Antimycobacterials had by far the highest risk of hepatotoxicity (OR 72), and NSAIDs among the lowest (OR 1.4). Data was collected for over 200 drugs.

Methods

Case-population analysis

Objectives

Identification of ALI cases – Case-population analysis

Results

Identification of controls – Case-control analysis

Risk of hospital admission for ALI

Risk of hospital admission for ALI

Index date: Date of first hospital admission for ALI.

Exposure: Case: all drug classes at the highest AIC level dispersed between 7 and 60 days preceding the date of 1st hospital admission for ALI (to avoid indication and prophylatic bias).

Reference population: number of patients with at least one interest drug dispersed over the study period (2010-2014), stratified to the whole French population.

Control: all drug classes dispensed in the same period as the identified cases.

Data analysis

Incidence rate of ALI: number of exposed cases over the study period per million users (MP) or patient-years (MPY) with 95% confidence intervals (95%CI).

Risk of ALI in exposed patients (Odds Ratio – OR, conditional logistic regression) compared to non-exposed patients (case-control analysis).

Table 1. Main drug classes (ATC level 2) exposure of adult ALI cases within 7-60 days preceding the index date and incidence of hospitalizations for ALI between 2010 and 2014

Table 2. Main drug classes (ATC level 2) exposure of adult ALI cases within 7-60 days preceding the index date and incidence of hospitalizations for ALI between 2010 and 2014

Table 3. Main drug classes (ATC level 2) exposure of adult ALI cases within 7-60 days preceding the index date and incidence of hospitalizations for ALI between 2010 and 2014

Figure 1. Identification procedure of ALI cases in SNDS between 2010 and 2014

Figure 2. Identification procedure of controls in EGB between 2014 and 2016

Figure 3. Risk of hospital admission for ALI

Figure 4. Risk of hospital admission for ALI between 2010 and 2014 (ATC level 2)

Figure 5. Risk of hospital admission for ALI based on previous exposure to drugs

Conclusion

The hospitalization risk for ALI with previous exposures to drugs was probably increased by the ICC-10 codes chosen, which selected for toxic liver injury, with a three times higher exposure to any drugs in cases than in controls.

Antimycobacterials had by far the highest risk of hepatotoxicity (OR 72), and NSAIDs among the lowest (OR 1.4). Data was collected for over 200 drugs.