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Metamizole and risk of hepatotoxicity –comparative cohort study of incidence of hepatic events in patients treated with metamizole vs. patients treated with paracetamol in IMS Disease Analyzer Germany between January 2009 and December 2018

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1. Background and aim

Cases of drug-induced liver injury (DILI) have been reviewed during metamizole PSUSA-00001997-201804 covering the period 11 April 2015 to 10 April 2018. The conclusion of the review by the Rapporteur was that there was insufficient evidence of a causal association at the moment, but the concerns remained. There were 7 case reports with a possible association to metamizole of which 3 cases had a possible association based on calculation of RUCAM scores.

Two published case reports of DILI associated with metamizole have demonstrated positive lymphocyte transformation tests (1, 2). One of the two cases presented with generalized exanthema and cholestatic hepatitis (1). The other case presented with acute hepatitis and severe jaundice (SGOT increase to 147 and ALP increase to 497 U/L) following re-exposure to metamizole (2).

Another published case report of DILI associated with metamizole concerned hepatocellular injury with associated renal failure within a few days after start of treatment with metamizole in combination with paracetamol (3). The current evidence consists mainly of individual case reports or case series and a single case control, the Berlin Case-Control Surveillance Study (4) which found a positive association of metamizole with liver injury in outpatients (OR=5.2 (2.0- 13.4)) and no association in inpatients (OR=1.0 (0.4, 2.2)). The cases were identified from a range of hospital admissions while the controls were selected from the same hospitals having an extensive list of possible control diseases.

When evaluating cases with DILI, current international recommendations for biochemical cut-offs for significant liver damage include any of the following (5):

- isolated increase in alanine aminotransferase (ALT) to at least 5 x upper limit of normal (ULN)
- increase in ALT to at least 3 x ULN in combination with an increase in bilirubin to at least 2 x ULN
- increase in alkaline phosphatase (ALP) to at least 2 x ULN in combination with an increase in gamma-glutamyl transferase in the absence of bone disease.

Based on the ratio of ALT to ALP the pattern of liver injury is classified as hepatocellular (≥5), cholestatic (≤2) or mixed (>2 to <5).

Liver biopsies in patients with DILI have shown a high prevalence of acute hepatitis, chronic hepatitis, acute cholestasis, chronic cholestasis and cholestatic hepatitis (5). However, among the histological findings are also e.g. granulomatous changes, steatosis, steatohepatitis, coagulative/confluent necrosis, massive/submassive necrosis, vascular injury, hepatocellular alteration, nodular regenerative hyperplasia and non-specific changes (5). Drugs known to cause liver injury typically have a characteristic pattern of clinical presentations and biopsy findings (6).

This study aims to quantify the incidence of hepatic events in patients treated with metamizole compared to patients treated with paracetamol.

2. Methods

2.1. Data source

IMRD-Germany collects computerised information from specialised and general primary care practices throughout Germany since 1982. Around 3% of GP practices are included in IMRD-Germany. Apart from an underrepresentation of young children in GP practices, GP practices in IMRD-Germany are

broadly representative of the German population in terms of gender, age and geographic region. Data from IMRD-Germany have been shown to be representative of German healthcare statistics (7). This study will be restricted to general practitioner (GP) practices as GPs have been identified as the main prescriber category for metamizole in the IMRD-Germany.

2.2. Study period

The study period will be from 1 January 2009 to 31 December 2018.

2.3. Study design

The study will be a comparative cohort study in incident users of metamizole and paracetamol.

2.4. Study population

The study population will not be restricted in terms of gender and age. Patients will be considered observable from the latest of their first consultation date and the start of practice availability and until the earliest of their last consultation date and the end of practice availability. In case of an interruption in practice availability >2 months out of every 12 months, the end of practice availability will be the start of the interruption. Patients with less than 365 days of observation and patients with a history of cancer (ICD 10 codes C00-C97), HIV (ICD 10 codes B20-B24), viral hepatitis (ICD 10 codes B15 to B19), liver disease (ICD 10 codes K70 to K77), or Budd-Chiari syndrome (ICD 10 code I82.0) will be excluded from the study. See also protocol section 2.8.2.

2.5. Study exposures

Metamizole will be identified by searching for the text string 'metamizol' in the substance name. Products containing plain metamizole will be included in the study. Combination products will be excluded as there is a possibility that other components of combination products have a hepatotoxic effect which will bias the results in unpredictable ways.

Paracetamol will be identified by searching for the text string 'paracetamol' in the substance name. Products containing plain paracetamol will be included in the study. Combination products will be excluded.

The study will be restricted to new users of metamizole and paracetamol. New users of both metamizole and paracetamol will not be included in the study. Paracetamol is considered an adequate comparator, because DILI associated with metamizole is assumed to be an idiosyncratic hypersensitivity reaction, in contrast to the pharmacological type-hepatotoxicity observed for paracetamol overdoses. Hypersensitivity reactions in general tend to occur within weeks to months after treatment initiation (8). Incident use will be defined as the first prescription for either metamizole or paracetamol during the study period in a patient with at least 365 days of observation and no prior prescription for metamizole or paracetamol.

2.6. Follow-up time

In order to take into account the duration of a prescription and allow time for a hypersensitivity reaction to develop, incident users of metamizole and paracetamol will be followed for up to 90 days after each prescription during the first 180 days (6 months) after treatment initiation (i.e. the first prescription). Drug exposure data during the first 6 months of treatment is considered sufficient to

capture the period of the highest risk of developing a hypersensitivity reaction. The maximum follow-up time per patient will be 180+90 (i.e. 270) days. Follow-up time will be censored at the first occurrence of an incident hepatic outcome event, in case of crossing over to the other treatment, or in case of a prescription for an excluded hepatotoxic drug, see protocol sections 2.8.2 and 2.9.1.

An extended follow-up period covering the first 365 days of treatment and a maximum follow up of 455 days will be included as a sensitivity analysis.

2.7. Identification of hepatic events and evaluation of incident hepatic events

The following ICD codes will be used in order to identify incident hepatic events:

- K71.0 Toxic liver disease with cholestasis
- K71.1 Toxic liver disease with hepatic necrosis
- K71.2-K71.6 Toxic liver disease with hepatitis
- K71.7-K71.9 Toxic liver disease, unspecified or with fibrosis and cirrhosis or other disorders of liver
- K72.0-K72.9 Hepatic failure, not elsewhere classified
- K75.2 Granulomatous hepatitis, not elsewhere classified
- K75.8-K75.9 Unspecified and other specified inflammatory liver disease
- K76.8-K76.9 Unspecified and other specified diseases of liver

The above outcomes will be considered in a composite outcome, and in case of sufficient data, also separately for toxic liver disease (ICD 10 code K71), hepatic failure not elsewhere classified (ICD 10 code K72) and other hepatic events (ICD 10 codes K75-K76).

Incident hepatic events will be defined as the first hepatic event that occurs within the specified risk period after start of treatment, excluding events that co-occur with a gall bladder, biliary tract or pancreas disorder (ICD 10 codes K80-K87) within a period of ±7 days. Events co-occurring with overdose (ICD 10 code T39: Poisoning by non-opioid analgesics, antipyretics and antirheumatics) will also be excluded.

2.8. Confounders

2.8.1. Alcohol use

Alcohol use will be identified ever up to the start of treatment by searching for ICD codes F10 (Mental and behavioural disorders due to use of alcohol), Z50.2 (Alcohol rehabilitation) and Z72.1 (Alcohol use).

2.8.2. Concomitant treatment associated with hepatotoxicity

Concomitant treatment with a list of hepatotoxic agents selected based on likelihood to cause hepatotoxicity (likelihood A and B), as suggested by a recently published review of documented

hepatotoxicity in the Liver Tox database (9), will be considered. The below actions will be taken with regard to the list of hepatotoxic agents:

1. Substances with high risk of hepatotoxicity that are taken in short treatments or as needed, when identified during a time period of 0-30 days prior to start of incident treatment, will be considered as confounders:

- NSAIDs associated with hepatotoxicity: Diclofenac, ibuprofen
- Antibiotics associated with hepatotoxicity: amoxicillin-clavulanate, minocycline, flucloxacillin, ofloxacillin, oxacillin, sulfamethoxazole/trimethoprim, sulfonamides, azithromycin, erythromycin, telithromycin, levofloxacin
- Antifungals associated with hepatotoxicity: Terbinafine, ketoconazole

2. Substances with high risk of hepatotoxicity that are taken as chronic treatment, when identified during a time period of 0-6 months prior to start of incident treatment, will exclude the patient from participation in the study:

Amiodarone, amodiaquine, anabolic steroids, azathioprine, 6-mercaptopurine, busulfan, carbamazepine, chlorpromazine, chlorzoxazone, cyproterone, dantrolene, didanosine, disulfiram, efavirenz, fluoxuridine, flutamide, gold salts, halothane, hydralazine, imatinib, infliximab, interferon alpha, peginterferon, interferon beta, irinotecan, isoniazid, methyldopa, nevirapine, nimesulide, phenobarbital, phenytoin, propylthiouracil, quinidine, pyrazinamide, rifampicin, stavudine, sulindac, tamoxifen, thioguanine and valproate.

3. Substances with a low risk of significant hepatic injury will not be considered as confounders:

- Contraceptives
- Atorvastatin and simvastatin
- Ticlopidine
- Heparin
- Allopurinol

2.8.3. Obesity

Obesity will be identified ever up to the start of treatment by searching for obesity events in the 'Smoking and obesity' events table, by searching for BMI, height and weight in the 'Test and prevention events' table, and by searching for the ICD code E66 (Obesity). The last recorded value will be used. Data from the 'Test and prevention events' table will only be considered in case of missing data on obesity events or an obesity diagnosis. A BMI above 30 will then be considered to represent obesity. Obesity is linked to an increased risk of non-alcoholic fatty liver disease, which is linked to an increased risk of steatohepatitis.

2.8.4. Diabetes mellitus

Diabetes mellitus will be identified ever up to the start of treatment by searching for the ICD codes E10 (Type 1 diabetes mellitus), E11 (Type 2 diabetes mellitus), E12 (Malnutrition-related diabetes mellitus), E13 (Other specified diabetes mellitus) and E14 (Unspecified diabetes mellitus). Patients with

diabetes have an increased risk of non-alcoholic fatty liver disease, which is linked to an increased risk of steatohepatitis.

2.8.5. Gall bladder, biliary tract or pancreas disorder

Hepatic events that co-occur with a gall bladder, biliary tract or pancreas disorder will be excluded, see section 2.7.

2.8.6. Cancer, liver disorder or viral hepatitis, and HIV

Patients with a history of cancer, liver disorder or viral hepatitis, or HIV will be excluded, see section 2.7.

2.9. Analysis

2.9.1. Incidence of hepatic events

From the start of the first incident treatment with either metamizole or paracetamol during the study period, patients will be followed up to 90 days after the prescription. In case of another prescription during this time period the observation period will be extended up to 90 days after the subsequent prescription. Patients will be observed for a maximum of 270 days after start of treatment. Time to first occurrence of an incident hepatic event will be compared for metamizole vs. paracetamol. Follow up will end at the earliest occurrence of any of the following for the patient:

- 91 days or more after the prescription in case of no subsequent prescription within 90 days
- incident hepatic event
- switch of treatment from metamizole to paracetamol or vice versa
- prescription for an excluded hepatotoxic drug: excluded hepatotoxic drugs are assumed to increase the risk of a hepatic event independently of the studied treatments, but are not assumed to alter the risk of a hepatic event due to the studied treatments.
- end of observation

A sensitivity analysis will also be performed, where patients are observed for a maximum of 455 days (365 days of treatment plus 90 days of follow-up).

2.8.2 Relative risk

Separate unadjusted and adjusted Cox Proportional Hazards regression models will be used to compare the rates of outcomes of interest for metamizole vs paracetamol cohort.

Confounders will be dealt with through exclusion and adjustment, see sections 2.4 and 2.8.

The analysis will be adjusted for age (continuous), gender and the identified confounders that will show an effect on the risk estimate (significant association in univariate models and more than 10% change in risk estimate).

Missing data will be dealt with through list-wise deletion (complete case analysis).

2.10. Strengths and limitations of the research methods

In Germany, patients are not required to register with a physician and are free to visit a physician of choice. For this reason, longitudinal follow up of patients is limited. Moreover, if a patient changes practice he/she is not recognised as the same patient in IMS Disease Analyzer.

Prescription records are the most complete records in IMS Disease Analyzer. However, doses and durations are not always recorded, which makes it difficult to estimate the total treatment duration and the treatment dose.

The extent to which diagnoses are recorded may also not be complete. Nevertheless, IMS Disease Analyzer in Germany has shown to be of value e.g. in the follow up of clinical events in patients treated with oral anticoagulants (10, 11).

The choice of comparator to metamizole could be argued. Paracetamol was considered as comparator due to the fact that it has not been linked to hepatotoxicity at recommended doses and due to the fact that plain paracetamol has similar uses as plain metamizole. However, metamizole is prescription-only medicine in Germany, whereas paracetamol can be purchased over the counter without a prescription. For this reason it cannot be excluded that some patients prescribed metamizole could also choose to take paracetamol. Over the counter purchases of paracetamol are not recorded in IMS Disease Analyzer.

The time period 2009 to 2018 was chosen so as to reflect as much as possible the contemporary use of metamizole and current diagnostics of DILI. This time period would also appear sufficient on the basis of extensive use of metamizole during the period.

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