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ORIGINAL RESEARCH ARTICLE

Is There an Increased Risk of Hepatotoxicity with Metamizole? A Comparative Cohort Study in Incident Users

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Abstract

Introduction The analgesic metamizole, which has been withdrawn from the market in several countries due to the risk of agranulocytosis but is still available on the market in Germany and some other countries, has been associated with liver injury in published case reports; however, epidemiological studies on the risk of liver injury are limited.

Objective The aim of this study was to compare the risk of liver injury up to 270 days after the first start of treatment with metamizole with the corresponding risk in patients starting treatment with paracetamol, using a retrospective cohort incident user design.

Methods The first prescription for either metamizole or paracetamol in the Intercontinental Medical Statistics (IMS)® Disease Analyzer Germany database during the study period (2009–2018) was identified in patients with at least 365 days of observation and no prior diagnosis of liver events, cancer or HIV, or treatment within the last 6 months with hepatotoxic drugs typically administered for chronic conditions. Each patient was followed for specific liver events for 90 days after the prescription. In case of a new prescription within 90 days, a new 90-day observation period started, up to a maximum of 270 days. Cox regression was used to compare the risk of liver injury in the two groups.

Results Metamizole was associated with a higher risk of liver injury compared with paracetamol (adjusted hazard ratio 1.69, 95% confidence interval 1.46–1.97). Sensitivity analyses were performed to evaluate the robustness of these findings. In all the sensitivity analyses, metamizole was still associated with a higher risk of liver injury, including an analysis where naproxen was used as a comparator instead of paracetamol.

Conclusions Results from this study support previous studies suggesting that metamizole is associated with a significant risk of liver injury. Nevertheless, a possible impact of residual confounding cannot be excluded.

1 Introduction

Metamizole (or dipyrone) is a non-addictive analgesic with analgesic, antipyretic and spasmolytic effects that was introduced in Germany in 1922. Due to the risk of agranulocytosis, metamizole has been withdrawn from the market in several countries but remains available in some countries, including Germany. It is indicated for severe acute

Key Points

Only limited data exist on the comparative risk of liver injury with metamizole. No previous studies have focused on first-ever users of metamizole.

This study aimed to compare the risk of liver injury with metamizole versus paracetamol up to 270 days after first initiation of treatment in patients with no history of liver disease.

An increased risk of liver injury that remained significant in sensitivity analyses was identified in patients starting treatment with metamizole compared with patients starting treatment with paracetamol, which supports that metamizole has a potential for liver toxicity, although an impact of residual confounding on the study results cannot be excluded.

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and chronic pain and also for fever that is not responding to other treatments [1].

Metamizole is extensively hepatically metabolized [2–4]. Severe metamizole intoxication can be associated with liver cell necrosis [4, 5]. Liver injury in the context of overdose may be accompanied by renal failure [4, 6]. Furthermore, liver injury in combination with renal failure has also been reported in the absence of overdose but with concomitant paracetamol treatment [7].

In recent years, it has become increasingly recognized that metamizole can also be hepatotoxic [8, 9] at normal doses and in the absence of concomitant hepatotoxic treatment, based on published case reports and case series with drug-induced liver injury (DILI) following treatment with metamizole [4, 9–15] (for an overview of published cases, please see Table 1). Four patients have required liver transplantation [9, 14, 15]. Reported Roussel Uclaf Causality Assessment Method (RUCAM) scores, where reported, have varied between 3 and 11 [9, 12, 14, 15], with at least 13 cases considered to have a probable or highly probable causal relationship to metamizole (RUCAM score ≥6). A positive rechallenge was recorded in nine patients [9, 13, 15]. Some 18 cases have also been supported by a positive monocyte-derived hepatocyte-like (MH) cell test result [9, 13], which, in patients with DILI and a positive rechallenge, has been shown to have a sensitivity of 92% and a specificity of 100% for the causative agent [13]. Positive lymphocyte transformation test (LTT) results suggestive of an immune-mediated reaction were found in a few further cases [10, 11, 14], although none of the above tests (the MH cell test or the LTT) have been approved as biomarkers for DILI [16] and RUCAM remains the most widely used method to assess causality [17]. Hence, there is growing evidence that metamizole can cause DILI, and it has now been proposed that metamizole qualifies as a medicine with definite hepatotoxic potential [9].

In the context of the review of cases of DILI reported in association with metamizole by regulatory authorities in Europe, collection of additional data on a possible causal association between metamizole and DILI was considered necessary. As metamizole is not available on the market in all EU countries, the study was undertaken in Germany where metamizole is still prescribed. A protocol for the study was published on the EU-PAS register (EUPAS 31864) prior to undertaking the study.

There is limited evidence from clinical trials [4] and epidemiological studies [12, 18] supporting or refuting an association between metamizole and DILI. A case-control study of patients hospitalized with acute liver injury in Barcelona evaluated drug consumption within 15 or 30 days, depending on whether the reaction was hepatocellular or cholestatic/mixed, by interviewing patients and comparing this information with drug consumption data in the population [18]. This study found a relative risk of 3.1 for metamizole with a 99% confidence interval (CI) of 0.4–11.4. The 95% CI was not provided. Another case-control study from Germany, the Berlin Case-Control Surveillance Study [12], found a positive association of metamizole with liver injury in outpatients (odds ratio [OR] 5.2, 95% CI 2.0–13.4). 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. The same study showed no significant association between metamizole and DILI in inpatients (OR 1.0; 95% CI 0.4–2.2) [12], however drug consumption patterns differ between outpatients and inpatients and treatment duration was not taken into account.

The aim of this study was to further investigate the association between metamizole and an increased risk of hepatic injury. We chose an incident user design with active comparator to allow for a comparison between patients who were similar regarding indication and decision to start treatment. Paracetamol was considered appropriate as a comparator because of its similar use for treatment of both fever and pain, and low risk of hepatotoxicity when used as recommended [19], although it was not the specific aim of the study to investigate if metamizole is more hepatotoxic than paracetamol, e.g. at equipotent doses.

Paracetamol is associated with predictable intrinsic liver injury [19–21] at repeated or slightly excessive doses [19, 22–27], caused by a reactive toxic metabolite [19, 21, 28] in the presence of insufficient glutathione [29]. Due to limited distance between dose response curves for liver injury relative to desired effects [30, 31], this is seen as a pharmacological effect. On the other hand, idiosyncratic liver injury involves the adaptive immune system [32–34]. Nevertheless, liver injury with paracetamol is still incompletely understood. Whereas repeated exposure can lead to liver adaptation and reduced risk of liver injury [35], subacute exposure might increase the risk of liver injury [36]. In exceptional cases, paracetamol has been suspected of inducing idiosyncratic or allergic hepatitis [37, 38].

It could be argued that metamizole has more restricted indications than paracetamol; however, metamizole is extensively prescribed by GPs in Germany, its use has increased by around 80% during the last decade, and a large proportion of use is believed to be outside of the restricted indications [39].

Due to a suspected immunological mechanism of liver injury, and in order to avoid depletion of susceptibles [40], it was considered important to study the first-ever exposure to metamizole in the database rather than any incident exposure.

Table 1 Published case reports and case series of drug-induced liver injury for metamizole

Main author, year of publication	No. of metamizole DILI cases	Reaction	Dechallenge, rechallenge	Duration of metamizole	RUCAM score	Testing of mechanism
Federmann, 1988 [10]	1	Icterus, increased ALT/AST, ALP and γ-GT	Reaction improved after discontinuation. No rechallenge	Reaction occurred within 2 h of re-exposure to metamizole after cholecystectomy. Treatment with metamizole 2 years earlier	NR	LTT positive to the metabolite 4-aminoantipyrine on three of five occasions during a period of 232 days
Herdeg, 2002 [11]	1	Exanthema, cholestatic hepatitis, liver biopsy: lymphocytic infiltration and perivenular confluent necrosis	Reaction improved after discontinuation and corticosteroid treatment. No rechallenge	Reaction occurred after a single dose	NR	LTT positive to metamizole and three metabolites
Douros, 2015 [12]	4[a]	ALT or AST >3 × ULN or total bilirubin >2 mg/dL	NR	NR	3–5	NR
Benesic, 2018 [13]	8	DILI with ALT ≥5 × ULN and/or AST ≥3 × ULN and bilirubin ≥2 × ULN or ALP ≥2 × ULN	One patient underwent rechallenge, with a positive result	12 days in one patient	NR	MH cell test was positive in eight DILI cases
Krisai, 2019 [14]	1	Liver failure resulting in transplantation. Liver biopsy showed acute hepatitis with diffuse panlobular massive necrosis and severe collapse of reticulin fibres	NA. Patient received liver transplant, which was followed by normalization of liver parameters	2 months	11	LTT positive to metamizole
Sebode, 2020 [15]	23	Two patients developed liver failure resulting in liver transplantation. Liver biopsy was performed in 17 patients, which showed moderate to severe liver inflammation with lymphocytic infiltrations in 13 patients. The biochemical pattern of DILI was hepatocellular in 61%, mixed in 22% and cholestatic in 17% of cases	Patients who did not experience liver failure improved following discontinuation of metamizole and corticosteroid treatment. Four patients were re-exposed to metamizole, which was followed by recurrence of liver injury	Median 4 weeks.	4–11 (median 7)	NR
Weber, 2020 [9]	10	Most patients had a hepatocellular pattern of DILI. One patient developed acute liver failure and required liver transplantation	Four patients underwent rechallenge, with a positive result	Median 52 days	6–9	MH cell test was positive in all cases

ALP alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *DILI* drug-induced liver injury, *γ-GT* γ-glutamyl transpeptidase, *LTT* lymphocyte transformation test, *MH* monocyte-derived hepatocyte-like, *NA* not applicable, *NR* not reported, *RUCAM* Roussel Uclaf Causality Assessment Method, *ULN* upper limit of normal

[a]A total of 13 DILI patients had received treatment with metamizole. Causality was considered possible in four patients

2 Methods

2.1 Study Design

This study was conducted using a comparative incident user cohort design.

2.2 Setting

2.2.1 Study Period

The study period was from January 2009 to December 2018.

2.2.2 Database

This study used the Intercontinental Medical Statistics (IMS)® Disease Analyzer Germany database, version June 2019, which has collected computerized information from specialized and general primary care practices throughout Germany since 1992, as metamizole is available and prescribed in Germany. General practitioners (GPs) were identified as the main prescriber category for metamizole in the database, and the study was therefore restricted to GP practices. Data from IMS® Disease Analyzer Germany has been shown to be representative of German healthcare statistics [41, 42]. Apart from an underrepresentation of young children, GP practices in IMS® Disease Analyzer Germany are broadly representative of the German population in terms of sex, age and geographic region. IMS® Disease Analyzer Germany uses WHO International Classification of Diseases, Tenth Revision (ICD-10) codes for the coding of diagnoses, and European Pharmaceutical Market Research Association (EphMRA) Anatomical Therapeutic Chemical (ATC) codes and names of active substances (ingredients) for the coding of medicines.

2.2.3 Exposure

Patients were followed for 90 days after their first prescription for metamizole or paracetamol. A risk window of 90 days was chosen to allow sufficient time for an immunological response to develop and be recorded in the database, considering that this involves time for the patient to seek health care for symptoms, time for diagnostic work-up, and, in case of a diagnosis received in secondary care, time for the patient to transfer the diagnosis to primary care at the next visit, in which case the diagnosis date would be provided as the date of the visit rather than the date of occurrence of the diagnosis. The usual treatment duration for a prescription was only around 7–14 days. If the patient started treatment on the same day, this would include around 2½ months after treatment discontinuation. DILI is more likely during treatment and up to 1 month after treatment discontinuation [43, 44], although some drugs are known to cause delayed liver injury that can arise more than 30 days after stopping treatment [9, 14, 15]. We included this extra time to increase the likelihood that any DILI that occurred in the patients would also be recorded by the GP.

In case of a new prescription during the 90-day risk window, a new follow-up period of 90 days started. Further prescriptions were then identified up to 180 days after the first prescription, resulting in a maximum follow-up time of 270 days for each patient. This total maximum length of follow-up was considered sufficient in order to observe potential immunological or hypersensitivity reactions that tend to occur within weeks to months after treatment initiation [45, 46]. RUCAM assigns a higher score (+2 vs. +1) for reactions that occur within 5–90 days, as opposed to more than 90 days after the start of treatment [44]. In reported DILI cases with metamizole, the reported median time to diagnosis has varied between 1 month [15] and 52 days [9], with one case resulting in liver transplantation occurring after 2 months of treatment [14]. However, a longer time window seemed appropriate in this study considering possible occasional symptomatic rather than continuous treatment.

2.2.4 Follow-Up

Patients were followed up for 90 days after each prescription, up to a maximum of 270 days after their first prescription. Follow-up ended earlier in case of switching to the other treatment group (start of treatment with paracetamol in a patient in the metamizole group, or vice versa), start of treatment with a medicine that excluded the patient from participation in the study, an outcome event, or the end of observation.

2.3 Participants

No restrictions were applied in terms of sex or age. Patients were considered observable between the date of the first consultation and the date of the last consultation in the practice and were required to have at least 365 days of observation in the database prior to their first use of either metamizole or paracetamol [47]. Patients were excluded if they received a first prescription for both metamizole and paracetamol on the same day, or if the

first prescription related to a multi-ingredient product, due to the possibility that other ingredients could have a hepatotoxic effect, which could bias the results in unpredictable ways. The exclusion of multi-ingredient products had no impact on metamizole as fewer than 10 patients were prescribed a multi-ingredient product containing metamizole during the study period.

Patients were excluded from the study if they had a history of cancer (ICD-10 codes C00–C97), HIV (ICD–10 codes B20–B24), viral hepatitis (ICD-10 codes B15–B19), liver disease (ICD-10 codes K70–K77) or Budd–Chiari syndrome (ICD-10 code I82.0). Patients were also excluded from the study if they had received treatment with medicines that are taken as chronic treatment or for treatment of cancer that have a high risk of hepatotoxicity (likelihood A and B, corresponding to 'at least 50' and '12–49' convincingly documented published case reports of clinically apparent idiosyncratic liver injury [48, 49]), as evidence of well-known potential for hepatotoxicity [49, 50] within a period of 6 months (182 days) prior to the start of treatment. These substances were amiodarone, anabolic corticosteroids, azathioprine, 6-mercaptopurine, busulfan, carbamazepine, chlorpromazine, chlorzoxazone, cyproterone, dantrolene, didanosine, disulfiram, efavirenz, flutamide, gold salts, hydralazine, imatinib, infliximab, interferon-α, peginterferon, interferon-β, irinotecan, isoniazid, methyldopa, nevirapine, phenobarbital, phenytoin, propylthiouracil, quinidine, pyrazinamide, rifampicin, stavudine, tamoxifen, and valproate.

2.4 Variables and Measurement

2.4.1 Outcome Events

We included as outcome events toxic liver disease (ICD-10 code K71), hepatic failure not elsewhere classified (ICD-10 code K72), nonspecific reactive hepatitis (ICD-10 code K75.2), granulomatous hepatitis not elsewhere classified (ICD-10 code K75.3), unspecified and other specified inflammatory liver disease (ICD-10 codes K75.8–K75.9), and unspecified and other specified diseases of liver (ICD-10 codes K76.8–K76.9). Outcome events that co-occurred with a gall bladder, biliary tract or pancreas disorder (ICD-10 codes K80–K87) within a period of ± 7 days were censored. Outcome events were also censored if the patient had, at any time, an event of overdose of analgesics, antipyretics or antirheumatics (ICD-10 code T39), but no such events were identified in the patients.

For the distribution of outcome events, toxic liver disease and hepatic failure were considered as separate categories. All other outcome events were considered as other hepatic events.

2.4.2 Exposures

All metamizole-containing products were identified by searching for substances containing the text string 'metamizol', and all paracetamol-containing products were identified by searching for substances containing the text string 'paracetamol'. An absence of multiple names for the same substance (e.g. acetaminophen for paracetamol or dipyrone for metamizole) had been verified by retrieving all substance names for analgesics (EphMRA ATC code N02). All products containing metamizole or paracetamol were identified regardless of ATC code. Only single-ingredient products were included in this study.

2.4.3 Potential Confounders

We considered the following potential confounders: sex, age, use of alcohol, and treatment with medicines taken in short treatments or as needed that are associated with a high risk of hepatotoxicity, diabetes and obesity. Age in years (i.e. 1-year intervals) at the start of treatment was included as a stratification variable.

Alcohol use was identified by searching the entire history of the patient, up to the date of starting treatment, for the following ICD-10 codes: F10 (Mental and behavioural disorders due to use of alcohol), Z50.2 (Alcohol rehabilitation) and Z72.1 (Alcohol use). Patients without a history of alcohol use codes were not considered to have a history of alcohol abuse or misuse.

Treatment with medicines with a high risk of hepatotoxicity (likelihood A and B) [50] that are taken in short treatments or as needed was identified within a period of 30 days before and up to the start of treatment. The identified substances belonged to the nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics and antifungals drug classes and included the following: amoxicillin-clavulanate, azithromycin, diclofenac, erythromycin, flucloxacillin, ibuprofen, ketoconazole, levofloxacin, minocycline, ofloxacin, oxacillin, sulfamethoxazole/trimethoprim, sulfonamides, telithromycin, and terbinafine.

Diabetes was identified by searching for the ICD-10 codes E10–E14 in the entire history of the patient up to the start of treatment. Patients without a history of diabetes codes were considered nondiabetic.

Obesity was identified by searching the entire history of the patient, up to the start of treatment, for an ICD-10 code of obesity (E66), an obesity event (IMS® Disease Analyzer Germany captures events of obesity and smoking as specific events and assigns a value of 'obese' or 'non-obese' to these events), or a measure of body mass index (BMI). The last recorded value before the start of treatment was used. BMI was only considered in case of missing data for obesity or

obesity events. A BMI >30 was considered to represent obesity. Patients with no information related to obesity were not classified with respect to obesity.

2.5 Statistical Methods

All analyses in the study were performed by the authors based on IMS® Disease Analyzer Germany. Multivariable Cox regression using SAS Enterprise Guide version 7.15 was used to compare the risk of hepatic injury in patients treated with metamizole versus paracetamol, adjusting for confounding variables (sex, age, use of alcohol, treatment with medicines taken in short treatments or as needed that are associated with a high risk of hepatotoxicity, diabetes). Analysis was based on patients with complete data. Hepatic outcome events were analyzed together. The proportional hazards assumption was assessed by visually inspecting that the survival curves did not cross, and by use of the Supremum test. A p-value of <0.05 was considered to violate the proportional hazards assumption. We also investigated the possibility of an interaction between age and sex and between sex and alcohol by introducing interaction variables. Less than 1% of patients had missing data on age or sex, whereas obesity information was only available in around 30% of patients. Patients with available obesity information were therefore analyzed separately, controlling also for confounding by obesity.

In addition to the main analysis, we undertook sensitivity analyses of the association between metamizole and liver injury to test if the association remained stable under different assumptions. In the first sensitivity analysis, we gave patients an equal opportunity to provide information on previous diseases and conditions by analyzing only the data within the previous 365 days, which was the required observation period for all patients. In the second sensitivity analysis, we restricted the results to adult patients aged 18–99 years (age is not recorded in patients older than 99 years in IMS® Disease Analyzer Germany). In the third sensitivity analysis, we considered infectious diseases, gallbladder, biliary tract or pancreas disorders, other abdominal symptoms and diseases, and pain (excluding abdominal pain) among diagnoses recorded on the date of start of treatment with metamizole or paracetamol as possible confounding factors for the association between metamizole and hepatic injury. In the third sensitivity analysis, backwards elimination with a p-value of 0.2 was used for variables to stay in the Cox regression analysis model [51].

As a further separate analysis, we considered naproxen instead of paracetamol as a comparator. The selection of naproxen was motivated by representativeness of NSAID use for musculoskeletal pain and avoidance of the most hepatotoxic NSAIDs [52–54].

3 Results

3.1 Participants

A total of 489,980 patients with a first prescription for metamizole and 143,871 patients with a first prescription for paracetamol were included in the study (see Fig. 1). Patients with a first prescription for metamizole were more likely to be excluded from participation in the study due to a history of cancer, liver disorder, viral hepatitis, or HIV (12.3% for metamizole vs. 4.4% for paracetamol) and patients with a first prescription for paracetamol were more likely to be excluded due to an insufficient observation period prior to the start of treatment (51.8% for paracetamol vs. 38.5% for metamizole). Less than 1% of patients in both groups had received excluded medications within 6 months prior to the start of treatment.

3.2 Descriptive Data

Characteristics of the included patients are shown in Table 2. Patients starting treatment with metamizole were older and more often female compared with patients starting treatment with paracetamol (mean age 54.6 years for metamizole and 36.6 years for paracetamol; 58.1% of metamizole patients and 49.3% of paracetamol patients were female). Confounding factors for hepatic injury were also more frequent among metamizole patients compared with paracetamol patients.

The reasons for censoring are shown in electronic supplementary Table S1 and differed between groups. Apart from outcome events, censoring due more than 90 days after the last prescription or due to prescription of an excluded medication was more frequent in patients treated with metamizole, whereas censoring due to crossing over to the other treatment group or due to the end of follow-up was more frequent in patients treated with paracetamol. The mean duration of total follow-up (maximum of 270 days) was shorter in patients treated with paracetamol (mean 81 days, standard deviation [SD] 30 days) compared with patients treated with metamizole (mean 91 days, SD 41 days).

3.3 Outcome Data

A total of 1920 patients had an outcome event, of whom 1723 patients were treated with metamizole and 197 patients were treated with paracetamol. The median time to an outcome event was 32 days (interquartile range 9–67 days). The distribution of outcome events over different types of hepatic diagnoses is shown in Table 3. The distribution of outcome events was similar for metamizole and paracetamol.

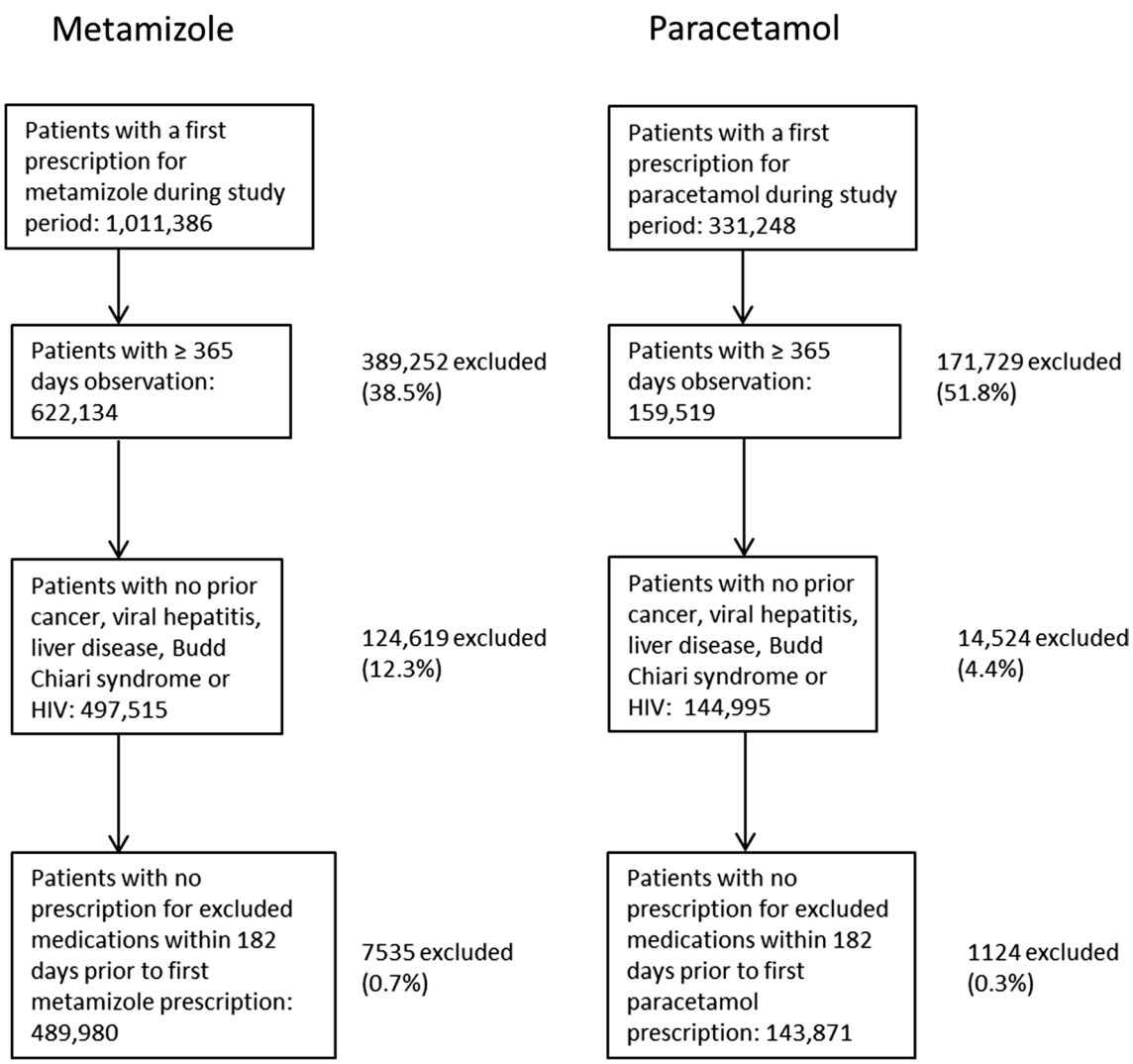

Fig. 1 Flowchart of patients included in the study

Furthermore, the time to an outcome event was not significantly different for the different types of hepatic diagnoses (p-value 0.22 for toxic liver disease or hepatic failure vs. remaining events, median two-sample test).

A comparison of survival curves for a hepatic outcome in patients treated with metamizole versus patients treated with paracetamol is shown in Fig. 2 for all patients, and for patients with known information on obesity. Survival curves include patients with at least 1 day of follow-up after the start of treatment.

3.4 Main Results

Compared with paracetamol, metamizole was associated with an increased adjusted hazard ratio (HR) of 1.69 (95% CI 1.46–1.97) for hepatic injury (Table 4). Separate results in patients with known information on obesity are provided in Table 5. The analyses were stratified by age, in years, due to significant non-proportional hazards for the age variable, which was confirmed graphically by looking at the survival curves. We also investigated the possibility of interaction between age and sex and between sex and alcohol, and significant interactions were identified; however, the effect of these interactions on the HR for metamizole was not considered to be of clinical importance and interaction variables were therefore not included in the model. Apart from age, obesity was also associated with non-proportional hazards. A comparison of survival curves in patients with and without obesity is shown in electronic supplementary Fig. S1. Survival curves for patients with and without obesity initially separated, then converged, and then separated again, but did not cross.

Table 2 Characteristics of patients included in the study

	Patients treated with metamizole [$n = 489,980$]	Patients treated with paracetamol [$n = 143,871$]
No. of female patients	284,852 (58.1)	70,910 (49.3)
No. of patients with missing sex	101 (0.0)	32 (0.0)
Mean age, years [SD]	54.6 [20.5]	36.6 [22.2]
No. of patients with missing age	3667 (0.7)	471 (0.3)
Prescription for confounding medication within 30 days prior to the start of study treatment	88,784 (18.1)	16,558 (11.5)
Alcohol abuse or misuse in history of the patient	7446 (1.5)	1218 (0.8)
Diabetes mellitus[a]	75,523 (15.4)	9481 (6.6)
Obese in latest information on obesity or BMI[b]	57,225 (11.7)	10,425 (7.2)
Non-obese in latest information on obesity or BMI	104,042 (21.2)	29,269 (20.3)
Information on obesity or BMI available	161,267 (32.9)	39,694 (27.6)
Median cumulative dose, g (interquartile range)[c]	25.0 [10.0–25.0]	10.0 [10.0–10.0]

Data are expressed as *n* (%) unless otherwise specified

SD standard deviation, *BMI* body mass index, *ICD-10* International Classification of Diseases, Tenth Revision

[a]Includes both type I and type II diabetes mellitus

[b]Obesity was defined as a WHO ICD-10 code of obesity (E66), a recorded event of 'obese', or a recorded BMI value >30

[c]Excluding 86 patients who had received metamizole products for which information on strength was missing, not allowing the dose to be calculated

Table 3 Distribution of hepatic outcomes over hepatic diagnoses

Type of hepatic outcome (ICD-10 codes)	Patients treated with metamizole [$n = 489,980$]	Patients treated with paracetamol [$n = 143,871$]
All hepatic outcomes	1723	197
Toxic liver disease [K71]	60 (3.7)	6 (3.0)
Hepatic failure [K72]	27 (1.7)	1 (0.5)
Other hepatic events [K75–K76]	1638 (95.1)	190 (96.4)

Data are expressed as *n* (%)

ICD-10 International Classification of Diseases, Tenth Revision

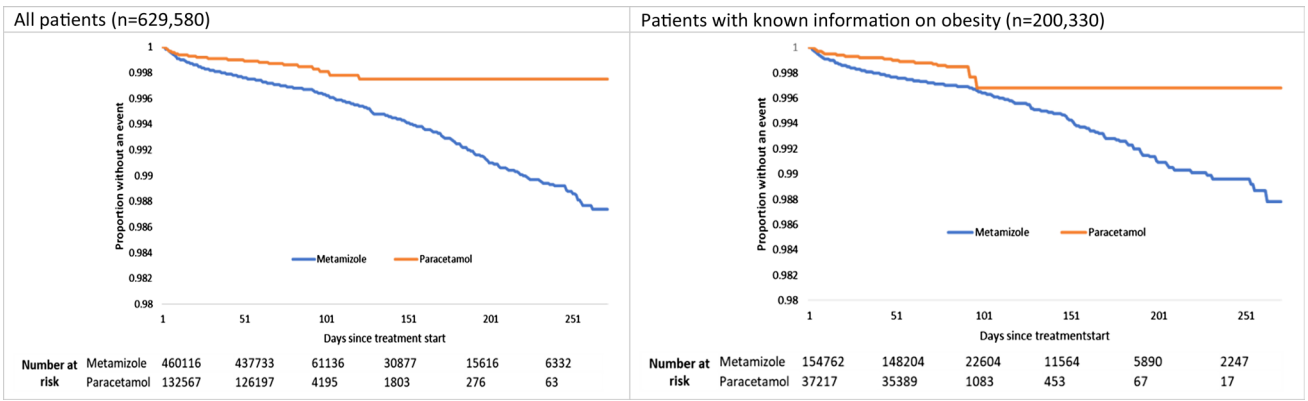

Fig. 2 Survival function in patients treated with metamizole versus patients treated with paracetamol

3.5 Other Analyses

As it seemed possible that differences in indications for treatment between patients in the two groups could have contributed to a higher risk estimate for metamizole compared with paracetamol, we undertook sensitivity analyses to further analyze the association between metamizole and liver injury; in all of the analyses, metamizole was still significantly associated with hepatic injury. The results of the first sensitivity analysis that included data on diagnoses and conditions within the previous 365 days only are shown in electronic supplementary Table S2. It shows a similar result as in the main analysis. The analysis included more patients than the main analysis because fewer patients were excluded due to prior diseases. The second sensitivity analysis in adult patients only also showed a similar result (electronic supplementary Table S3), while the third sensitivity analysis that considered a larger number of covariates showed a slightly lower but still significantly increased HR for metamizole (electronic supplementary Table S4) [see the electronic supplementary text for how the different variables were defined]. Abdominal diseases and symptoms showed non-proportional hazards, but there was no evidence of crossing of survival curves (electronic supplementary Fig. S2).

In a separate analysis, we also compared metamizole with naproxen. The characteristics of patients treated with metamizole versus patients treated with naproxen are shown in electronic supplementary Table S5. This comparison includes a higher number of patients treated with metamizole than the comparison with paracetamol because more patients had a first prescription for metamizole with no prior prescription for naproxen, whereas some of the patients had a prior paracetamol prescription and were therefore allocated to the paracetamol group. Compared with patients treated with paracetamol, patients treated with naproxen were more similar to patients treated with metamizole. The analysis comparing patients starting metamizole with patients starting naproxen also showed an increased HR for metamizole (electronic supplementary

Table 4 Multivariable analysis of time to hepatic outcome in patients treated with metamizole versus patients treated with paracetamol ($n = 629{,}580$ patients)

	HR	95% CI	Supremum test PH[a]
Metamizole (metamizole vs. paracetamol)[b]	1.69	1.46–1.97	$p = 0.137$
Alcohol abuse or misuse in history of the patient	1.66	1.28–2.15	$p = 0.985$
Sex (female vs. male)	0.90	0.83–0.99	$p = 0.494$
Presence of any confounding medication	0.88	0.78–0.99	$p = 0.338$
Diabetes mellitus[c]	0.97	0.85–1.10	$p = 0.527$

CI confidence interval, *HR* hazard ratio, *PH* proportional hazards

The HR is adjusted for all other variables in the table. Results have been stratified by age, in years

[a]A non-significant *p*-value for the Supremum test indicates that the assumption of proportional hazards is not violated

[b]Limiting follow-up to the first 90 days in the main multivariable analysis, the HR for metamizole still remained significant (HR 1.90, 95% CI 1.63–2.22)

[c]Includes both type I and type II diabetes mellitus

Table 5 Multivariable analysis of time to hepatic outcome in patients treated with metamizole versus paracetamol for the subset of the population for which information on obesity was recorded ($n = 200{,}330$ patients)

	HR	95% CI	Supremum test PH[a]
Metamizole (metamizole vs. paracetamol)	1.72	1.43–2.50	$p = 0.18$
Alcohol abuse or misuse in history of the patient	1.35	0.82–2.22	$p = 0.651$
Sex (female vs. male)	0.97	0.82–1.14	$p = 0.932$
Presence of any confounding medication	0.99	0.81–1.21	$p = 0.462$
Diabetes mellitus[b]	0.94	0.77–1.14	$p = 0.575$
Obesity[c]	1.24	1.05–1.46	$p = 0.014$

CI confidence interval, *HR* hazard ratio, *PH* proportional hazards, *BMI* body mass index, *ICD-10* International Classification of Diseases, Tenth Revision

The HR is adjusted for all other variables in the table. Results have been stratified by age, in years

[a]A non-significant *p*-value for the Supremum test indicates that the assumption of proportional hazards is not violated

[b]Includes both type I and type II diabetes mellitus

[c]Obesity was defined as a WHO ICD-10 code of obesity (E66), a recorded event of 'obese', or a recorded BMI value >30

Table S6). The flowchart for patients in each of the two cohorts is shown in electronic supplementary Fig. S3. As naproxen may be preferentially prescribed to patients with musculoskeletal disorders, the analysis was also repeated in patients who had a diagnosis of musculoskeletal disorder (ICD-10 code M) on the start of treatment date (electronic supplementary Table S7). In that analysis, metamizole was also associated with an increased HR for hepatic injury versus naproxen.

4 Discussion

4.1 Key Results

We found an increased HR for hepatic injury after initiation of treatment with metamizole compared with initiation of treatment with paracetamol, which remained in all the sensitivity analyses that were undertaken to further investigate the association between metamizole and hepatic injury. The HR was also increased for hepatic injury with metamizole versus naproxen. These results indicate a possible increased risk of DILI with metamizole. However, it is important to point out that most patients initiating treatment with metamizole were aged 18 years or older and the study could therefore not provide any insight into the risk of liver injury in children.

4.2 Strengths and Limitations

This analysis has some strengths. First, we included patients at the time of their first identified prescription for metamizole or paracetamol in the database, which is vital in order to capture hypersensitivity reactions that occur within the first few weeks to months after the initial exposure. Repeated exposures after an initial sensitization period, even if such exposures were incident, would result in a lower risk of hypersensitivity reactions due to the depletion of susceptibles [40, 55, 56]. In this regard, our study may be more useful compared with studies that did not consider the cumulative duration of use of metamizole [12, 18]. Second, the follow-up period was relatively short in order to increase the likelihood that the patient was still under active surveillance by the prescribing physician, and, third, patients were required to have a minimum observation period prior to the start of treatment to ensure that the first treatment was incident and to collect sufficient data on baseline variables.

Our study also has limitations. In Germany, patients are not required to register with a physician and are free to visit their physician of choice. For this reason, longitudinal follow-up of patients may be limited and all healthcare encounters by the patient may not be captured. Moreover, if a patient visits another practice, he/she is not recognized as the same patient in IMS® Disease Analyzer Germany. We attempted to minimize these risks by choosing patients who had a history of visiting the same practice and by selecting a relatively short follow-up period after the start of treatment. Nevertheless, IMS® Disease Analyzer Germany has shown to be of value, e.g. in the follow-up of clinical events in patients treated with oral anticoagulants [57, 58].

Another limitation is the possibility that risk factors for hepatic injury could be incompletely recorded in patients treated with metamizole, and that these risk factors, if known, including the potential use of herbal medicines, could have explained the difference in the risk of liver injury between patients initiating treatment with metamizole and patients initiating treatment with paracetamol. However, considering that metamizole was still associated with an increased risk of liver injury compared with naproxen, despite the fact that the patients in this comparison were more similar, even when the analysis was restricted to patients with a musculoskeletal disorder, it seems unlikely that a difference in risk factors for liver injury alone could explain the findings in this study.

We included a broad range of ICD-10 codes for hepatic events and it is possible that some of the codes have low validity for DILI. A previous study has shown that acute liver injury was more specifically coded at discharge from hospital than in outpatients [59]. That study also found that the validity of different codes was not consistent across databases [59]. Our study was conducted in GP patients where non-specific liver events were the most frequently recorded outcome events. We also did not have access to liver biochemical test results. This calls for caution in the interpretation of the findings of our study. When our study was conducted, DILI was not listed as an adverse reaction to metamizole in Germany. Knowledge of the association between metamizole and DILI is therefore unlikely to have had an impact on the results of this study.

A further limitation is that metamizole was only available on prescription, whereas paracetamol was also available over-the-counter (OTC), which could lead to the possibility that some patients in the metamizole group also use paracetamol without prescription, whereas such use may be less likely in the paracetamol group. If such concomitant use is extensive, it could be argued that an increased risk of hepatic events could be due to an interaction between metamizole and paracetamol rather than due to metamizole alone. The likelihood of liver injury with paracetamol when used as recommended is regarded as low [19] but may not be negligible [22–26]. Due to the widespread availability of paracetamol OTC, it is also possible that the paracetamol group may be less restricted to true incident users. However, as hepatotoxicity due to treatment with paracetamol is mainly dose-dependent [22, 60] and not unpredictable, the

restriction to incident users would have little impact on the rate of hepatic events in patients treated with paracetamol.

A period of 90 days after each prescription was chosen to capture the period of risk of a hypersensitivity reaction, allowing for a likely exposure duration and enough time after the end of exposure for events to occur and be recorded, while at the same time considering that a longer period of follow-up could dilute the risk estimate. The maximum duration of follow-up was 270 days. However, the actual duration of total follow-up was shorter in patients treated with paracetamol compared with patients treated with metamizole, hence there were more limited data relating to longer follow-up times in patients treated with paracetamol compared with patients treated with metamizole. However, metamizole was still associated with a significantly increased HR compared with paracetamol when the follow-up time was restricted to 90 days (Table 3, footnote).

Female sex is a known risk factor for DILI [61], although this is not shown for all types of DILI, and it is also possible that female sex is mainly a risk factor in older patients [62]. In our study, we identified an interaction between sex and age, but, overall, female sex was not associated with an increased risk.

4.3 Relevance

Metamizole has been on the market in Germany for almost 100 years. During the last 20 years, emerging evidence suggests that metamizole can cause significant hepatotoxicity in individual patients [9–15]. This study was conducted to provide further epidemiological evidence to support or refute the association. The results of this study are in line with the statement that there may be a significant risk of hepatic injury with metamizole that is currently underrated [15]. However, epidemiological studies that allow a better classification of the liver injury and RUCAM scores in individual cases are needed to provide a more definitive answer regarding the risk of liver injury with metamizole.

4.4 Conclusion

We found an increased risk of hepatic injury in adult patients who initiated first-ever treatment with metamizole versus paracetamol, which is considered to have a low risk of hepatotoxicity when used as recommended, in the IMS® Disease Analyzer Germany database. The findings are in line with findings in a previous case-control study in outpatients from Berlin that also suggested an association between metamizole and hepatic injury, and with published cases. Our findings provide further support for the association but should be viewed cautiously and in conjunction with data from other studies, as residual confounding could not be excluded.

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Declarations

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Conflicts of interest Karin Hedenmalm, Alexandra Pacurariu, Jim Slattery, Xavier Kurz, Gianmario Candore and Rob Flynn are employees of the European Medicines Agency and have no conflicts of interest to declare in relation to this article.

Ethics approval This study was carried out using a deanonymized database (IMS® Disease Analyzer Germany), for which ethics approval was not required.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material The analyses conducted in this study were performed by the authors based on the IMS® Disease Analyzer Germany database, version June 2019. The study has been registered in the EUPAS register (EUPAS 31864). Analytic data sets and custom codes can be made available upon request from the authors.

Code Availability Not applicable.

Author contributions All authors contributed to the study design and analysis of results. Karin Hedenmalm drafted the manuscript with contributions from all other authors. All authors read and approved the final version.

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