Eur J Clin Pharmacol (2015) 71:209–217
DOI 10.1007/s00228-014-1781-z

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Hematological safety of metamizole: retrospective analysis of WHO and Swiss spontaneous safety reports

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Received: 29 April 2014 / Accepted: 4 November 2014 / Published online: 18 November 2014

Abstract
Purpose Since the 1970s, the use of metamizole is controversial due to the risk of agranulocytosis. The aim of this study was to analyze individual case safety reports (ICSRs) of metamizole-associated hematological adverse drug reactions (ADRs).
Methods International and Swiss metamizole-associated ICSR concerning selected hematological ADR were retrieved from VigiBase™, the World Health Organization Global Database of ICSR, and the Swiss Pharmacovigilance Database. We evaluated demographic data, co-medication, drug administration information, dose and duration of metamizole treatment, as well as the latency time of ADR, their course, and severity. The subgroup analysis of Swiss reports allowed us to analyze cases with fatal outcome more in depth and to estimate a rough minimal incidence rate.
Results A total of 1417 international and 77 Swiss reports were analyzed. Around 52 % of the international and 33 % of the Swiss metamizole-associated hematological ADR occurred within a latency time of ≤7 days. More women were affected. The annual number of hematological reports and those with fatal outcome increased over the last years parallel to metamizole sales figures. In Switzerland, the minimal incidence rate of agranulocytosis was 0.46–1.63 cases per million person-days of use (2006–2012). Female sex, old age, pancytopenia, and co-medication with methotrexate were striking characteristics of the seven Swiss fatal cases.
Conclusions Metamizole-associated hematological ADR remain frequently reported. This is underscored by increasing annual reporting rates, which mainly reflect growing metamizole use. Early detection of myelotoxicity and avoidance of other myelotoxic substances such as methotrexate are important measures for preventing fatalities.

Keywords Metamizole (dipyrone) · Agranulocytosis · Hematological safety · Pharmacovigilance

Introduction

Metamizole, also known as dipyrone, is an old antipyretic and analgesic drug with a controversial history. Although metamizole has poor anti-inflammatory effects, it is often, probably improperly, classified as a non-steroidal anti-inflammatory drug (NSAID). The pharmacological mechanism of action is still not entirely understood. Inhibition of cyclooxygenase (COX) enzymes by metamizole has been demonstrated, but the corresponding IC50 values show a high variability between 2.55 and >400 μmol/L (Ibuprofen: IC50 values COX-1 12–42 μmol/L, Naproxen: IC50 value COX-1 0.3–24 μmol/L) [1–4]. Other mechanisms of action have been proposed, including stimulation of endogenous cannabinoid receptors [5].

For years, the safety profile, in particular the risk of blood disorders including agranulocytosis, has been controversially discussed. Estimated incidences for agranulocytosis range from 1:3000 users a year to 1:1,000,000 users a week [6, 7].

Electronic supplementary material The online version of this article (doi:10.1007/s00228-014-1781-z) contains supplementary material, which is available to authorized users.

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Due to the risk of agranulocytosis, metamizole was banned or withdrawn from the market in many countries (e.g. Great Britain, USA, Sweden, Japan, and Australia), while it is currently on the market in other countries and parts of the world (Switzerland, Germany, France, Spain, Latin and South America, Far East, and Africa) [8, 9].

Supporters of metamizole emphasize the advantages of metamizole over classical NSAIDs, especially the better gastrointestinal and renal tolerability [10]. A meta-analysis of several epidemiologic studies of serious adverse effects associated with different analgesics demonstrated that the absolute risk of mortality associated with metamizole is 25 deaths per 100 million users, which is in the same range as for paracetamol but much lower than for NSAIDs [11].

As the prescription rate of metamizole in Switzerland is increasing and since we had received several reports of metamizole-associated hematological adverse reactions, we decided to analyze the international and Swiss hematological pharmacovigilance data of this drug.

Methods

Study design and selection of individual case safety reports

This retrospective descriptive study is based on selected individual case safety reports (ICSRs) from the World Health Organization (WHO) global database VigiBase™ and, for a more detailed subgroup analysis, from the Pharmacovigilance database of the Swiss Drug Authority Swissmedic. We included only ICSR with metamizole as suspected or interacting drug associated with adverse drug reaction (ADR) terms corresponding to the WHO adverse reaction terminology (WHO-ART) "preferred terms" agranulocytosis, granulocytopenia, leucopenia, white blood cell abnormal not otherwise specified, pancytopenia, anemia aplastic, aplasia bone marrow, and marrow depression.

Recording of individual hematological case safety reports

International data

We received the coded data elements of the international metamizole-associated ICSR from the WHO global database VigiBase™ as a Microsoft Excel file. Since the international ICSR did not contain a narrative, verification of coding, adding codes or recoding could not be performed. The following data were analyzed: demographic data (age at ADR onset and gender), route of administration, daily dose, duration of treatment, cumulative dose, reported ADR and their causality assessments, latency time, duration of ADR, number of suspected drugs, and total number of drugs. Using the available coded dosage information, therapy and ADR dates, we calculated the daily dose, cumulative dose, duration of treatment, latency time, and duration of the ADR. The latency time was defined as the period between the metamizole start date and the date of ADR onset. For all international metamizole-associated hematological ICSR, we analyzed the annual reporting rate, reporting rate for fatal outcome, and cumulative reporting rates stratified per country. ICSR with unlikely or not assessable causality assessment or with a negative latency time (ADR occurred before metamizole administration) were excluded. If more than one metamizole preparation was listed in a ICSR, we did not use the data concerning the metamizole causality assessment, start and stop date of metamizole treatment, outcome of reported ADR, dechallenge and rechallenge information, or route of administration for the final analysis due to difficulties in handling the various data.

Swiss data

We received coded data elements of the Swiss metamizole-associated ICSR from the pharmacovigilance database of Swissmedic accompanied by the original ICSR with the case narrative in a portable document file. The case narrative contained more detailed information about the course of each ADR and allowed us to analyze co-medication and cases with fatal outcome more in depth. Additionally, we could estimate a rough minimal incidence rate. We reviewed the information of the case narratives and, in case of discrepancies between the narrative and the coded information, we recoded according to the narrative. The WHO-ART codes for reported ADRs were first verified with the narrative according to the definitions for blood dyscrasias [12, 13]. Afterwards, they were recorded as follows: If in an ICSR, a patient had received neutropenia ("preferred term") with fever (preferred term), we recoded the "included term" febrile neutropenia which belongs to the preferred term agranulocytosis. We recoded the terms only, if neutrophil counts were in accordance with the definition of agranulocytosis [12, 13]. In cases with fatal outcome, we recorded the day of death as the stop date of the ADR. In cases without ADR stopping date, we added the date, if it was obvious from the reported laboratory values or if it was mentioned in the narrative. General statements of ADR courses, for example "the hemogram improved within three weeks" without an exact reported stopping date, were recorded as 21 days. Therapy options such as administration of granulocyte-colony stimulating factor (G-CSF), antibiotics, transfer of the patient to a hospital's intensive care unit, or withdrawal of the drug were also recorded.

For the calculation of the daily and cumulative dose, we coded or recoded the data according to the narrative as follows: If possible, we calculated the daily and the cumulative doses according to the coded dosage information. If

metamizole was prescribed as an "as required" medication and metamizole intake and dosage regimen could be assured, we interpreted metamizole as being dosed maximally (4 g per day). If the intake was uncertain or unknown, we did not calculate the daily or cumulative dose for this ICSR. Cumulative drug doses reported as circa 60 g were recorded as exactly 60 g. A single administration of metamizole was recorded as therapy duration of 1 day. Other possible coding terms for time specification such as week(s), month(s), or year(s) were counted as 7, 30, and 365 days, respectively. When only the month and year (MM.YYYY) of the start or stop date was reported, we counted the recorded month as a full month (30 days). Coded time terms such as day(s), short term, and long term without more specific explanations were not used for the calculation of daily or cumulative dose or therapy duration. For co-suspected drugs, we coded and analyzed generic names and the corresponding ATC codes. In addition to the annual reporting rate of metamizole-associated hematological ICSR, we estimated a rough minimal incidence for agranulocytosis using annual sales figures of all Swiss metamizole preparations. The Swiss annual sales figures were obtained from the respective marked authorization holders. They were first expressed as defined daily dose (DDD) and were pooled afterwards.

Statistical analysis

Descriptive analysis was performed using Microsoft Office Excel (2010) and SPSS for Windows software (version 21). For variables with normally distributed numeric values, the arithmetic mean and standard deviation were calculated. For variables without normally distributed values, median and range were determined.

Results

Between June 22, 1968, and January 25, 2013, 1475 ICSR concerning metamizole-associated hematological ADR were transmitted to Vigibase™. After excluding ICSR according to the defined exclusion criteria, 1417 international ICSR remained for analysis. Between 1991 and December 31, 2012, the National Pharmacovigilance Center at Swissmedic received 85 ICSR of metamizole-associated hematological ADR. After the exclusion of ICSR using the previously defined exclusion criteria, 77 ICSR remained for the subgroup analysis.

Table 1 summarizes the findings of the international and Swiss data. Concerning ADR terms, agranulocytosis was listed most often in both datasets in almost one third of the reports. This was followed by leucopenia in one fifth and granulocytopenia in approximately 10 % of the reports. The other terms concerned adverse drug reactions with a decrease in all blood cell lines.

In both datasets, around two thirds of reports concerned women and the median age was almost 60 years. When stratified for age, there were no apparent differences between international and Swiss cases, showing highest numbers in the age group of 70–79 years (18–19 %) and lowest numbers of ICSR in the age groups 0–9 years (1–2 %) and 10–19 years (3–6 %). For detailed information about the age categories, see supplemental Table 1. While 43 % (n=610) of the international cases were reported as serious, this number reached 90 % (n=69) for Swiss reports.

As shown in Table 2, the daily dose was within the recommended range in both datasets. The duration of treatment could be calculated for 765 international and 63 Swiss ICSR, resulting in a median duration of 8 days (range 1 day to 9 years) and 13 days (range 1 to 594 days), respectively. Among the 63 Swiss ICSR with known treatment duration, almost half of the patients (44 %, n=27) received metamizole for ≤7 days. As a consequence of the large range regarding treatment duration, the corresponding cumulative doses also showed a wide range. For 858 international ICSR, the latency time could be calculated, resulting in a median of 7 days until the diagnosis of the blood disorder, while the median latency time in the Swiss ICSR was 14 days. In 442 (52 %) international and 22 (33 %) Swiss hematological ICSR, the ADR onset was within the first week after start of treatment. This is shown in Fig. 1, which displays the latency time distribution for the international ICSR stratified by weekly periods. The latency time distribution of the Swiss reports was similar (data not shown). The median number of concomitant drugs per report was 3 and 4 in the international and Swiss dataset, respectively. Also, the median number of suspected drugs per report (including metamizole), was similar, namely 1 in the international and 2 in the Swiss dataset. In 436 (31 %) international ICSR, metamizole was reported as the only suspected drug, whereas in the Swiss dataset, this was the case in only 13 (17 %) reports. In Swiss reports, co-suspected drugs were 28 anti-invective agents followed by 23 nervous system drugs and 8 drugs for acid-related disorders (see supplemental Table 2 for further information).

In the Swiss reports, causality for metamizole was never judged as certain, unknown, or not assessable. In two thirds of the reports, the causality for metamizole was judged as possible and in one third as probable. A rechallenge was reported in 45 (3 %) international ICSR. In rechallenged patients, the ADR reoccurred in almost half of the cases (n=23). In 16 ICSR, the rechallenge outcome was unknown and in 6 ICSR, the rechallenge was negative. None of the patients was rechallenged in Switzerland.

In Switzerland, 31 (40 %) patients with metamizole-associated hematological toxicity received G-CSF and 33 (42 %) patients were treated with antibiotics. Patients with

Table 1 Characteristics of international (1968-01/2013) and Swiss individual case safety reports (1991–2012) of metamizole-associated hematological adverse drug reactions

Characteristics	Total international ICSR (*n*=1417)	Total subgroup of Swiss ICSR (*n*=77)
Reported hematological WHO-ART terms [number (%)]		
Agranulocytosis	920 (57)	47 (61)
Leucopenia	349 (21)	12 (16)
Granulocytopenia	166 (10)	9 (12)
Pancytopenia	120 (7)	8 (10)
Anemia aplastic	29 (2)	1 (1)
Marrow depression	26 (2)	NR
Aplasia bone marrow	18 (1)	NR
WBC abnormal NOS	1 (0)	NR
Female [number (%)]	876 (62)	51 (66)
Male [number (%)]	517 (36)	26 (34)
Age at ADR diagnosis [years; median (range)]	57 (1–96)	59 (9–96)
Fatal outcome [number (%)]	186 (13)	7 (9)
Total number of drugs per report [median (range)]	3 (1–53)	4 (1–19)
Number of suspected drug per report [median (range)]	1 (1–11)	2 (1–9)
Metamizole causality rating [number (%)]	1628 terms[a] (100)	77 terms (100)
Certain	104 (6)	–
Probable	393 (24)	19 (25)
Possible	503 (31)	58 (75)
Not assessable	252 (15)	–
Unknown	376 (23)	–

[a] More terms than cases due to more than one adverse drug reaction per report in some cases

NR not reported, ICSR individual case safety reports, NOS not otherwise specified, WBC with blood cell

G-CSF treatment had a mean duration of the ADR of 9 days (*n*=31), whereas the patients without explicitly mentioned G-CSF treatment showed a mean duration of 6.6 days (*n*=42). In four cases, therapy with G-CSF was explicitly omitted. These patients had a mean ADR duration of 9.5 days. The most often reported underlying diseases in the Swiss dataset were

Table 2 Metamizole administration information retrieved from international (1968-01/2013) and Swiss individual case safety reports (1991–2012) of metamizole-associated hematological adverse drug reactions

Characteristics	International ICSR (*n*=1417)	Subgroup Swiss ICSR (*n*=77)
Daily dose [mg; (SD or range)]	2865 (2201) (*n*=196)	2226 (1169) (*n*=57)
Oral	1700 (500–10,000) (*n*=174)	n.d.
Parenteral	4000 (500–12,000) (*n*=122)	n.d.
Cumulative dose [g; median (range)]	20 (0.5–3048) (*n*=296)	19.5 (0.5–1188) (*n*=56)
Oral	22,6 (0.5–3048) (*n*=174)	n.d.
Parenteral	18 (0.5–498) (*n*=122)	n.d.
Route of administration [number (%)]		
Oral	789 (60)	62 (81)
Parenteral	317 (24)	11 (14)
Duration treatment [days; median (range)]	8 (1–3303)	13 (1–594)
Latency time [days; median (range)][a]	7 (1–3305)	14 (1–594)

The maximal daily dose of metamizole is 4000 mg

[a] Time from the start of the metamizole therapy till the adverse drug reaction was diagnosed

ICSR individual case safety reports, n number, n.d. not differentiated

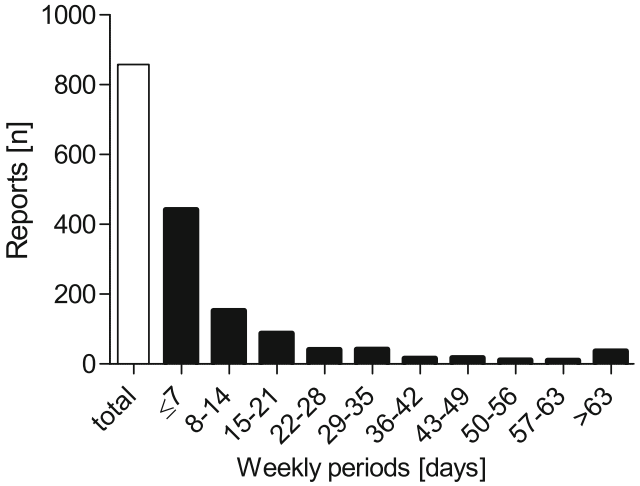

Fig. 1 Latency times stratified by weekly periods for metamizole-associated hematological adverse drug reactions among 858 reports reported to VigiBase™, the WHO Global Database of Individual Case Safety Reports (ICSRs), between 1968 and 01/2013

diseases of the circulatory system and injuries and diseases of the musculoskeletal system (see supplemental table 3 for more information).

Figure 2 shows the international annual reporting rate for metamizole-associated hematological ADR and the reporting rate of cases with fatal outcome. There was a first rise of the international reporting rate in 2008 (76 ICSR) followed by a remarkable increase in 2010 (219 ICSR). Most ICSR were submitted by Germany (44 %), followed by Spain (35 %), Switzerland (6 %), Italy (2 %), and Sweden (2 %). In Switzerland, the annual reporting rate was stable until 2005 with zero to two reports per year. Thereafter, the reporting rate increased remarkably (2006: 7 reports; 2007: 6 reports; 2008: 2 reports; 2009: 5 reports; 2010: 16 reports; 2011: 14 reports; 2012: 15 reports). In total, 186 (13 %) metamizole-associated hematological ICSR with fatal outcome have been reported to the WHO, the first in 1968 and 85 since 2008. In Switzerland, seven ICSR (9 %) with a fatal outcome were reported, the first in 2006, two cases in 2011 and four in 2012. The fatal Swiss cases are described in detail in supplementary Table 4. Six of the 7 cases were women. The metamizole dosage was in the therapeutic range in all cases and the median latency time until detection of the ADR was 14 days (range 4 to 594 days). In Table 3, characteristics of the seven Swiss cases with fatal outcome were compared with the 70 surviving cases. Among the cases with fatal outcome, there were more females, more patients with triple blood cell line injury (43 % versus 10 % among non-fatal cases), fatal cases were in median 11 years older, and in 4 of the 7 fatal cases, there was a co-treatment with methotrexate. Three of the four patients with methotrexate therapy received an immunosuppressive low dose regimen and two of them had received only one single dose of methotrexate. The proportion of certain characteristics such as sex, number of affected cell lines, and co-treatment with methotrexate were not statistically different between patients with fatal outcome and surviving patients.

Finally, the Swiss annual reporting rates of metamizole-associated agranulocytosis were compared with pooled Swiss sales figures of all metamizole preparations on the Swiss market. The sales figures were available from 2006–2012 and were converted to DDD. As shown in Fig. 3, the course of these two variables was comparable during the observation period, suggesting that the observed increase in ICSR is mainly the result of growing metamizole use. Using the sales figures, we could calculate minimal incidence rates. For agranulocytosis, this was 0.46–1.63 cases per million person-days.

Discussion

We evaluated data from the international pharmacovigilance database Vigibase™ and Swiss ICSR regarding metamizole-associated hematological ADR. In addition, the subgroup analysis of the more detailed Swiss ICSR allowed us to evaluate some specific issues such as comorbidities and co-suspected drugs as well as analysis of fatal cases. Furthermore, we could obtain a rough estimate of a minimal incidence rate of metamizole-associated agranulocytosis in Switzerland.

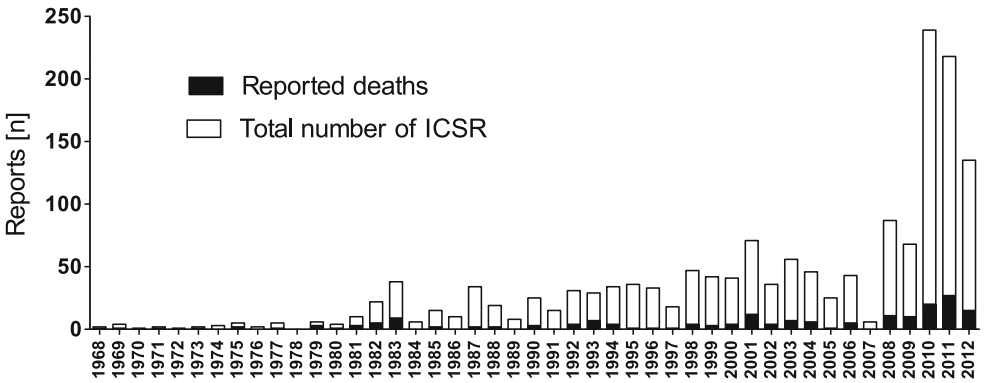

Fig. 2 International annual cumulative reporting rate of metamizole-associated hematological adverse drug reactions and reporting rate of cases with fatal outcome, retrieved from VigiBase™, the WHO Global Database of Individual Case Safety Reports (ICSR), between 1968 and 01/2013

Table 3 Comparison of fatal and non-fatal Swiss individual case safety reports of metamizole-associated hematological adverse drug reactions between 1991 and 2012 (n=77)

	Fatal	Non-fatal
Total number of cases	7	70
Number of females	6 (86 %)	45 (64 %)
Age (years), mean (SD)	66 (22)	55 (21)
Daily dose (mg/day), mean (SD)	2286 (958)	2881 (2221)
Cumulative dose (g), median (range)	21 (10.5–1188)	19.5 (0.5–252)
Cumulative number of treatment days, median (range)	14 (4–594)	13 (1–365)
White blood cell line affected, only	4 (57 %)	58 (83 %)
Two blood cell lines affected	0 (0 %)	5 (7 %)
All three blood cell lines affected	3 (43 %)	7 (10 %)
Number of cases with methotrexate as co-suspected drug	4 (57 %)	0 (0 %)

The maximal daily dose of metamizole is 4000 mg

The percentages of certain variables (sex, number of affected cell lines, co-treatment with methotrexate) were not statistically different between patients with fatal outcome and surviving patients

SD standard deviation

All age groups were affected by metamizole-associated hematological ADR, although more ICSR for elderly people (median age close to 60 years in both data sets) were reported. An increased incidence of hematological disorders in older patients has been reported in several population-based studies of drug-induced agranulocytosis [14, 15]. However, since no data about the exposure of specific age groups to metamizole are available, our data do not allow the conclusion that metamizole-associated hematological ADR occur more frequently in older patients. Similarly, the reporting rate for metamizole-associated hematological ADR was higher for women than men, both in the Swiss and the international ICSR dataset. This finding is in line with previous studies of drug-induced agranulocytosis and, more specifically, also with metamizole-associated agranulocytosis [8, 16, 17]. Again, our data support the results of these studies but do, due to a lack of specific exposure data, per se not allow the conclusion that metamizole-associated agranulocytosis is more frequent in females.

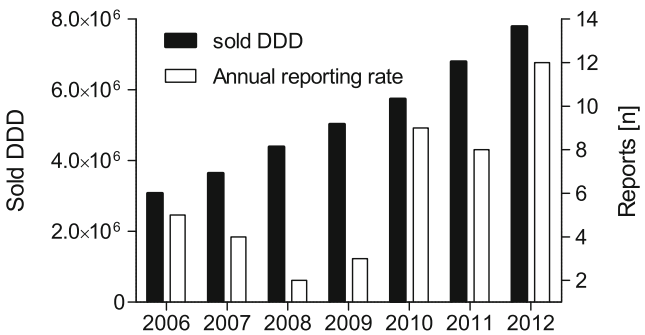

Fig. 3 Annual reporting rate of metamizole-associated agranulocytosis and the course of sold defined daily doses in Switzerland between 2006 and 2012

The average daily dose in reported cases of metamizole-associated hematological ADR was within the recommended range according to the product information. This finding argues against a typical dose-dependent toxicity of metamizole and favors toxicity associated with the presence of immunological or metabolic susceptibility factors in affected patients. Another important factor regarding the mechanism of toxicity is the latency time, although this parameter depends also on other factors than disease mechanism such as frequency of blood monitoring, severity of symptoms, and/or vigilance of doctors. Our data showed that in 33 % of the Swiss and in 52 % of the international ICSR, hematotoxicity appeared during the first week of treatment. In support of this finding, a systematic review including 980 drug-associated agranulocytosis case reports described a median metamizole exposure of only 2 days until hematological abnormalities appeared [18]. These findings are also in agreement with the case control study of Ibanez et al. [19]. Furthermore, 88 % of the Swiss ICSR and 96 % of the international hematological ADR occurred within 2 months of metamizole treatment. These findings agree well with a Swedish study, where 92 % of the cases occurred within the first 2 months [8]. Interestingly, these findings concerning metamizole are very similar to those reported for clozapine, where >80 % of patients with agranulocytosis were observed during the first 3 months of treatment [20]. Considering the lack of accompanying immunological features in most patients with metamizole-associated myelotoxicity, both a metabolic and an immunological mechanism are possible.

In several European studies, the mortality rate of drug-induced agranulocytosis decreased over the last years from 10 to 16 % to approximately 5 % [21]. This was considered to be a consequence of the therapy with G-CSF and with broad-spectrum antibiotics [8, 21]. Our data, however, do not support this assumption. We observed an increase of reported fatal cases in parallel with the increased reporting rate and use of metamizole in Switzerland, despite the option for G-CSF treatment. Since only 40 % of the Swiss patients were treated with G-CSF, this finding may be explained by a selection bias. It can be assumed that patients with more severe hematological ADR were treated preferentially with G-CSF.

The reporting rate of metamizole-associated blood dyscrasias with fatal outcome in the Swiss and international dataset increased over time, in particular in 2010 and 2011. The Swiss data suggest that the increased use of metamizole is the main reason for the increased number of reported fatal cases (see Fig. 3). In their review, Andrès et al. listed age >65 years, septicemia and/or shock, metabolic disorders such as renal failure, and a neutrophil count below 0.1 G/L as poor prognostic factors for drug-induced agranulocytosis [21]. These risk factors could also be identified in the Swiss cases with

fatal outcome. Five of the seven patients were over 65 years, and patients with a fatal outcome were 11 years older than those who recovered. In four of the seven fatal cases, septicemia was reported as cause of death and all fatal cases had neutrophil counts below 0.1 G/L. Furthermore, the proportion of patients in whom all three blood cell lines were affected was higher among patients with fatal outcome than in those who recovered.

Two additional potential risk factors for a fatal outcome identified in our study are female sex and co-treatment with methotrexate. In agreement with the overrepresentation of females in the entire dataset, six out of the seven patients with a fatal outcome were females. Importantly, methotrexate was considered as co-suspected drug in four out of seven fatal cases and in none of the non-fatal cases. Three of these patients were on low-dose (immunosuppressive) methotrexate, two of them were on long-term treatment, and one of them had received only a single dose. In addition, one patient with T-cell lymphoma had been treated with an oncological dose (single dose of 5500 mg) of methotrexate. In this patient, methotrexate appears to be the more likely reason for myelotoxicity than metamizole. Methotrexate-associated myelotoxicity is dose-dependent. Since methotrexate is mainly eliminated by the kidney, impaired renal function is associated with increased exposure and with an increased risk for myelotoxicity [22]. Unfortunately, no serum creatinine concentrations have been reported or could be retrieved in patients with low-dose methotrexate before the diagnosis of myelotoxicity. Since low-dose methotrexate is used as an immunosuppressant in autoimmune diseases such as rheumatoid arthritis and women are more likely to be affected by autoimmune diseases, this may at least partially explain the female predominance for fatalities in metamizole-associated myelotoxicity.

Between 2006 and 2012, the pooled annual Swiss sales figures of all metamizole preparations on the Swiss market increased constantly by about 800,000 DDD per year. The annual reporting rate for metamizole-associated agranulocytosis also increased remarkably between 2006 and 2012, but the absolute numbers remained small, with an annual reporting rate for all blood dyscrasias between 2 and 16 and for agranulocytosis between 2 and 12 reports per year. Overall, the annual reporting rates paralleled the sales figures and therefore probably the use of metamizole in Switzerland, although with annual fluctuations. These fluctuations can be explained by changes in the reporting rate for pharmacovigilance data. This is influenced by many different factors, in particular by underreporting and selective reporting [23].

In 2002, Hedenmalm et al. [8] reviewed all spontaneous reports of serious metamizole-associated blood dyscrasia in Sweden and estimated the incidence for agranulocytosis associated with metamizole to be 1 in 1439 prescriptions. Similarly, Baeckerstroem et al. [24] analyzed spontaneous reports of agranulocytosis and the use pattern of metamizole in Swedish inpatients and outpatients. They calculated the risk of metamizole-associated agranulocytosis to be approximately 1 in 31,000 metamizole-treated inpatients and 1 in 1400 outpatients. In our study, we were able to estimate a minimal incidence rate for metamizole-associated agranulocytosis in Switzerland using the annual reporting rates and annual metamizole sales figures expressed as DDD. The estimated incidence rate was 0.46–1.63 per million person-days, which was within the range of the incidence rate in the International Agranulocytosis and Aplastic Anemia Study (IAAA study) of 0.3–4.0 per million person-days [6, 8]. Our incidence rate is higher than reported in a Polish study with an incidence rate of 0.2 per million person-days [16]. A detailed comparison with the reported incidence rates of agranulocytosis in Sweden (at least 1 per 1439 prescriptions) is not possible due to different estimation methods and different units [8]. Taking into account the median treatment until agranulocytosis occurred (13 days in Swiss patients) it can be assumed that the incidence rate in Sweden is higher than in Switzerland. It has to be considered, however, that the Swiss incidence rate may be higher due to underreporting. It is well known that only approximately 6 % of all ADR are spontaneously reported to the pharmacovigilance systems [25].

Limitations

This study is based on spontaneously reported metamizole-associated ICSR. As stated above, underreporting and missing data in spontaneous reports are well-known problems in this type of studies. Reasons for missing data are unavailable information or the reporter did not consider certain facts as relevant. Furthermore, the standardized requirements for reporting ADR changed over the last decades, and the ICSR include progressively more information. In addition, ICSR derive from different sources (countries, National Pharmacovigilance Centers and companies) and were written and coded by different reporters with potentially different coding policies. Therefore, heterogeneity of ICSR must be taken into account when interpreting data from pharmacovigilance databases.

Conclusions

In patients treated with metamizole, we estimated an annual incidence rate for agranulocytosis of 0.46–1.63 per million person-days, which is within the range of the IAAA study [6]. This is a minimal risk, since underreporting is known to be substantial for pharmacovigilance data. Female sex, triple blood cell line dyscrasia, older age, and concomitant treatment with methotrexate were identified risk factors for fatal outcome. A large proportion of the Swiss (33 %) and the

international cases (52 %) occurred during the first 7 days of metamizole treatment, compatible with an immunologic or a toxic mechanism in predisposed patients. Taking into account the rapid onset of metamizole-associated agranulocytosis, close monitoring of the patient starting already in the first week of treatment is essential to detect the onset of myelotoxicity as early as possible. Information of the patients to self-identify the first symptoms of myelotoxicity, to immediately stop metamizole intake, and to consult a doctor may be crucial to identify affected patients as soon as possible. Metamizole prescribing should be conservative, and the prescriber should outweigh the risk for myelotoxicity against the adverse reactions of possible alternatives [11].

Acknowledgments The authors would like to thank Sara Hult, member of the analysis team of the Uppsala Monitoring Centre, the WHO Collaborating Centre for International Drug Monitoring, for providing the data and for answering our questions. We also would like to thank Guy Levy from the Vigilance Unit of Swissmedic for his collaboration. We thank also Sanofi-Aventis SA, Streuli Pharma AG, and Sintetica SA for providing the sales figures of their metamizole preparations in Switzerland. We thank also the Senglet-Foundation, the foundation for the promotion of young pharmaceutical researchers in Basel, for their financial support.

Author contribution Performed research: LB, AT, PE, ARB. Analyzed data: LB, AT, MH, SK, ARB. Wrote manuscript: LB, SK, ARB. All authors contributed to the review and final approval of the manuscript.

Conflict of interest The authors declare that there are no conflicts of interest regarding this work.

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Accompanying statement

The data for this work were obtained from the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden and from the Swiss health authority, Swissmedic, in Berne, Switzerland. Data from spontaneous reporting are inhomogeneous as a result of different

reporting policies worldwide and are vulnerable to underreporting and reporting bias. The information contained in this work is therefore not homogeneous, at least with respect to origin and also to likelihood that the pharmaceutical product caused the adverse reaction. The conclusions drawn based on these data do not necessarily represent the opinion of the World Health Organization or of Swissmedic.