CORRESPONDENCE

Letters to the Editor

The Epidemiology of Acute Liver Failure

Results of a Population-Based Study Including 25 Million State-Insured Individuals

by Dr. med. Nina Weiler, Dr. med. Andreas Schlotmann, Prof. Dr. med. Andreas Anton Schnitzbauer, Prof. Dr. med. Stefan Zeuzem, and PD Dr. med. Martin-Walter Welker in issue 4/2020

Metamizole Has Been Overlooked as a Trigger for Acute Liver Injury and Acute Liver Failure

We read the article by Weiler et al. on the epidemiology of acute liver failure (ALF) in Germany with great interest (1). The article clearly illustrates that the rates at which substances cause drug-induced liver injury (DILI) differ in the international comparison. The authors showed that phenprocoumon is a relatively common cause of ALF in Germany, whereas American registry studies of DILI do not make any mention of phenprocoumon, probably because of the more common use of warfarin (2). Furthermore, awareness of potential hepatotoxicity is vital for recognizing and notifying this condition. In this context we wish to mention our case series of 23 patients with severe icteric hepatitis owing to metamizole intake, with metamizole a contributing causal factor in two cases of ALF (3). Liver injury has thus far not been included in the adverse effects for metamizole. Except for our study, only individual case reports of liver injury after metamizole administration exist (4). The study reported by Weiler et al. does not identify metamizole as a triggering medication either, which we explain with lacking awareness regarding liver injury due to metamizole, with consequently lacking reporting of cases. The medicines report regarding metamizole in the same issue of *Deutsches Ärzteblatt* calls for documenting in detail the perioperative use of metamizole in the discharge notes, to enable those in charge of subsequent treatment to recognize the signs of agranulocytosis early on. On the basis of our study, this also holds true for categorizing acute icteric hepatitis or acute liver failure after an inpatient stay and use of metamizole.

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The authors declare that no conflict of interest exists.

"Retrospective" as Well as "Retrolective"

Weiler et al. reported a secondary analysis of data on acute liver failure (1). They analyzed administrative data from the statutory health insurance company *Allgemeine Ortskrankenkassen* (AOK). The authors described their design as a population-based study using prospectively collected data. In actual fact, however, the study is a "scientific study with data whose primary use is not of a scientific nature" (2). The question was not defined before the data were collected, nor were data collected about the question (for example, by means of examination) or recorded from information regarding healthcare services for the question (for example, by means of a questionnaire). The mixture of data was therefore random with regard to the research question. Earlier, Lorenz already pointed out the problems in categorizing observational studies as prospective or retrospective (3). According to Lorenz, the analysis reported by Weiler et al. is retrospective, because it considers past events, as well as "retrolective," because it does not collect new data on the events of interest. The difference between a prospective population based study of acute liver failure and the presented secondary analysis is also economically relevant. While carrying out the secondary analysis might have incurred about €100 000 in costs, a prospective population based study and 4652 cases would have cost several million Euros. An unambiguous and uniform terminology regarding study types is essential for

interpreting empirically gained data, in view of the growing range of methods—for example, using Big Data or methods of artificial intelligence. Such a terminology would support recipients of publications in terms of awareness of strengths and limitations of the different study types. This terminology is currently lacking.

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In Reply:

We thank Drs. Sebode et al. for highlighting the hepatotoxic potential of metamizole. The publications they mention are the only two publications on metamizole and drug-induced liver injury (DILI) or acute liver failure (ALF), probably due to the fact that metamizole is no longer licensed in many countries because of the risk of agranulocytosis (1). In our study we did not explicitly search for (thus far unknown) drugs with the risk of DILI or ALF, but evaluated drugs known to be associated with acute liver failure from different publications (2, 3). For this reason we did not mention metamizole. It also should be considered that our method was not able to reflect over-the-counter medication. Therefore, a connection between prescriptions and ALF cannot be established on the basis of health insurance data. Identifying the cause of ALF is often difficult. On the basis of the data of Sebode and colleagues, metamizole should in future be considered as a cause of DILI or ALF.

Population-based studies investigate a specific question in a defined group, and the results should be transferable to a general population (4). Therefore, the difficulty lies in selecting a sample that is representative of the total (5). Several variations of study designs are possible—for example, a case-control study or cross sectional study—and the data collection may be prospective or retrospective. The study we presented is a retrospective population-based incidence study. Evaluating the association between disease and source was only the secondary study aim. Concerning Swart and Schmitt's Standardized Reporting Of Secondary data Analyses"(STROSA) criteria, as cited by Strausberg, the publication contains the suggested components. In particular, the limitations of the study regarding the AOK members as adequate sample of the general population were discussed in detail. However, since ALF is not notifiable, a representative and prospective data collection is intricate. Data collected prospectively by specialized liver centers are biased by selection and may not represent the general population.

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