

LETTER TO THE EDITOR

Further evidence for the hepatotoxic potential of metamizole

We read with great interest the commentary by Björnsson “Liver injury associated with the analgetic drug metamizole.”¹ Metamizole is an analgetic and antipyretic drug, which has been taken from the market in the United States and the United Kingdom mainly due to the risk of causing severe agranulocytosis, but is still widely used in many Latin American, Asian, and European countries.² Especially in Germany, the use of metamizole has markedly increased in recent years.³ However, despite its extensive hepatic metabolism, the potential of metamizole to cause drug-induced liver injury (DILI) has been disregarded for many years, and only few cases have been reported.⁴ Björnsson emphasizes¹ that including recently published cases by Sebode et al.,⁵ approximately 40 patients with metamizole-induced liver injury have been reported worldwide, which qualifies metamizole as a Category B drug causing DILI according to the categorization system of LiverTox (<http://livertox.nih.gov>).⁶ As stated by the LiverTox “likelihood score,” Category A drugs are considered to have a definite hepatotoxic potential with a positive rechallenge reported for almost 90% of the drugs, while Category B drugs are highly likely to cause DILI.^{6,7} An agent is considered a Category B drug in case 12 to 50 patients with DILI due to this agent have been published whereas Category A requires more than 50 cases reported.

To further assess the hepatotoxic potential of metamizole, we analysed the data of our prospective study on the effects of potentially hepatotoxic drugs (ClinicalTrials.gov: NCT 02353455) conducted at the University Hospital Munich (LMU, Munich). Since March 2013, 379 patients with suspected drug-induced liver injury have been included. DILI diagnosis was based on clinical and laboratory findings, the Roussel Uclaf Causality Assessment Method (RUCAM), and expert opinion including long-term observation. To support the diagnosis, the monocyte-derived hepatocyte-like (MH) cell test, employing hepatocyte-like cells generated from the individual patient's blood monocytes, was performed as described earlier.^{8,9}

We identified 10 patients with DILI for which causality assessment revealed metamizole as the most likely causative agent. All of the patients had used concomitant medication, but presented with high RUCAM scores for metamizole: In nine cases, the RUCAM score was 6–8 (probable) and in one case even 9 (highly probable with positive rechallenge). Four of these patients had a positive rechallenge. Causality assessment was supported by the MH cell test, for which a sensitivity and specificity of 92% and 100%,

respectively, have been shown previously in a selected cohort of DILI patients with positive rechallenge.¹⁰ In accordance with Sebode et al.,⁵ we observed a hepatocellular phenotype in most cases. The median latency between initiation of metamizole therapy and onset of liver injury was 52 days, and median average daily dose was 1000 mg. The median follow-up was 9 months. While one patient developed acute liver failure with the need for liver transplantation, all the other patients were in remission at the end of follow-up.

In conclusion, as part of our prospective study on the hepatotoxic potential of drugs, we identified 10 patients with metamizole-induced DILI, who presented with a similar pattern as the previously described cases.^{1,5} Metamizole was the most likely causative agent with RUCAM scores of 6 to 9 and a positive rechallenge in 40% of the cases. We therefore support Björnsson's statement that the hepatotoxic potential of metamizole has been clearly demonstrated by now. Moreover, with our additional 10 cases, metamizole can be listed as a Category A drug inducing DILI. The right labelling of the drug with liver injury as a potential adverse event should help to guide clinicians in the future and to avoid under-diagnosing and under-reporting of metamizole-induced liver injury.

ACKNOWLEDGEMENT

We want to acknowledge the excellent technical support by Monika Hofstetter.


S.W. received funding by the Friedrich Baur Foundation. A.B. received funding by Federal Ministry for Economic Affairs and Energy (Bundesministerium für Wirtschaft und Energie – BMWi) EXIST grant no. 03EFT9BY56. A.B. and A.G. received funding by StMWI (Bayerisches Staatsministerium für Wirtschaft, Landesentwicklung und Energie – StMWI) m4-award grant no. 1330/68362/34/2013 and StMWI grant Bay-TOU1510-0003. Open access funding enabled and organized by Projekt DEAL.

COMPETING INTERESTS

Dr. Andreas Benesic owns stock in, was employed by, and owns intellectual property rights in MetaHeps GmbH. Prof. Alexander L. Gerbes owns stock in MetaHeps GmbH. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results. Sabine Weber declares no conflict of interest.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2020 The Authors. British Journal of Clinical Pharmacology published by John Wiley & Sons Ltd on behalf of British Pharmacological Society

Sabine Weber¹ 
 Andreas Benesic^{1,2}
 Alexander L. Gerbes¹

¹Department of Medicine II, Liver Centre Munich, University Hospital,
 LMU Munich, Munich, Germany

²MetaHeps GmbH, Martinsried, Germany

Correspondence

Sabine Weber, Department of Medicine II, Liver Centre Munich,
 University Hospital Munich, LMU Munich, Marchioninstr. 15, 81377
 Munich, Bavaria, Germany.
 Email: sabine.weber@med.uni-muenchen.de

ORCID

Sabine Weber  <https://orcid.org/0000-0001-7077-8078>

REFERENCES

1. Bjornsson ES. Liver injury associated with the analgetic drug metamizole. *Br J Clin Pharmacol.* 2020;86(7):1248–1250. <https://doi.org/10.1111/bcp.14294>
2. Andrade S, Bartels DB, Lange R, Sandford L, Gurwitz J. Safety of metamizole: a systematic review of the literature. *J Clin Pharm Ther.* 2016; 41(5):459–477.
3. Huber M, Andersohn F, Sarganas G, et al. Metamizole-induced agranulocytosis revisited: results from the prospective Berlin case-control surveillance study. *Eur J Clin Pharmacol.* 2015;71(2): 219–227.
4. Lutz M. Metamizole (dipyrone) and the liver: a review of the literature. *J Clin Pharmacol.* 2019;59(11):1433–1442.
5. Sebode M, Reike-Kunze M, Weidemann S, et al. Metamizole: an underrated agent causing severe idiosyncratic drug-induced liver injury. *Br J Clin Pharmacol.* 2020;86(7):1406–1415. <https://doi.org/10.1111/bcp.14254>
6. Bjornsson ES, Hoofnagle JH. Categorization of drugs implicated in causing liver injury: critical assessment based on published case reports. *Hepatology.* 2016;63(2):590–603.
7. Benichou C, Danan G, Flahault A. Causality assessment of adverse reactions to drugs—II. An original model for validation of drug causality assessment methods: case reports with positive rechallenge. *J Clin Epidemiol.* 1993;46(11):1331–1336.
8. Benesic A, Leitl A, Gerbes AL. Monocyte-derived hepatocyte-like cells for causality assessment of idiosyncratic drug-induced liver injury. *Gut.* 2016;65(9):1555–1563.
9. Benesic A, Rahm NL, Ernst S, Gerbes AL. Human monocyte-derived cells with individual hepatocyte characteristics: a novel tool for personalized in vitro studies. *Lab Invest.* 2012;92(6): 926–936.
10. Benesic A, Rotter I, Dragoi D, Weber S, Buchholtz ML, Gerbes AL. Development and validation of a test to identify drugs that cause idiosyncratic drug-induced liver injury. *Clin Gastroenterol Hepatol.* 2018;16(9):1488–1494.e5