

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastrointestinal Pathophysiology*

Manuscript NO: 70501

Title: Evaluating the regulation of transporter proteins and P-glycoprotein in rats with cholestasis and its implication for digoxin clearance

Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05352358

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: China

Author's Country/Territory: United States

Manuscript submission date: 2021-08-09

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-09-13 14:19

Reviewer performed review: 2021-09-19 15:23

Review time: 6 Days and 1 Hour

Scientific quality	☐ Grade A: Excellent ☐ Grade B: Very good ☒ Grade C: Good ☐ Grade D: Fair ☐ Grade E: Do not publish
Language quality	☐ Grade A: Priority publishing ☒ Grade B: Minor language polishing ☐ Grade C: A great deal of language polishing ☐ Grade D: Rejection
Conclusion	☐ Accept (High priority) ☐ Accept (General priority) ☐ Minor revision ☒ Major revision ☐ Rejection
Re-review	☒ Yes ☐ No

Peer-reviewer statements	Peer-Review: [☒] Anonymous [☐] Onymous Conflicts-of-Interest: [☐] Yes [☒] No
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SPECIFIC COMMENTS TO AUTHORS

This study only observed the changes in the expression of several transporters in the BDL model. The changes of these proteins may have an impact on the metabolism of digoxin, but the expression sites, uptake and excretion functions of these proteins are different. Theoretically, it is still difficult to infer the specific mechanism affecting the metabolism of digoxin. Therefore, as the author said, It is also necessary to understand the specific indicators such as tissue distribution and concentration of digoxin

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Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03475479

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Associate Professor

Reviewer's Country/Territory: Japan

Author's Country/Territory: United States

Manuscript submission date: 2021-08-09

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-09-27 02:57

Reviewer performed review: 2021-09-27 09:34

Review time: 6 Hours

Scientific quality	☐ Grade A: Excellent ☐ Grade B: Very good ☐ Grade C: Good ☐ Grade D: Fair ☒ Grade E: Do not publish
Language quality	☐ Grade A: Priority publishing ☒ Grade B: Minor language polishing ☐ Grade C: A great deal of language polishing ☐ Grade D: Rejection
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Re-review	☐ Yes ☒ No

Peer-reviewer statements	Peer-Review: [☒] Anonymous [☐] Onymous Conflicts-of-Interest: [☐] Yes [☒] No
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SPECIFIC COMMENTS TO AUTHORS

Authors evaluated the expression of MDR, OATP1A4 and OATP4C1 in BDL rat model and the change of clearance of digoxin. The expression level of MDR, OATP1A4 and OATP4C1 was changed after BDL. The clearance of digoxin was decreased after BDL. These were as might be expected ones. If authors would like to evaluate digoxin clearance according to each transporter expression, authors should examine cells with knock-in or knock-out experiments with each transporter genes.

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Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 02567669

Position: Editorial Board

Academic degree: MD

Professional title: Emeritus Professor

Reviewer's Country/Territory: Germany

Author's Country/Territory: United States

Manuscript submission date: 2021-08-09

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-09-29 07:26

Reviewer performed review: 2021-10-05 19:36

Review time: 6 Days and 12 Hours

Scientific quality	☐ Grade A: Excellent ☐ Grade B: Very good ☒ Grade C: Good ☐ Grade D: Fair ☐ Grade E: Do not publish
Language quality	☐ Grade A: Priority publishing ☒ Grade B: Minor language polishing ☐ Grade C: A great deal of language polishing ☐ Grade D: Rejection
Conclusion	☐ Accept (High priority) ☐ Accept (General priority) ☐ Minor revision ☒ Major revision ☐ Rejection
Re-review	☒ Yes ☐ No

Peer-reviewer statements	Peer-Review: ☒ Anonymous ☐ Onymous Conflicts-of-Interest: ☐ Yes ☒ No
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SPECIFIC COMMENTS TO AUTHORS

This is a diligently performed study to evaluate the effect of experimental cholestasis on 3 membrane transporters of digoxin in liver, small intestine, and kidney. The authors find different up- or downregulation of the transporters, proven by Western blotting and by quantitative PCR. The effects on digoxin clearance in experimental animals is well discussed. For a better understanding for a not so familiar reader it would be helpful to include a small Table indicating the effect of BDL on the three transporters in the three organs. As a clinician, I would like to ask for potential clinical implications of this interesting study. Is digoxin clearance affected by cholestatic human liver diseases? Which other drugs are affected in cholestasis? The three transporters are not specific only for digoxin but surely for other drugs, too. A small inaccuracy: Digitalis glycosides were the mainstay of therapy in congestive heart failure, but this is history.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 02567669

Position: Editorial Board

Academic degree: MD

Professional title: Emeritus Professor

Reviewer's Country/Territory: Germany

Author's Country/Territory: United States

Manuscript submission date: 2021-08-09

Reviewer chosen by: Jing-Jie Wang (Online Science Editor)

Reviewer accepted review: 2021-12-06 07:55

Reviewer performed review: 2021-12-06 08:05

Review time: 1 Hour

Scientific quality	☐ Grade A: Excellent ☒ Grade B: Very good ☐ Grade C: Good ☐ Grade D: Fair ☐ Grade E: Do not publish
Language quality	☒ Grade A: Priority publishing ☐ Grade B: Minor language polishing ☐ Grade C: A great deal of language polishing ☐ Grade D: Rejection
Conclusion	☐ Accept (High priority) ☒ Accept (General priority) ☐ Minor revision ☐ Major revision ☐ Rejection
Peer-reviewer	Peer-Review: ☒ Anonymous ☐ Onymous



**Baishideng
Publishing
Group**

7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
<https://www.wjgnet.com>

statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The revised version of the manuscript can be accepted.