Letter to the Editors

Authors' response to Hermann *et al.* Minimum quality criteria are needed in the assessment and communication of unexpected drug safety findings of marketed products from RCTsKoenraad Blot¹ & Martin C. Michel²¹elbion, Leuven, Belgium and ²Department of Pharmacology, Johannes Gutenberg University, Mainz, Germany

Hermann *et al.* [1] suggest that minimum quality criteria are needed to communicate unexpected drug safety findings from randomized clinical trials and imply that our report on unexpected frequent hepatotoxicity in patients receiving flupirtine for the treatment of overactive bladder syndrome [2] does not meet such criteria. As the brief report format of our paper did not allow an extensive description of trial details, we welcome this opportunity to shed more light on the matter.

Hermann *et al.* suggest a faulty randomization or different baseline characteristics of the treatment groups as possible explanations for the observed hepatotoxicity in flupirtine-treated patients. However, our report was based on a randomized, double-blind and double-dummy study. The flupirtine formulation used in the study was a marketed retard formulation of flupirtine (Trancolong® 200 mg, Dr Kade Pharmazeutische Fabrik GmbH, Berlin, Germany). All medications used in the study were overencapsulated and identical in appearance. The labels on the medication containers (blister packs and kit boxes) showed identical lot numbers for drug and placebo. A validated interactive voice-response system was used to randomize subjects. It is therefore unlikely that insufficient blinding or randomization bias might have created a selection bias, which is also clear from the demographics table in our article.

We disagree with the assessment by Hermann *et al.* that the decision to stop the study was flawed because it was based on 'single observations of liver test abnormalities' and a 'limited number of patients'. On the contrary, we feel strongly that the decision to stop the study was ethically unavoidable in the interest of patient safety when eight patients with critically high alanine aminotransferase (ALT) values (more than three times the upper normal limit) were identified, of whom seven were receiving flupirtine treatment. The projected incidence of ALT

increases more than five times the upper normal limit in subjects with at least 6 weeks of flupirtine treatment was 11% (five out of an estimated 46 flupirtine patients; 95% confidence interval 4.1–24.4%). The decision to terminate the study was validated when end-of-study measurements were made in all patients and revealed critically high ALT and/or aspartate aminotransferase values in 14 of 84 flupirtine (16.7%, including nine cases of more than five times the upper normal limit) but only two of 82 placebo (2.4%) and none of 41 tolterodine patients (0%). In patients treated with flupirtine for at least 6 weeks, the incidence of critically high liver enzymes was 31%. Importantly, all cases occurred prior to the step up to the 600 mg dose.

Thorough review of subject demographics, comorbidities and comedications, as well as possible centre or country effects, did not provide alternative explanations for the observed ALT increases (Table S1). The consistent temporal association with flupirtine use and the virtual absence of similar cases in the placebo and tolterodine groups made it hard to avoid the conclusion that the drug was at fault, especially as similar numbers of liver function test (LFT) increases were observed in patients returning for their study discontinuation visit.

Referring to unpublished pharmacokinetic data from the subjects with elevated LFTs, Hermann *et al.* suggest that the switch from 400 to 600 mg daily flupirtine may have resulted in nonlinear kinetics with a threefold increase in exposure. We consider this representation to be misleading. This group of 10 patients had flupirtine plasma concentrations at 2 weeks that were very similar to those of the patients who did not develop LFT increases (mean $\pm$ SD: 831 $\pm$ 363 vs. 787 $\pm$ 326 ng ml⁻¹, respectively). The values at 8 weeks (540 vs. 829 ng ml⁻¹, respectively) was based on only four patients and the one for the 12 week sample on only three patients owing to the premature

discontinuation of the study. These small sample sizes do not allow meaningful comparisons of exposure between weeks 8 and 12. The maximum flupirtine concentration in the group with LFT increases was of the same order of magnitude as in the group without LFT abnormalities (2250 vs. 1926 ng ml⁻¹, respectively). Moreover, the seven patients with abnormal LFTs which led to study discontinuation were all patients who had not yet been exposed to the 600 mg dose.

Finally, Hermann *et al.* imply that our article does not meet minimum quality requirements for a report on drug-induced liver injury. This allegation is based on articles dealing with the reporting of drug-induced liver injury in the context of spontaneously reported adverse drug reactions. Indeed, spontaneous adverse drug reaction reporting typically comes from a situation where underreporting is rampant and the 'drug usage denominator' elusive. In such cases, concomitant medication can act as a confounder and limit the interpretation of the findings. However, as ours was a randomized clinical trial with blinded control groups and balanced baseline characteristics, assignment of causality is straightforward and reliable; the relative risk of developing liver dysfunction on flupirtine treatment (all patients combined) vs. control groups was 10.3 (95% confidence interval 2.39–43.93, $P < 0.0001$).

The authors' suggestion that our observations may have been the result of hepatotoxicity due to concomitant medications presupposes a clustering of rare events in the flupirtine group. If we assume that LFT elevations more than five times the upper normal limit do not occur spontaneously, and that drug-induced liver injury has a likelihood of 1 in 10 000 at the most, then the probability of a clustering of nine such cases due to idiosyncratic reactions is 1 in 10³⁶. We are of the opinion that a causal role of flupirtine is a much more likely explanation.

Competing Interests

Martin C. Michel is an employee of Boehringer Ingelheim Pharma GmbH & Co. KG and has received research support, consultancy or lecturer honoraria in the OAB field from the following companies: Allergan, Astellas, Bayer and Pfizer. At the time of the events described in the article, Koenraad Blot received consulting fees as Chief Medical Officer of elbion NV. elbion owned the rights to the flupirtine devel-

opment in overactive bladder and was the sponsor of the study. It is currently in liquidation.

REFERENCES

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1

Peak ALT values, treatment duration and comedication for all subjects with ALT rises to >3× upper normal limit (ULN).

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