Letter to the Editors

Authors' response to Dr Reiter

Darren G. Craig,¹ Peter C. Hayes² & Kenneth J. Simpson²

¹Scottish Liver Transplantation Unit, Royal Infirmary of Edinburgh, Little France, Edinburgh EH16 4SA, UK and ²Division of Clinical and Surgical Sciences, University of Edinburgh, Edinburgh EH16 4SA, UK

We are very grateful to the editors for allowing us the opportunity to respond to the issues raised by Dr Reiter [1] following his analysis of our data from our two recent publications in the *British Journal of Clinical Pharmacology* (BJCP) [2, 3]. We fully acknowledge the seriousness of our omission in not citing our earlier paper [2]. This highly regrettable oversight stemmed from the close temporal nature of the drafting and review process of the two manuscripts. We sincerely apologize that we did not notify the BJCP Editorial Office about the acceptance of the first BJCP manuscript when submitting the second paper to the journal. We wish to assure all concerned that this did not arise from a deliberate attempt to hide this information and subvert the integrity of the scientific review process and publication policies of the BJCP and other peer review journals, which we fully support. We have reviewed the publication process within our group and communicated the importance of reference to all previous work to ensure that this highly regrettable omission does not occur in the future.

Dr Reiter correctly identifies that both BJCP studies result from analysis of a prospectively collected cohort of 938 patients admitted to the Scottish Liver Transplantation Unit over a 16 year period, of whom 663 had taken a paracetamol overdose [1]. The two studies explore different hypotheses related to paracetamol overdose. The first BJCP study examines the impact of suicidal ideation upon outcome, and demonstrates, paradoxically, that deliberate overdoses are associated with reduced mortality [2]. The second study explores the time course of the overdose, and demonstrates that repeated, staggered dosing of paracetamol is associated with adverse outcomes [3]. The impact of time course of overdose is further explored in the second study by analysing the impact of delayed hospital presentation amongst single time point overdoses, and demonstrates the adverse impact of 'delay to N-acetyl cysteine'. The second study also details the reasoning for the staggered overdoses, identifying the common use of paracetamol for the relief of pain.

We would like to correct the errors made by Dr Reiter in his table. These may stem from an incorrect assumption that all intentional overdoses were taken at a single time point and, conversely, that all unintentional overdoses were staggered, and that the overdose categories analysed in the two papers are therefore interchangeable. This is a common misconception, and we welcome the opportunity to clarify this point. Dr Reiter suggests that the number of staggered cases ($n = 161$) in the most recent paper is very similar to the sum of cases defined in our previous paper as unintentional ($n = 110$) and patients in whom no clear history of suicidal ideation was available ($n = 53$) [1]. However, this ignores the 52 cases excluded from the total ($n = 663$) cohort in our most recent paper due to an incomplete overdose time course history. This is the same group described in our original paper, as 'patients with unobtainable overdose history'. To further clarify this point, expand and correct Dr Reiter's analysis, as demonstrated in Figure 1 there are effectively five overdose categories: single time point suicidal ($n = 443$); staggered suicidal ($n = 47$); staggered accidental ($n = 114$); single time point accidental ($n = 6$); and cases where one or both elements of the time course or suicidal ideation were unknown ($n = 53$). The last four subgroups are all associated with a higher risk of adverse outcomes and should be classified as high risk (Figure 1). Other errors included in the table are as follows: an assumed mortality for the intention unknown group is stated to be '20/24', when in the original paper this was clearly stated as 36/53 cases (67.9%) and Dr Reiter's unintentional mortality rate of 38.2% is incorrect and should read as 42.7% (47/110 cases).

The clear message from the two BJCP papers is that atypical overdose patterns are associated with poor outcomes and should be treated as high risk. We hope that our most recent paper [3] helps to highlight the dangers of repeatedly exceeding the recommended dose of paracetamol and the importance of checking for inadvertent consumption of more than one paracetamol-containing product when self-medicating for pain control; a public

Figure 1

Survival curves of patients with paracetamol-induced acute severe liver injury according to the suicidal ideation and time course pattern of overdose. ---, single time point suicidal; —, staggered suicidal; - · - · -, staggered accidental; —, single time point accidental; —, unknown

health message that we consistently and repeatedly stated during the many interviews associated with the publication of this second article. We again thank the editors of the *BJCP* for giving us the opportunity of publicly stating our sincere regret in not citing our earlier *BJCP* paper. Although unintentional, we fully accept the seriousness of this omission and will ensure that this does not occur in future submissions.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no

support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

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CORRESPONDENCE

Dr Darren G. Craig MBChB MRCP, Scottish Liver Transplantation Unit, Royal Infirmary of Edinburgh, Little France, Edinburgh EH16 4SA, UK.

Tel.: +44 13 1242 1717

Fax: +44 13 1242 1633

E-mail: darrencraig@doctors.org.uk