Protein-derived acetaminophen-cysteine detection from chronic APAP is not dose-dependent

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Dear Editor,

In their 2015 JMT article, O'Malley and colleagues discussed measuring acetaminophen-cysteine (APAP-CYS) adducts in patients who self-reported ingestions of supratherapeutic concentrations of acetaminophen for greater than 2 weeks. [1] As APAP-CYS adducts are formed when the toxic metabolite NAPQI binds to cysteine, it is possible that high APAP-CYS adduct concentrations could provide early evidence of APAP-induced liver injury. While our group enjoyed reading the article, certain points were discussed that we wanted to clarify with the authors.

Our main concern is that the data provided does not support the authors' primary conclusion that there is an APAP dose-dependent generation of APAP-CYS adducts. When the patient-reported doses of APAP and APAP-CYS adducts are mapped on a scatter plot, the graph actually produces a negative correlation (see Fig. 1). Moreover, regardless of using the Pearson Product Moment or Spearman analysis, the correlation coefficients remain negative, indicating an inverse relationship of APAP dose with APAP-CYS adduct concentration. The correlation coefficients are not statistically significant but do not suggest a direct dose-dependent

relationship. One possible explanation for this counter-intuitive finding is a degradation of the sample as described in a prior study [2], although the authors do mention this possibility in their limitations.

One further concern is that it is known that patients have a limited ability to recognize which medications contain acetaminophen [3]. Although the authors attempted to correct this with pictures of common products, self-report and recall bias also come into consideration when collecting retrospective data. It may have been advisable to collect daily questionnaires or medication diaries from participants, rather than just self-reporting in order to improve concordance with actual product, timing, and dosages of the medication [4].

We agree with the authors that more study is needed to understand the clinical significance of APAP-CYS adduct concentrations as they relate to toxicity and prognosis. With that knowledge, it may indeed be possible to harness measurement of these concentrations in a way that can be beneficial to patients. Unfortunately, at this time and with the data provided, we cannot say that APAP-CYS adducts are related to the APAP dose in a repeat supratherapeutic ingestion.

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Fig. 1 Scatter plot of acetaminophen dose and protein-derived APAP-CYS showing linear regression line and negative correlation between reported APAP dose and APAP-CYS

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