Title: Judging value of ammonia measurement on lactulose dosing: Apples and oranges?

The central role of ammonia in the pathogenesis of hepatic encephalopathy (HE) is well recognized(1). However, the measurement of ammonia for the management of HE is controversial. Haj and Rockey attempted to clarify this dispute (2) with a retrospective study in a large number of patients in a US single center hospital. They found the dose of lactulose administered to patients did not differ in those with either elevated or normal ammonia, concluding that ammonia levels do not guide therapy in the management of HE. This conclusion needs to be examined carefully.

In the study, forty-six percent (551 patients) of the patients who were hospitalized with overt HE had ammonia measured. From these measurements, 60% were defined as being hyperammonemic using a cut-off for blood ammonia > 72uM. This requires discussion. Firstly, there is a strong selection bias since 54% of patients diagnosed with overt HE did not have their ammonia measured and no reason was provided. Secondly, 72uM cut-off needs to be justified as this level of ammonia is exceedingly high to be defined as 'normal' since it was recently demonstrated that an ammonia value of 79.5uM is independently associated with death within the next 28 days (3). Therefore, 40% patients with 'normal' ammonia levels is overstated and most likely inaccurate as the diagnosis of HE is not compatible with normal ammonia levels (4). Thirdly, measuring ammonia is delicate and the acquisition of samples for ammonia measurement, as well as transport and analysis details were not declared. Sample transport must be on ice to avoid erroneous values and measurements must be made within 30-60 min(5). In addition, reference range of ammonia as well as biochemical analyzer and assay used needs to be provided. The above mentioned particulars can impact ammonia quantitatively which leaves the presented ammonia data unreliable.

The primary outcome of their retrospective study was the total amount of lactulose given for the management of HE within the first 48hrs (time when 3-4 movements per day are routinely achieved). The authors concluded that there was no correlation between the amount of lactulose given and levels of ammonia, signifying higher blood ammonia did not entail a more aggressive dose of lactulose. However, it is unclear what guided the dosing of lactulose. Nevertheless, it can be speculated that more lactulose was administered since either constipation was not resolved or HE was persisting. Furthermore, independent of whether ammonia was high or not, or of the precipitating event, all patients received similar volumes of lactulose. This is curious as, in clinical practice, one would primarily use lactulose for patients with constipation and gastrointestinal bleeding and considerably less in those presenting with diarrhea, severe dehydration, renal dysfunction or infection (4). Remarkably, patients where infection was the precipitating factor (42%), lactulose was administered. Despite this, the authors focus on incomplete and potentially inaccurate measurements of ammonia to conclude that the dose of lactulose administered was not influenced by blood ammonia levels.

Finally, lactulose is a non-absorbable disaccharide, which acts as an osmotic laxative to treat constipation, a precipitating factor of HE. Currently in North America, lactulose and rifaximin are the only currently available options for the treatment of HE. Lactulose was never approved by the FDA and although used widely, there is no clear regulatory guidance on the indications and doses to be used. Rifaximin was approved by the FDA for the recurrence of HE, as secondary prophylaxis, and not for the treatment of an acute episode of HE-hospitalization (4). There is only very low quality data on dose response of ammonia reduction or HE improvement with lactulose dosing. Furthermore, only a handful of trials exist comparing lactulose with placebo on ammonia levels in the acute setting.

According to the study of Haj and Rockey, it is clear lactulose was not used to lower ammonia as lactulose was administered irrelevant of blood ammonia levels. An efficient ammonia reducing agent

remains an unmet care gap, which would mandate ammonia measurements, improve management (differential diagnosis) and guide appropriate treatment for patients suffering from HE. Furthermore, blood ammonia levels have recently been recognized as prognostic and predictive biomarkers for the risk of developing overt HE (3,6–8). This strengthens the value of monitoring and treating blood ammonia.

Based upon an unsound, poorly designed retrospective study, we believe Haj and Rockey's conclusion that ammonia levels do not change the management of these patients is potentially flawed. Prospective studies are needed to thoroughly appreciate the comprehensive role ammonia plays in the spectrum of HE.

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