Reviewer's report

Title: Long-term continuous N-carbamylglutamate treatment in frequently decompensated propionic acidemia: a case report

Version: 0 Date: 12 Oct 2017

Reviewer: Sufin Yap

Reviewer's report:

1. Do you believe the case report is authentic?

Yes

2. Do you have any ethical concerns? Please consider if local Institutional Review Board approval or ethical approval was obtained (if appropriate) and if the patient (or their parent or guardian in the case of children under 18) gave written, informed consent to publish this case and any accompanying images. A statement to this effect should appear in the manuscript.

Comments: No ethical concerns

The manuscript submission entitled 'Long term continuous N-carbamylglutamate treatment in frequently decompensated propionic acidemia: case report' is a current topic for discussion in the field. However, the reported stand alone single case does not add any added information to the already available knowledge/data on the topic.

The following are my opinion and comments on some aspects of the report:

1. ABSTRACT: The authors claim this case report to be the 'first long term clinical experience...'. This is however not the first case report on the long term use of N Carbamylglutamate (NCG) in propionic acidaemia (PA). The authors have included in their reference (number 7; Burlina et al 2016) and this paper reported a total of 8 patients on long term use of NCG (n=4 with methylmalonic acidaemia; n=4 with PA).

2. CASE PRESENTATION:

Pg4, Line 7: The protein intake of 0.8g/kg/day when well, is low when compared to the FAO/WHO/UNU (2017) recommended safe protein intake of 1.77-1.31g/k/day in infants from
0-1 years of life (Baumgartner et al 2014). The need to use isoleucine and valine supplements as single amino acids supports insufficient protein intake on the whole. Patients with carefully titrated protein intake according to their tolerance rarely require supplements of single amino acids. Decrease in branched chain amino acids may be a side effect of treatment and should be reviewed carefully (Scholl-Burgi et al, JIMD 2012). The blood isoleucine levels were not reported, however, in general when a patient is on a protein restricted diet, an isoleucine level <25umol/L should warn of protein deficiency in the patient and if isoleucine <15umol/L, the diet should be adjusted in order to correct the overall protein deficiency while balancing with metabolic control. Protein malnutrition can cause vomiting.

Pg4, Line 15: The authors reported growth parameters below normal range and bone mineral density (BMD) in the 'osteoporotic range' which could be a result of insufficient protein prescribed compounded by the frequent use of emergency regimens which lowers the protein intake further.

Page 4, Line 20: The authors state that 'Persistent hyperammoneamia and frequent metabolic attacks prompted recurrent administration of ammonia scavengers (sodium phenylbutyrate, sodium benzoate and ....'). Sodium phenylbutyrate should not be used in established PA patients as it further enhances the depletion of the glutamine/glutamate pool. In acute hyperammonaemia, the use of sodium phenylbutyrate should be stopped once a diagnosis of propionic acideamia is made. 'Persistent hyperammoneamia' indicates metabolic imbalance and requires investigations and treatment of the underlying cause with nutritional adjustments (Baumgartner et al 2014).

Pg4, Line 26: Mean and SD plasma ammonia levels before and after NCG treatment were compared by the authors, however, the authors failed to include the number of samples included in the calculation for the means. It is important to ensure that sufficient data has been included, before any comparison can be made without prejudice.

Pg5, Line 2: The authors commented that plasma glutamine was low throughout NCG treatment period with glycine levels being high which increased over time. The authors continue with 'ammonia scavengers were gradually stopped....', this suggests that there is an overlap period whereby both CGA and ammonia scavengers have been given together. It is unclear as to whether it included sodium phenylbutyrate, which would reduce the plasma glutamine levels. The low glutamines could also indicate and support insufficient protein intake. On the other hand, the high and increasing glycine suggests that there is overall poor metabolic control of the PA, in the absence of hyperammonaemia.

Pg5, Line 6: The authors noted that there was a gradual increased in protein intake since the start of NCG treatment, however the NCG treatment period coincides with the anabolic pre-pubertal growth period and this could be a reason as to why there is an increased protein tolerance as is seen with many other metabolic conditions (eg. Phenylketonuria, homocystinuria, urea cycle
defects). BMD values were noted to have improved however, it has to be considered that the patient was assessed at the time of bone growth and accruement.

3. DISCUSSION: The authors claim that their report is the 'first long term clinical experience with continuous administration of NCG...due to PA', despite referencing Burlina et al 2016 paper which reported on the same. It is therefore misleading for the authors to conclude as such.

4. TABLE 1: When comparing the various metabolites before and after NCG treatment, the authors have not included the following: the reference ranges, the number of readings before and while on NCG treatment and when were the metabolites readings collected (when well or when unwell; at clinic visits or during hospital admissions for decompensation). The statistics provided may have to be qualified and re-analysed, taking into account the number of reading before and while on NCG treatment.

The authors in the text of the manuscript have reported that there were 78 hospital admissions before the use of long term NCG (0-9yrs old) and two admissions while on NCG treatment (9-15 yrs old). Despite the high number of hospital admissions before the use of long term NCG, it would seem that the number of measurements included for each metabolite is rather few (range n=15-20). The above points demonstrate a lack of clarity on what is being compared and its associated statistical value.

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An article of limited interest

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Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited
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