Normal dose paracetamol in muscular dystrophy patients – is it normal?

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Abstract

A 16-year-old male with Becker muscular dystrophy was admitted to hospital with a significant liver injury due to paracetamol. The dosage of paracetamol ingested was within current guidance yet there was sudden derangement of liver function. The patient was treated with five days of N-acetyl cysteine to which he responded, with his alanine aminotransferase improving from 5,599 to 652 and international normalised ratio from 5.0 to 0.9. He had risk factors for paracetamol toxicity as he was malnourished and had muscular dystrophy. The purpose of this case report is to highlight that despite prescribing approved dosages of paracetamol some patients may have toxicity due to altered body composition and pharmacokinetics.

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Introduction

Becker muscular dystrophy is a muscle wasting genetic condition caused by a mutation in the dystrophin gene. This causes dystrophin to be produced in muscles leading to muscle fibre break down and causing muscle weakness. This condition is related to, but generally less severe than Duchenne muscular dystrophy. The age of onset varies greatly as does the degree of muscle wasting.

Paracetamol in adults is usually dosed by weight, depending on the body weight being more or less than 50kg. In children it is dosed by their age up to 16-17 years old. The standard licensed adult dose for paracetamol is a maximum of four grams over 24 hours orally or intravenously. Following this current prescribing guideline would put certain patient groups at risk of hepatotoxicity as this case highlights.

Patients with muscular dystrophy therefore have a very different body mass composition. This needs to be taken into consideration when prescribing medication, especially commonly used ones such as paracetamol.

Case presentation

A 16-year-old male with a background of Becker muscular dystrophy was admitted to our care initially with dysphagia needing nasogastric feeding to maintain his weight. He was wheelchair bound, lived with his family and was cognitively appropriate, performing well at school.

During this time he has was given paracetamol for muscular pain. He was prescribed a regular dosage of one gram as needed, up to four times a day. His weight was 50kg with normal liver function tests and he had only a low creatinine and urea. He received eight grams of paracetamol over four days in liquid form (Figure 1). On day four he was noted to have a significant rise in his alanine aminotransferase (ALT) from 126 to 3,249. His international normalised ratio (INR) was also found to be raised at 2.8. He was started on N-acetyl cysteine as a precaution. His paracetamol level was 21mg/L at six hours from his last dose.

Over the next 48 hours his ALT levels peaked at 5,599, AST 5,498, albumin 28 and an INR of 5.0. His bilirubin remained

Figure 1 Paracetamol dosage and subsequent biochemistry

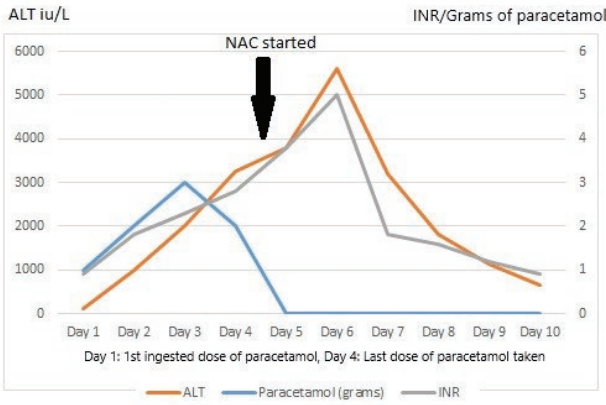

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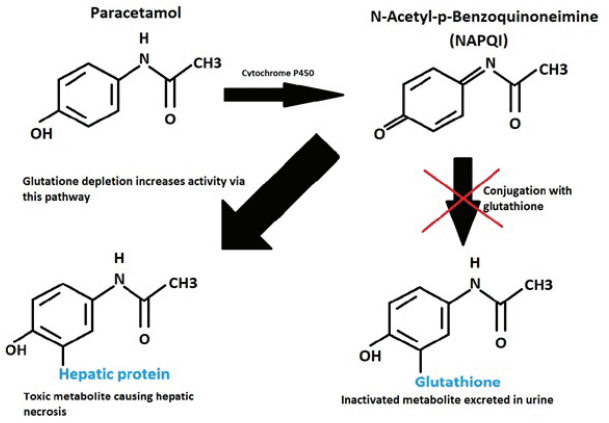
Figure 2 Paracetamol metabolism pathway



within normal limits and he did not show any symptoms of encephalopathy. By day ten his ALT had fallen to 652 with his INR normalising to 0.9. He had remained on continuous N-acetyl cysteine infusion since derangement of his liver function tests. His acute liver screen did not have any positive results and his US liver with both portal and hepatic vessel dopplers were unremarkable. After thorough review of his medication chart, clinical and drug history, including a discussion with his paediatric gastroenterologist, it was felt that his hepatic injury was due to paracetamol since there was no other congenital, viral, hepatotoxic drug ingestion or other aetiologies possible. He recovered well and was discharged once his social issues had been resolved. Subsequent blood tests as an outpatient at day 24 showed liver synthetic and non-synthetic function had returned to their normal ranges (ALT 56 and INR 1.1).

Discussion

Paracetamol is metabolised in the liver, where the majority of the drug is conjugated via glucoronidation and sulfation, yielding non-toxic metabolites. The remainder is oxidated via the cytochrome P450 pathway which produces N-acetyl-p-benzoquinoneimine (NAPQI) as shown in Figure 2. This hepatotoxic metabolite can be conjugated with glutathione to form a non-toxic product. In cases where the stores of glutathione are depleted, such as in paracetamol overdose and when more NAPQI is produced due to saturation of other non-toxic pathways, the accumulation of NAPQI can cause liver damage and necrosis.

There have been similar cases reported but with varying circumstances: most relating to young patients (<18-years-old) and muscular dystrophies[1,2,3]. In previous cases patients had age adequate weight, were dosed adequately to their age/weight, malnourished, acutely unwell (intensive care admissions) and their range of paracetamol intake was from 12 – 24 grams over 3 - 11 days. There have also been cases of adults without muscular dystrophy in similar circumstances who have had acute liver injury related to normal paracetamol dosages[4].

Different reasons have been considered. Malnutrition, which is a common theme can lead to glutathione depletion and therefore a lower threshold for hepatotoxicity. Glutathione is stored in skeletal muscles, the reduced muscle mass in dystrophic patients reduces this reservoir leading to a lower threshold for liver damage. Paracetamol is a moderately water and lipid soluble organic acid which will distribute into muscle after ingestion. With a smaller muscle mass in patients with muscular dystrophy this can lead to increased plasma concentrations of paracetamol[5]. In the acute phases of illness and post-surgery it has been postulated that the stress response and the associated catabolic changes can also put these patients at higher risk of glutathione depletion[6]. There is also evidence that patients with muscular dystrophy have increased oxidative stress and changes in how they modulate this inflammatory process which could further lower their threshold for liver injury[7]. Other factors such as altered pharmacokinetics, cytochrome P450 inhibitors and increased co-administration of medications will certainly play a role in potentiating the toxicity of NAPQI.

In this patient considering his age and weight (50kg), he would have been suitable for a maximum of four grams of paracetamol over 24 hours. According to the UK National Poisons Information Service it would be very unlikely for doses consistently less than 75mg/kg in a 24 hour period to cause toxicity (in this case up to a total of 3,750mg) which the patient did not exceed at any point and would not be considered an overdose[8]. Even with his diagnosis of Becker muscular dystrophy, for his age he had significant muscle wasting and consequently his weight of 50kg will be of a different composition compared to people without muscular dystrophy. His nutritional state was also poor before and during his admission which will have put him at a higher risk of glutathione deficiency. He was not otherwise on hepatotoxic medication and not acutely unwell. It is likely that a combination of these factors caused his significant liver injury despite a relatively low amount of paracetamol ingestion.

Conclusion

This case highlights that certain patient groups are at high risk of medication induced liver injury despite following national guidance on prescribing. More care needs to be given to patients with reduced muscle mass, malnutrition, critical illness and factors that affect their pharmacokinetics since usual dosages may not be suitable for them. If these patients do exhibit signs of liver injury there should be a low threshold for initiation of NAC treatment. The current British National formulary (BNF) cautions on prescribing paracetamol do not include muscular dystrophy or muscular wasting diseases. The BNF has mentioned the risks of prescribing in <50kg body weight and malnutrition; and that some patients are at increased risk of toxicity despite therapeutic doses. However, it does not go as far as specifying muscle wasting conditions as a caution[9]. The learning point from this case is that patients with muscular dystrophies are at increased risk of paracetamol induced hepatotoxicity even after accounting for other risk factors. Although further investigation is needed to identify a safe prescribing approach to paracetamol in these conditions, this case suggests that muscular dystrophies should certainly be added to the cautions list to prevent similar situations and the need for close liver monitoring.

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