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LETTER TO THE EDITOR

When to treat paracetamol overdose

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In a recent review, Koppen *et al.* appraised the treatment guidelines for N-acetylcysteine use in NAPQI-mediated paracetamol toxicity.[1] The authors concluded that unlike new UK guidelines, it was unnecessary to lower the current treatment line in the Netherlands. As the authors are aware, the main drive behind the change in UK guidelines comes out of the concern that a small minority of patients below the treatment line remain at risk of hepatic injury. Whether or not this guidance is a cost-effective approach is indeed debatable. However, clinicians need to be acutely aware that there is a spectrum of risk that cannot be easily stratified by a nomogram, which solely considers serum paracetamol level and the time since ingestion. It is already known that younger children and neonates may be at greater risk due to deficient glucuronide conjugation, although this population was not considered in the construction of the original Rumack-Matthew nomogram.[2,3] Furthermore, the nomogram may not adequately guide treatment of overdose with modified-release preparations and also relies heavily on accurate recall of dose timing.[4]

Current guidelines issued by the Dutch National Poisoning Information Centre (NVIC) recommend N-acetylcysteine treatment at a lower serum paracetamol level of 75 mg/l at four hours post-ingestion for certain patients at high risk of hepatotoxicity, such as those with chronic liver disease or malnutrition. Whilst this is lower than the current UK treatment line which starts at 100 mg/l, the Commission on Human Medicines has found that risk factor assessment may be poorly carried out and many known risk factors are imprecise and difficult to assess clinically, particularly in the acute setting.[5] In particular, a clinical history is unreliable when paracetamol overdose is combined with alcohol consumption, other drugs of abuse or a psychiatric history, as is often the case. It is perfectly conceivable that an initial assessment may miss some patients with a severe glutathione deficiency state and pre-existing liver disease who are taking hepatic enzyme inducers. These patients may require treatment even if not indicated by clinical guidance. As a result, there is a risk of delaying treatment when there is a clear time-sensitive benefit in early administration of N-acetylcysteine. UK guidelines have aimed to simplify the decision to treat by utilising a single treatment line which seeks to remove the need to assess for the risk factors of hepatotoxicity.

Regardless of where the treatment line is set, a clinical judgement remains an absolute necessity with current evidence supporting rapid empirical treatment in cases of uncertainty. Additionally, the authors suggest that the main drawback of UK guidelines will be the overtreatment with N-acetylcysteine which would potentially lead to an increased incidence of adverse effects. However, where the treatment line is set should be informed solely by the attendant risk of hepatotoxicity and should not be guided by the side effects of N-acetylcysteine, which whilst common are rarely serious. This is reflected by the recent change in UK guidelines which removed hypersensitivity as a contraindication to N-acetylcysteine treatment. Currently, there are no specific contraindications to N-acetylcysteine treatment of paracetamol overdose in the UK.[5]

It is important to be wary of the small minority of at risk patients who fall below the treatment line. A number of case reports have described patients who failed to receive N-acetylcysteine treatment due to a serum paracetamol level below the treatment line, who subsequently died of fulminant hepatic failure.[6] Despite the additional high-risk treatment line used in the Netherlands, the patient may not be able to provide an accurate clinical history both in terms of the time since the overdose and the risk factors for hepatotoxicity. Further studies are still needed to explore patient risk factors besides serum paracetamol level at a given time, as well as to guide the specifics of N-acetylcysteine treatment, namely the dose, route of administration and treatment duration.

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REPLY

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We appreciate the comments regarding our recommendations of the guidelines for N-acetylcysteine treatment in case of paracetamol intoxications.

We fully agree that there is a spectrum of risk which is difficult to stratify by a nomogram based on serum plasma levels and time of ingestion, and that a nomogram is merely a tool in the clinical decision-making process. Clinicians need to be aware of the different risk groups of patients who cannot be simply treated based on the 150 mg/l nomogram line. We therefore recommend N-acetylcysteine treatment at lower paracetamol plasma values for patients with chronic alcohol abuse, liver insufficiency, malnutrition and/or dehydration and with co-ingestion of medication that might interfere with paracetamol metabolism. In addition, when the time of ingestion is not certain, we recommend N-acetylcysteine treatment. When glucuronide conjugation is not yet optimal, especially in prematurely born children and neonates, N-acetylcysteine treatment at lower plasma concentrations may also be indicated. However, also in very young children, total paracetamol elimination is comparable with that in adults, regardless of the reduced glucuronidation. In fact, children between 1-5 years are less susceptible to paracetamol toxicity.[1]

Using a nomogram and consciously deciding upon the best treatment strategy for an individual patient with paracetamol poisoning will always remain the cornerstone of good clinical practice. Good clinical practice in our view also includes preventing patients from being overtreated.

We agree that possible side effects of N-acetylcysteine should never be a reason to withhold N-acetylcysteine treatment, since the beneficial effects of N-acetylcysteine outweigh its side effects. As the side effects of N-acetylcysteine in general are not that severe, in that regard, overtreatment is not likely to cause major problems, although several UK studies have shown that (mild) side effects are quite common.[2] If treatment was actually unnecessary, that is a burden to the patient. Besides, sending patients to hospital for further evaluation and treatment tremendously increases healthcare costs. As we also mention in our review, the estimation regarding costs for each saved life when the nomogram line is adapted from 150 mg/l to 100 mg/l is around £ 17.4 M (€ 21 M).[3]

We firmly believe that the current Dutch nomogram is of good value in the clinical decision-making process and provides adequate guidance for the optimal treatment strategy in individual patients.

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