IRISH MEDICINES BOARD

Paracetamol overdose: New guidance on treatment with intravenous acetylcysteine

The Irish Medicines Board (IMB) has approved new simplified guidance on the treatment of paracetamol overdose with intravenous acetylcysteine (Parvolex). The simplified guidance is aligned with the findings of a review undertaken by the Commission on Human Medicines (CHM – UK) and includes an updated treatment nomogram.

A summary of the updated guidance for healthcare professionals is as follows:

- The previous treatment nomogram has been amended to a single treatment line (previously high risk line) so all patients with a plasma paracetamol level of 100mg/litre at 4 hours are recommended to have treatment (figure 1).Regardless of risk factors for hepatoxicity, all patients with a timed plasma paracetamol level on or above a single treatment line joining points of 100 mg/L at 4 hours and 15 mg/L at 15 hours after ingestion should receive acetylcysteine (Parvolex) based on this new treatment nomogram.
- This new nomogram (figure 1) will thus be a single line joining the points of 100mg/L at 4 hours and 15mg/L at 15 hours after ingestion of paracetamol on or above which all patients should receive treatment with acetylcysteine.
- Where there is doubt over the timing of paracetmol ingestion including when ingestion has occurred over a period of one hour or more (i.e. staggered overdose), acetylcysteine should be given without delay (that is, the nomogram should not be used).
- To minimise the risk of anaphylactoid reactions, initial loading dose infusion should be increased from 15 minutes to 60 minutes.
- To minimise the risk of administration errors, a clear comprehensive weight-based dosage table will be included in the product information for both adults and children.
- Hypersensitivity has been removed as a contraindication to the administration of acetylcysteine.

Background

Acetylcysteine (Parvolex) is licensed for the treatment of paracetamol poisoning. Its mode of action is to reduce the hepatic toxicity of NAPQI (n-acetyl-p-benzo-quinoneimine) which is the highly reactive intermediate metabolite produced following ingestion of a high dose of paracetamol. Acetylcysteine acts as a precursor for the synthesis of glutathione and, therefore, maintains cellular glutathione at a level sufficient to inactivate NAPQI.

Paracetamol overdose can result in liver damage which may be fatal. Intravenous acetylcysteine (Parvolex) is the antidote to treat paracetamol overdose and is highly efficacious in preventing liver damage if administered within 8 hours of the overdose. After this time efficacy of acetylcysteine declines progressively.

New simplified guidance on the treatment of acute paracetmol overdose with acetylcysteine has been released following an evidence-based review by the Commission on Human Medicines (CHM – UK).

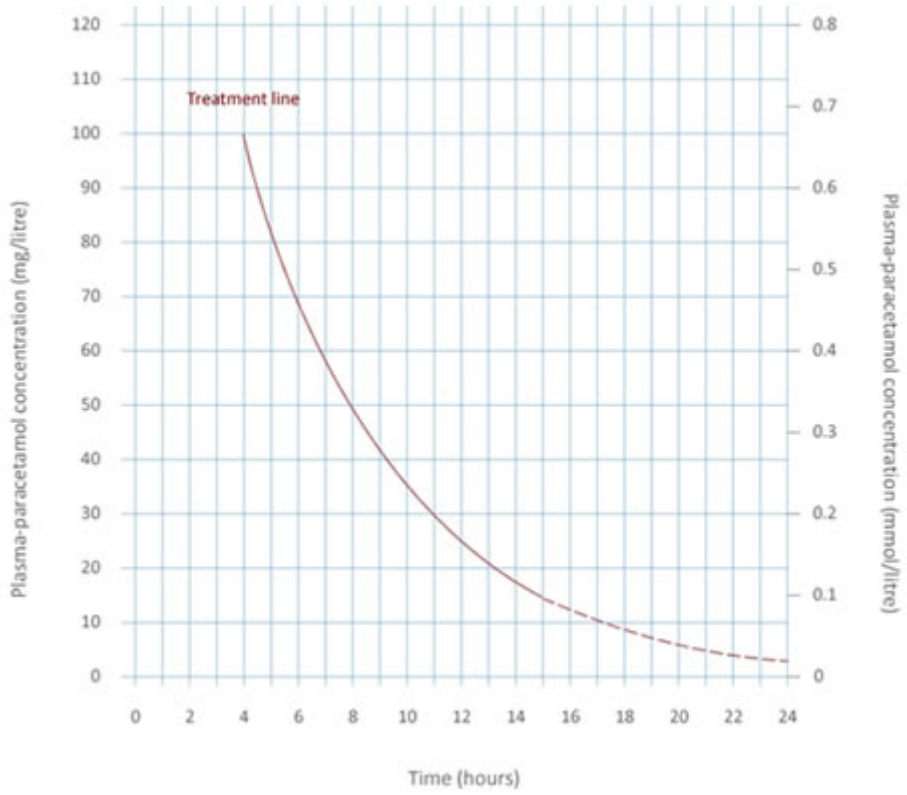
The IMB has also assessed the proposed changes to the product information and following discussion with its advisory committee for human medicines (ACHM), has approved the changes to the Parvolex product information.

It is now recommended that treatment of paracetamol poisoning is simplified and a number of changes to the SmPC for acetylcysteine (Parvolex) are proposed.

Previously healthcare professionals treating patients for paracetamol overdose were advised to assess for risk factors of hepatotoxicity (i.e. poor nutritional intake, chronic alcohol consumption, concomitant medications etc.). This assessment of risk factors resulted in two separate lines on the treatment nomogram-one for patients with risk factors and one for those without risk factors.

The previous treatment nomogram has been amended to a single treatment line (previously high risk line) so all patients with a plasma paracetamol level of 100mg/litre at 4 hours are recommended to have treatment (figure 1).

Figure 1: New treatment nomogram for paracetamol overdose



In the past there have been a number of reports of administration errors with intravenous acetylcysteine, some of which have the potential to result in significant harm. A contributing factor to these errors was the dosing regimen for acetylcysteine. One important recommendation is the introduction of weight-based dosage tables for adults and children. This will remove the need to calculate the dose.

Since the majority of common dose-related adverse reactions occur within the first hour of the initial acetylcysteine infusion, enough evidence is available to support extending the time of initial infusion from 15 minutes to 60 minutes in order to reduce the incidence of adverse reactions. There are now no specific contraindications to acetylcysteine including known hypersensitivity to any of the ingredients in the product. Even if patients have had a previous reaction to acetylcysteine, the benefits of treating a paracetamol overdose outweigh the risks and acetylcysteine should be given. Healthcare professionals treating patients with paracetamol toxicity should consult with the relevant clinical experts, as necessary.

Key messages

All patients with a timed plasma paracetamol level on or above a single treatment line joining points of 100mg/L at 4 hours and 15mg/L at 15 hours after ingestion should receive acetylcysteine (Parvolex) based on a new treatment nomogram, regardless of risk factors for hepatotoxicity (see Figure 1 above).

Where there is doubt over the timing of paracetamol ingestion, including when ingestion has occurred over a period of one hour or more (that is 'staggered overdose'), acetylcysyeine should be given without delay.

An increase in the duration of administration of the first dose of intravenous acetylcysteine from 15 minutes to 60 minutes.

Removal of hypersensitivity as a contraindication to treatment with acetylcysteine.

The provision of weight-based acetylcysteine dosing tables for adults and children.