Application to Change the Status of Methionine or N-acetylcysteine on the Model List

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1. **N-acetylcysteine (NAC) and methionine** are on the Model List for treatment of acetaminophen poisoning. This review of effectiveness found that they were similar in efficacy. N-acetylcysteine has an advantage in that it can be given orally or parenterally while methionine is an oral medicine. NAC is rapidly hydrolysed to cysteine while methionine must be converted to cysteine and theoretically may have a slower onset of action than NAC. The advantage of methionine is that it appears to be much cheaper than NAC. Since the reported efficacy of the two medicines is similar, one should consider price in selecting one for the List and include the other under the square box symbol as an alternate.

2. WHO focal point: undetermined

3. Organization consulted: none

4. INN: DL Methionine, N-acetylcysteine

5. Formulation: all formulations

6. International availability: not applicable

7. The individual medicine is recommended for change in status.

8. Public health relevance: not applicable

9. Dosing:

For paracetamol overdose, the oral loading dose of N-Acetylcysteine (NAC) given is a 140 mg/kg solution of 5% NAC (the commercially available 10% and 20% solutions are generally diluted with water and sometimes other carbonated and non-carbonated beverages). Following the loading dose, an additional 17 oral doses are given (70 mg/kg of 5% solution) every four hours for a total of 1330 mg/kg solution in a period of 72 hours.

For a paracetamol overdose with methionine as the treatment option, the dosage requirements are substantially increased: 2.5g every four hours up to a to a total of 10 grams.
There is no need for any special facilities or skills

10. Comparative Effectiveness of N-Acetylcysteine vs. DL-Methionine:

N-acetylcysteine and DL-methionine are both currently used in the treatment of acute paracetamol poisoning, however N-acetylcysteine is currently used much more frequently as the standard of care. A recent Cochrane meta-analysis (Brok et al 2006) reviewed the efficacy of various interventions for paracetamol overdose. The study analyzed the limited number of available randomized trials on the use of N-acetylcysteine and methionine, in addition to performing an exploratory analysis of quasi-randomized studies and observational studies, which met appropriate inclusion criteria.

The study’s overall conclusion was that both drugs demonstrate comparable effectiveness at decreasing the risk of hepatotoxicity following paracetamol poisoning and that the superiority of N-acetylcysteine to DL-methionine remains unproven. The comparison of the two drugs in table 1 of the study illustrates a similar effectiveness in preventing both mortality (0% vs 0%) and hepatotoxicity (6% vs 9%) when administered within the first 10 hours, with N-acetylcysteine demonstrating a slightly more effective treatment.

One randomized controlled trial (Keays 1991) found N-acetylcysteine to be associated with significantly reduced mortality compared with placebo in patients suffering from fulminant hepatic failure secondary to paracetamol overdose. An additional observational study illustrated a correlation between N-acetylcysteine treatments and significantly reduced mortality and coma risk. (Harrison 1990)

A key observational study (Prescott 1979) found that N-acetylcysteine dramatically reduced severe liver damage when given within 10 hours of paracetamol overdose compared with supportive treatment (2% vs 58%). Although there was a high risk of bias from this study due to the small sample size and the use of historical support groups, N-acetylcysteine has remained the drug of choice since the study was performed. Subsequent historical data show that overall mortality has decreased from 3-5% to 0.7% following the inclusion of N-acetylcysteine in standard care. (Brok et al 2006)

Both drugs are thought to act in a similar pathway through the facilitation of de novo GSH synthesis in the liver. The hepatotoxicity from paracetamol overdose is primarily due to a depletion in these GSH stores, which allows highly reactive NAPQI metabolites to accumulate and covalently bind to intracellular macromolecules. A study conducted on mice showed a faster onset of GSH repletion with N-acetylcysteine than with methionine. (Skoglund 1986) This difference suggests a utilization of the liver’s natural conversion pathway of methionine to cysteine, and a primary use of L-cysteine as the main precursor for de novo GSH synthesis.

A review of four non-randomized studies concluded that oral methionine, oral NAC, and IV NAC are all highly efficient at preventing death when administered within 10 hours. (Vale 1995) In addition, each of these treatment regimens proved to be superior to supportive treatment at preventing severe liver damage (7% for oral methionine, 16% for oral acetylcysteine, 2% for IV acetylcysteine, and 58% for supportive treatment). (Vale 1981)
Here is table 1 from the Cochrane Collaboration report showing the data on efficacy of the medicines used to treat paracetamol overdose (2).

Table 1. Antidotes for paracetamol overdose

<table>
<thead>
<tr>
<th></th>
<th>Cysteamine</th>
<th>Methionine</th>
<th>Dimercaprol N-acetylcysteine</th>
<th>Supportive treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment delay:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 h to 10 h</td>
<td>0/97 (0%)</td>
<td>0/143 (0%)</td>
<td>1/26 (4%)</td>
<td>0/949 (0%)</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
<td>No data</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>4/61 (7%)</td>
<td>13/143 (9%)</td>
<td>No data</td>
<td>58/949 (6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No data</td>
</tr>
<tr>
<td>10 h to 24 h</td>
<td>2/24 (8%)</td>
<td>2/41 (5%)</td>
<td>No data</td>
<td>16/1366 (1%)</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
<td>No data</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>16/28 (57%)</td>
<td>17/41 (38%)</td>
<td>No data</td>
<td>359/1366 (25%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No data</td>
</tr>
<tr>
<td>All (0 h to 24 h)</td>
<td>3/133 (2%)</td>
<td>2/197 (1%)</td>
<td>1/26 (4%)</td>
<td>16/2315 (0.7%)</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
<td>5/90 (6%)</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>21/107 (20%)</td>
<td>31/197 (16%)</td>
<td>No data</td>
<td>418/2315 (18%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>52/90 (58%)</td>
</tr>
</tbody>
</table>

Patients included from:  
Burkharl 1990; Buckley 1999b; Parker 1990; Prescott 1979; Smilkstein 1989; Smilkstein 1991; Woo 2000; Ayonrinde 2005  
(0-12 h and 12-24 h); Kerr 2005 (0-8 h and 8-24+ h)  
Douglas 1976; Hamlyn 1981; Prescott 1979
References


11. Comparative Evidence of Safety

Oral methionine has been associated with adverse effects of nausea, vomiting, drowsiness, and irritability. (Martindale) It has also rarely been associated with an aggravation of hepatic encephalopathy in patients with established liver damage, although this was limited to late-stage administration of methionine. (Meredith 1978)

N-acetylcysteine has been most commonly associated with anaphylactoid reactions such as rash and pruritis, which may be accompanied by flushing, nausea, bronchoconstriction, angioedema, and hypertension. Anaphylactoid reactions occur more often with intravenous
administration. When NAC is given in appropriate doses, the frequency of these anaphylactoid reactions are between 0.3 and 3%. Some studies suggest that anaphylactoid reactions to N-acetylcysteine can be effectively treated with antihistamines. Other adverse effects observed with N-acetylcysteine include arthralgia, blurred vision, disturbances of liver function, acidosis, convulsions, and cardiac or respiratory arrest. (Martindale)

Overall, the evidence of safety of N-acetylcysteine is much better understood than that of methionine due to its frequent use as the standard of care for paracetamol poisoning over the last thirty years in addition to its use in the treatment of cystic fibrosis.

12. Comparative cost:

The cost of NAC well surpasses the cost of Methionine. A course of NAC in 1984 was approximately 29GBP, whereas a course of Methionine was just 0.62GBP (Mant, 1984). Furthermore, a 2008 report further corroborated the approximate cost reporting the expense of one oral dose of NAC around 50 USD; this coincides with the aforementioned data a few decades prior (Heard, 2008)


2009 US Red Book prices
Acetylcysteine, 500 gm, $343-$447
20% 10 ml amps 3 amps $24.45 - $45.90
DL Methionine 500 gm $14 - $78.

13. Regulatory status: Not applicable

14. Pharmacopoeial standards:

Pharmacopoeial standards are widely available for both drugs. Methionine is available in the US, European, Vietnamese, and International Pharmacopoeias. The pharmacopoeial standards available for oral but not IV administration of methionine.

N-Acetylcysteine is available in the US, European, and Chinese Pharmacopoeias. Specific pharmacopoeial standards are available for both oral and IV administration of N-acetylcysteine.

15. Text for Model Formulary: not applicable

Addendum

Because of the unexpected results that both medicines are equally effective according to the Cochrane Review, we tried to learn from the published literature how NAC became the standard of care despite its higher price. An outline of this follows:
The group of Mitchell, Jollow, Potter, Gillette and Brodie at NIH found the mechanism of acetaminophen toxicity and enhancing glutathione in the liver protected mice. (1).

Mercaptamine was used clinically to treat these poisoned people but caused much toxicity and limited efficacy.

Vale in 1974 started treating with methionine which was available in the UK. He published his series of 132 patients in 1981 (2).

Rumach started to treat with oral acetylcysteine in 1976 based on a paper by by Piperno and Berssenbruegge in 1976 showing in mice that acetylcysteine was better than cysteamine (3). Rumach published a series of 662 cases in 1981 (4). In 1983, he published a review (5) stating that he used acetylcysteine because it was shown superior to both methionine and cysteamine. The evidence for this was cited as the paper by Piperno and Berssenbruegge (3). But in this paper acetylcysteine was compared to cysteamine only. Methionine was not included in this study. Prescott also started to use acetylcysteine in 1976 because he could give it IV while methionine and cysteamine were not available to give IV in Scotland. He published 87 cases in 1979 (6).

The patients reported by Vale, Prescott, and Rumach did well if the antidote was given early enough after the ingestion.

Chemically, the methionine must go to cysteine to make glutathione. Acetylcysteine is rapidly hydrolysed to cysteine which then goes to glutathione. So, theoretically, since methionine requires a synthesis step to cysteine, it would have a slower onset of action than acetylcysteine.

**Interpretation**

It appears that both methionine and acetylcysteine are equally effective clinically in treating acetaminophen poisoning. Treatment should start within 10-12 hours after the ingestion. The development of acetylcysteine as the standard of care appears to rest on two factors. One is the interpretation of the Piperno paper by Rumach with his using oral acetylcysteine in his huge North American continent-wide study of 662 poisoned subjects. The other was the ready availability of an acetylcysteine formulation that could be given IV by Prescott in Scotland at the same time to 87 patients. This compares to only 30 patients treated with methionine by Crome, et al published in 1976 (7) and 132 patients published by this group in 1981 (2). Thus publications of many treated patients with acetylcysteine in 1979 and 1981 compared to a smaller number treated with methionine published in 1981 and the erroneous statement that NAC was found superior to Methionine in the Piperno study led to the acceptance of acetylcysteine as the standard of care.

Under these circumstances, one should consider price seriously in selecting which drug is recommended for the Model List and which should be included as the drug meant by the square box on the List. If one accepts that the drugs have equal efficacy and safety, then Methionine is the more cost-effective and should be the example chosen for the Model List.
References for Addendum


