Acetylcysteine

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 4. Antidotes and other substances used in poisonings > 4.2. Antidotes and other substances used in poisonings > Specific

EMLc | ATC codes: V03AB23

Indication	Acute or subacute hepatic failure ICD11 code: DB91
INN	Acetylcysteine
Medicine type	Chemical agent
List type	Core
Formulations	**Parenteral > General injections > IV:** 200 mg per mL in 10 mL ampoule **Oral > Liquid:** 10% (EMLc) ; 20% (EMLc)
EML status history	Application rejected in 2021 (TRS 1035)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Acetylcysteine
DrugBank	Acetylcysteine

Expert Committee recommendation

The Expert Committee noted acute liver failure is relatively rare, but has a range of etiologies, including medicine-associated toxicity, viral infections and other causes. In some cases, liver transplant is needed and the prognosis can be poor with high short-term mortality, particularly where transplantation is unavailable. N-acetylcysteine is currently included in the Model lists for use as an antidote to paracetamol overdose. The Committee noted this application is for expanding the indication of N-acetylcysteine to conditions where acute liver failure is mediated by glutathione deficiency, including dengue and other causes of viral hepatitis, mushroom toxicity, alcoholic hepatitis and heat stroke. These conditions affect numerous people, especially in low- and middle-income countries. From the review of the literature presented, the Committee considered that the effects of N-acetylcysteine on mortality, need for transplant and duration of hospitalization are still not established because of the very low certainty of the available evidence. The Committee noted the heterogeneous effects across different patient populations, and the limited information on patient age or severity of illness due to insufficient trial data. The Committee also noted the lack of clinical guidelines on the use of N-acetylcysteine for indications other than paracetamol-induced liver toxicity. In addition, the Committee noted that N-acetylcysteine does not have regulatory approval for indications other than paracetamol overdose. The Expert Committee therefore did not recommend listing N-acetylcysteine for the new indication of non-paracetamol-induced acute liver failure because of limited confidence in the estimates of benefits. The Committee considered that higher quality studies may be feasible and would be beneficial to inform any future consideration for listing N-acetylcysteine.

Background

Acetylcysteine injection was added to the EML in 1999 and to the EMLc in 2007 for the treatment of paracetamol poisoning. The oral formulation was added in 2009.

Public health relevance

Acute liver failure is a serious clinical condition, with high morbidity and mortality in the absence of supportive clinical care and potentially liver transplantation (1,2). It affects all age groups, and there are many causes. This application focuses on acute liver failure with known involvement of glutathione, since this protein is targeted by N-acetylcysteine. Acute viral hepatitis infections are responsible for most cases of acute liver failure globally, with variation in causative viral pathogen in different regions (e.g. hepatitis A, B, E; dengue virus) (3). It has been estimated that 390 million dengue virus infections occur a year, of which 96 million show clinical symptoms (of any severity of disease) (4). A growing number of reports describe links between climate variations and the emergence of “climate-sensitive infectious diseases”, which would include all of the mosquito-borne diseases, including dengue, chikungunya and Zika virus disease (5), suggesting the global burden these diseases could be worsening. Dengue is endemic in more than 120 countries, with about 3.9 billion people at risk of infection (6). Liver injury and failure may complicate the disease course in a substantial portion of individuals affected by dengue; in an analysis of 347 patients hospitalized for dengue during one outbreak in Thailand, 219 patients (63%) had hepatic failure (7). Heat stroke is another cause of acute liver failure. The global incidence of heat stroke is difficult to estimate due to lack of an accepted system to capture and report cases. In the USA, for example, one study estimated more than 4100 emergency department visits for heat stroke occur each year, an annual national incidence rate of 1.34 visits/100 000 people and a case fatality rate of 3.4% (8). Amatoxin toxicity from consumption of poisonous mushrooms is a global problem, although it is difficult to estimate incidence because of the great likelihood of underreporting. While more common in some regions such as Europe, the literature includes reports of mushroom poisoning in many regions around the world. People with mushroom poisoning who develop acute liver failure have a poor prognosis in the absence of considerable supportive care and potentially liver transplantation (9,10). Acute liver failure caused by excess alcohol intake is another serious condition, with an estimated 30 day mortality of 30% (11). The exact incidence is unknown, but some estimates suggest that up to 20% of alcoholics suffer from acute liver failure (12). The estimated global prevalence of heavy episodic drinking was about 18% in 2016, and such drinking was more common in some areas such as Eastern Europe and sub-Saharan Africa (13), suggesting that some regions may be at risk of an increased prevalence of this type of acute liver failure.

Benefits

General non-paracetamol-induced acute liver failure A 2015 systematic review and meta-analysis of four clinical trials (616 participants, 331 receiving N-acetylcysteine (oral or intravenously) and 285 controls) evaluated the efficacy and safety of N-acetylcysteine in non-paracetamol-associated acute liver failure (14). For the outcome of overall survival, no significant difference was identified between treatment groups (71% versus 67%; odds ratio (OR) 1.16, 95% confidence interval (CI) 0.81 to 1.67. Significant differences favouring the N-acetylcysteine group were observed for the outcomes of transplant-free survival (41% versus 30%, OR 1.61, 95% CI 1.11 to 2.34) and post-transplantation survival (85.7% versus 71.4%, OR 2.44, 95% CI 1.11 to 5.37). A randomized study of 80 patients with non-paracetamol-induced acute liver failure evaluated the effect of N-acetylcysteine treatment on mortality, as well as efficacy and safety (15). More patients (72.5%) survived in the N-acetylcysteine group than in the control group (47.5%; P = 0.025) and among those who survived, the length of hospital stay was about 2.5 days shorter in the group treated with N-acetylcysteine (P = 0.002). Heat stroke-associated acute liver failure Three case reports have suggested improvement in liver function and other clinical outcomes associated with use of intravenous N-acetylcysteine in patients with heat-related acute liver failure (16–18). Severe acute alcoholic hepatitis A systematic review of 22 studies (2621 participants) evaluated the comparative effectiveness of five pharmacological interventions for the treatment of acute alcoholic hepatitis requiring hospitalization (19). A

network meta-analysis found good-quality evidence that corticosteroids alone (relative risk (RR) 0.54, 95% credible interval (CrI) 0.39 to 0.73), or in combination with N-acetylcysteine (RR 0.15, 95% CI 0.05 to 0.39) or pentoxifylline (RR 0.53, 95% CrI 0.36 to 0.78), reduce the risk of short-term mortality. Addition of N-acetylcysteine to corticosteroids may be superior to corticosteroids alone for reducing short-term mortality. No treatment was effective in reducing medium-term mortality. Mushroom-induced acute liver failure A systematic review of 13 studies (506 participants) evaluated the efficacy and safety of N-acetylcysteine in patients suffering amatoxin intoxication (20). Mortality in patients treated with N-acetylcysteine was 8% excluding liver transplant cases and 11% including liver transplant cases. The liver transplantation rate was 4.3%. Various laboratory values related to liver function and coagulopathy improved over 4–7 days after mushroom ingestion. Anaphylactic reactions occurred in 5% of cases. The review concluded that N-acetylcysteine treatment, combined with other therapies, appears to be safe and beneficial in this type of poisoning. Acute viral hepatitis Two small retrospective case series describe N-acetylcysteine use in children with acute liver failure in the context of acute viral hepatitis (21,22). Hepatitis A was the most common etiology. Both reports indicated improvement of liver enzymes and coagulation parameters and satisfactory medication tolerance with the use of N-acetylcysteine in this population. Dengue A retrospective cohort study (23), five case series (24–28), and seven case reports (29–35) including a total of 43 patients with dengue infection receiving N-acetylcysteine in addition to usual care were identified. Dengue-related illnesses ranged in severity, but no patients appeared to have mild disease. Outcome measures included liver function tests, mortality, measures of morbidity such as need for transplant, length of hospital stay and other laboratory measures relevant to dengue and its sequelae. All patients recovered except for three patients with disease level III–IV who already had dengue-associated acute liver failure before treatment. In one case with dengue-associated severe hepatitis (a 53-year-old), liver enzymes reached peak values of aspartate aminotransferase of 16261 U/L and alanine aminotransferases of 4545 U/L on day 4 of admission (day 7 of illness) before N-acetylcysteine treatment (31). After treatment, there was marked improvement in liver enzyme values, with levels dropping by more than half after 48 hours of treatment. In a retrospective case series, 13 people with moderate to severe hepatitis received N-acetylcysteine and had hepatic recovery faster than less sick patients who did not receive N-acetylcysteine (23). The application also summarized data from case series and case reports that described gradual normalization of liver function tests in patients receiving N-acetylcysteine for moderate to severe dengue.

Harms

The safety and tolerability profile of N-acetylcysteine as an antidote for the treatment of paracetamol poisoning is well established. Adverse events observed in the literature presented in the application are consistent with the broader evidence on N-acetylcysteine.

Cost / cost effectiveness

No cost–effectiveness data were presented in the application. N-acetylcysteine is widely used globally and is generally affordable. Considering liver transplantation as an extreme outcome of acute liver failure, liver transplantation has varied costs and availability in different settings; in the USA, for example, it has been reported that the average liver transplant costs more than US$ 800 000 per patient (36). The resources required for transplant and follow-up are likely substantial in most settings, compounded further by the limited availability of organs for transplant. The comparatively low cost of N-acetylcysteine and the potential for averting significant adverse outcomes later, such as the need for liver transplantation, would suggest it is a cost-effective treatment.

WHO guidelines

WHO guidelines for the management of acute liver failure are not currently available.

Availability

N-acetylcysteine is widely available across the world. To date, N-acetylcysteine does not have regulatory approval for the prevention or treatment of liver injury from causes other than paracetamol overdose.

Other considerations

The applicants reviewed a set of data from a phenome-wide association study (PheWAS). These studies can identify diseases or conditions (phenotypes) that are associated with a specific gene/genetic variant (37). PheWAS makes use of existing data from the Exomechip genotyping platform (about 250 000 coding variants across the protein coding region of the genome) and electronic health records of about 35 000 patients. Because PheWAS rationale can be applied to identify other types of phenotypic manifestations of pharmacological targeting (such as with N-acetylcysteine) of a given gene product in humans, these methods are used for drug repurposing (38). As a glutathione synthetase “stimulator”, N-acetylcysteine is hepatoprotective. This is has been established in its use in paracetamol overdose. The phenotypes associated with a missense single nucleotide polymorphism (R418Q) in the glutathione synthetase gene are risk-causing, so in this regard we can say the single nucleotide polymorphism is behaving as a glutathione synthetase inhibitor (the opposite of the drug). Thus, a variety of liver phenotypes strengthens the inference that decreased glutathione synthetase is associated with a broad range of liver injury, as is true in the etiologies of acute liver failure represented in the current application. Comments were received from the WHO Department of Neglected Tropical Diseases. The technical department advised that the evidence presented in the application for incorporation of N-acetylcysteine for treatment of dengue-associated liver injury or failure is based on incomplete reports. Further studies are needed to strengthen the evidence. It must be very clear that including N-acetylcysteine as an essential medicine does not represent a recommendation for its use in dengue-induced liver failure. The technical department had no objection to including N-acetylcysteine as an essential medicine for liver failure in general, if there are sufficient data in the application.

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