**N-ACETYLCYSTEINE**

- Used to treat acetaminophen poisoning

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**PHARM PROFILE**

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\[N\text{-acetyl-para-benzoquinone-imine (NAPQI)}\].\(^1\) This reactive metabolite is inactivated by conjugation with glutathione.\(^4,5\) In acetaminophen overdose, NAPQI is formed in amounts sufficient to deplete hepatic and erythrocyte glutathione reserves.\(^3,5\) NAPQI also binds covalently to cellular macromolecules, mediates the conversion of hemoglobin to methemoglobin, and induces Heinz body formation.\(^5\) The presence of Heinz bodies increases the osmotic fragility of erythrocytes, leading to hemolysis and anemia.\(^4,5\) Furthermore, large doses of acetaminophen produce activated oxygen free radicals that cause an inflammatory process.\(^7\)

**PHARMACOKINETICS AND PHARMACOLOGY**

In humans, NAC is rapidly and completely absorbed in the gastrointestinal tract after oral administration.\(^8\) Peak plasma concentration is reached less than an hour after ingestion.\(^9\) NAC diffuses into most body tissues, including the lungs, liver, and kidneys.\(^8\) Extensive first-pass metabolism by the small intestine and liver results in the formation of cysteine and inorganic sulfate.\(^10\) The plasma half-life of NAC is 2.15 hours.\(^11\)

NAC acts by several mechanisms. Its main action is replenishment of intracellular glutathione stores.\(^1\) Glutathione, one of the most important antioxidants and detoxifiers in the body, is a tripeptide consisting of glutamic acid, cysteine, and glycine.\(^12\) As food and several metabolic pathways supply glutamic acid and glycine, attention is focused on providing cysteine to the patient. In vivo, NAC is rapidly metabolized to cysteine, which is an essential amino acid required for the synthesis of glutathione.\(^12\) The second action of NAC is detoxification of the reactive metabolite. The sulphydryl group of NAC may bind the reactive metabolite NAPQI, which is inactivated and excreted.\(^1\) Third, NAC treatment increases the fraction of acetaminophen excreted as the sulfate conjugate.\(^13\) In cats treated with acetaminophen and NAC, the plasma half-life of acetaminophen is approximately half (2.3 hours) of that in cats treated with acetaminophen alone.\(^14\)

**INDICATIONS**

NAC is very effective in the treatment of acetaminophen poisoning.\(^1\) Although it is most effective if less than 12 hours has elapsed since ingestion of high doses of acetaminophen, NAC is still recommended up to 36 to 80 hours after acetaminophen ingestion.\(^4,15\) NAC can reduce the extent of liver injury. In humans, NAC infusion is...
Client Counseling Information

- NAC is the antidote of choice for the treatment of acetaminophen toxicity in dogs and cats.
- Oral administration of NAC typically causes nausea and vomiting.
- Adverse reactions to treatment are relatively common but rarely serious.

used selectively to treat some forms of acute liver failure. NAC may also improve hepatic microcirculation. It enhances endogenous production of nitric oxide, which dilates hepatic vessels and improves hepatic blood flow. NAC also acts as a scavenger of oxygen free radicals and can reduce the extent of methemoglobinemia.

NAC is also used as a mucolytic agent in the adjunctive treatment of bronchopulmonary disorders. The sulphydryl group in the molecule acts directly to split disulfide linkages between mucoprotein molecular complexes, resulting in depolymerization and decreased mucus viscosity. NAC is also used to treat ulcerative keratitis and appears to have some clinical usefulness as a chelating agent in the treatment of acute heavy metal poisoning (mercury, arsenic, copper).

CAUTIONS

NAC can cause phlebitis when administered perivascularly; and rapid intravenous administration can cause hypotension, bronchospasm, and flushing. Reactions can be minimized by giving each dose very slowly. When given orally, NAC typically causes nausea and vomiting.

No teratogenic or embryotoxic effects have been observed in reproduction studies in rabbits and rats.

ACUTE TOXICITY

The LD₅₀ of intravenous NAC in dogs is 700 mg/kg.

DRUG INTERACTIONS

Because activated charcoal may adsorb NAC, thereby reducing its effectiveness, NAC should not be given within 2 hours of administering activated charcoal. Administration of activated charcoal may exacerbate vomiting and lead to aspiration. A strong antiemetic agent (metoclopramide, 0.4 mg/kg IV) may be necessary to prevent emesis.

DOSAGE AND ADMINISTRATION

In dogs and cats, NAC should be given intravenously or orally but has a pungent aroma. In swine, rectal administration results in effective absorption into the systemic circulation. This represents a potential alternative route for the administration of NAC to dogs.

Some veterinarians prefer slow bolus intravenous injection because of the vomiting associated with acetaminophen poisoning. NAC should be given intravenously at an initial dose of 140 mg/kg (280 mg/kg in severe toxicity) and then at a maintenance rate of 70 mg/kg every 6 hours for seven treatments. The 10% or 20% NAC solution should be diluted to a 5% concentration with 5% dextrose. Each dose is infused over 30 to 60 minutes through a peripheral intravenous catheter using an inline 0.2-µm millipore filter. Beneficial effects are expected within 48 hours after initial therapy. Cimetidine can have an additive effect and is administered at a loading dose of 10 mg/kg followed by 5 mg/kg every 6 hours for 48 hours. To reduce methemoglobin to hemoglobin, ascorbic acid can be administered at a dose of 30 mg/kg IV every 6 hours until the cyanosis is no longer apparent. Fluid therapy with added sodium bicarbonate may be needed in severe cases to reverse metabolic acidosis. Corticoids and antihistamines are contraindicated.

Plasma or urine concentrations of acetaminophen are of predictive value. Acetaminophen toxicity is dose dependent. Hematogram with methemoglobin value (particularly in cats), detection of Heinz bodies in the erythrocytes, and acid–base status should be determined. Hepatocellular damage may be monitored by assays of aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase, and prothrombin time, particularly in dogs.

PREPARATIONS

NAC is currently not approved by the FDA for use in dogs and cats, although it is available in human pharmaceutical preparations (Mucomyst, Bristol-Myers Squibb; Mucosol, Dey Labs). It is sold both as a 10% or 20% solution for inhalation and in vials containing 4, 10, or 30 ml for oral administration. No intravenous NAC preparation is available in the United States. Because the commercially available NAC solution is sterile (oral treatment), patients may be safely treated with the oral NAC formulation administered via the intravenous route.

STORAGE AND HANDLING

Unopened vials of NAC should be stored below 25°C and protected from light. Open vials should be kept refrigerated and used within 96 hours for oral treatment. The solution color may change in the opened bottle, but this does not significantly impair the drug’s safety or efficacy.

REFERENCES


