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Utility of Acetylcysteine in Treating Poisonings and Adverse Drug Reactions

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Abstract

As recognition of the role of free radicals and reactive toxins in the pathogenesis of disease, poisoning, and adverse drug reactions has evolved, interest in the use of acetylcysteine as a modulator of these effects has steadily increased in recent years. Acetylcysteine is commonly thought to serve as a glutathione precursor and consequently can increase or sustain intracellular glutathione which scavenges reactive oxygen species caused by toxins or subsequent tissue injury. At least 10 additional mechanisms of action for acetylcysteine have been demonstrated in various laboratory models, but a unifying framework of its actions is still to be proposed.

This paper reviews the current experimental and therapeutic status of acetylcysteine for the treatment of poisonings and adverse drug reactions. Of the 45 potential uses of acetylcysteine that were identified for the treatment of poisonings or adverse drug reactions, 14 of the toxic effects have little support for its use while promising results have been demonstrated for 27 toxicities. Currently, treatment of acute paracetamol (acetaminophen) poisoning is the only widely accepted clinical indication for acetylcysteine as a treatment for poisoning or adverse drug reactions. In many clinical situations acetylcysteine is used empirically utilising modifications of dosage regimens employed for paracetamol poisoning.

Often it is difficult to determine the benefit of therapy with acetylcysteine owing to the nature of the toxicity being treated, the use of other therapies, the presence of comorbid conditions, and the small number of patients studied. The diverse and positive nature of the investigations suggest that there is considerable promise in acetylcysteine as a research tool and pharmacological agent.

As knowledge of the role of free radicals and reactive toxins in the pathogenesis of disease, poisoning, and adverse drug reactions has evolved in the past half-century,[1-3] interest in acetylcysteine[2,3] has steadily increased, particularly in the past decade. Acetylcysteine, a derivative of the amino acid cysteine, possesses a sulfhydryl moiety (-SH, also referred to as a thiol group) which is similar to several endogenous compounds (fig. 1) that are thought to play a significant role in cellular response to disease and injury.[1-3] It is commonly thought that acetylcysteine serves as a glutathione precursor and thereby can increase or sustain intracellular glutathione which scavenges reactive oxygen species caused by toxins directly or indirectly by subsequent tissue injury. Several additional mechanisms of action for acetylcysteine have been demonstrated in laboratory models (table I) and are described in this paper, but a unifying framework of its actions is still to be discovered.

This paper reviews the current status of the utility of acetylcysteine for the treatment of poisonings and adverse drug reactions and expands upon previous reports.[4,5] Although a mechanistic analysis of the applications of acetylcysteine would be desirable, it is premature because of evolving knowledge of its true actions. In this review we endeavoured to describe the variety of uses of acetylcysteine without regard to classifying its proposed actions. We have chosen to include all pertinent reports that could be identified by multiple literature search strategies and have made no exclusions based on the quality of the investigations.

Since the potential applications of acetylcysteine for the treatment of poisonings and adverse drug reactions are varied and increasing in number, a review of current work in this area may stimulate further research and a better understanding of its potential uses.

1. α-Amanitin

Evidence in mice indicates that depletion of hepatic glutathione content may be an early event that precedes liver dysfunction with sublethal doses of α-amanitin, a toxic constituent of Amanita mushrooms.[6] By preventing early changes in hepatic glutathione homeostasis by the administration of acetylcysteine the toxicity of α-amanitin may be averted.

On this basis, 99 patients who had ingested mushrooms containing α-amanitin were treated with an intravenous regimen of an acetylcysteine 150 mg/kg loading dose followed by 50 mg/kg every 4 hours.[7] The drug was given for at least 72 hours and started within 40 hours of the mushroom ingestion. On admission to the hospital, 77% of the patients exhibited biochemical evidence of moderate to severe liver injury with 2 patients eventually developing renal failure and 6% of the patients dying. Compared with patients untreated with acetylcysteine in other case series, the 6% mortality rate of this series compared favourably with the 10 to 30% mortality of the historical control individuals. The investigators concluded that the extreme variability of the clinical course of α-amanita mushroom poisoning makes interpretation of the results difficult, but acetylcysteine may prove to be beneficial. No serious adverse effects of the acetylcysteine therapy were observed, but 2 patients developed an erythematous rash.

An efficacy study investigated mice given a single dose of acetylcysteine to determine its ability to prevent delayed hepatotoxicity of α-amanitin.[8] Two experimental groups received intraperitoneal injections of α-amanitin 0.6 mg/kg followed by normal saline 1ml or acetylcysteine 1.2 g/kg 4 hours later. A third group received saline 1ml followed by acetylcysteine 1.2 g/kg at 4 hours. One-half of the number in each group was sacrificed at

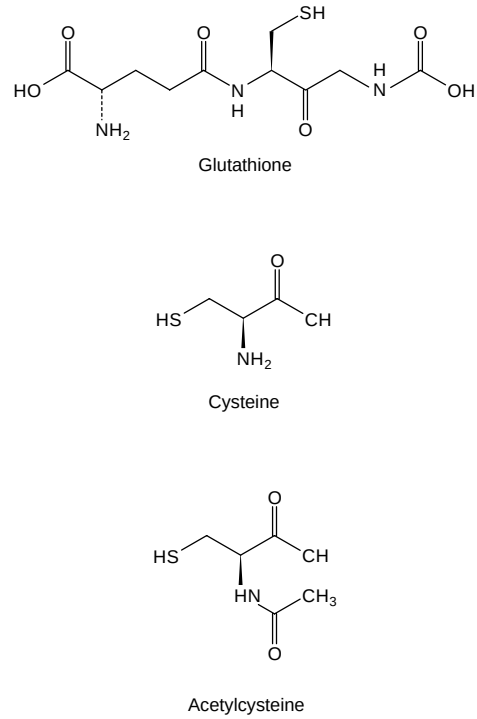

Fig. 1. Chemical structures of sulfhydryl-containing compounds.

Table I. Potential mechanisms for acetylcysteine-modulating toxic actions of drugs and chemicals

Potential mechanism	Example
Prevent binding or uptake of reactive or toxic species to cells or cellular components	Cadmium, cyclophosphamide, mercury
Increase synthesis of endogenous substrate, e.g. glutathione, for detoxification	Paracetamol (acetaminophen), phenytoin
Direct binding of toxic species to acetylcysteine	Arsenic, cisplatin
Reduce toxic species to the parent drug	Paracetamol
Act as a surrogate substrate, e.g. glutathione, for detoxification	Cisplatin, alcohol (ethanol), paracetamol
Enhance nitric oxide-mediated vasorelaxation of microcirculation	Hepatonecrosis, paracetamol
Scavenge oxygen free-radicals produced directly by the drug or metabolite	Carbon tetrachloride
Scavenge oxygen free-radicals produced indirectly as a consequence of tissue necrosis	Hepatonecrosis
Enhance elimination of toxin	Methylmercury
Immunomodulation	Hypersensitivity reactions
General antioxidant effect	Nitrite

48 hours and the remaining mice were observed for 7 days for survival. At 48 hours, mice receiving α-amanitin had average values for AST and ALT of 13 133 ± 2657 (units not stated) and 16 276 ± 3097 (units not stated), respectively. Groups receiving acetylcysteine exhibited average AST and ALT values of 12 967 ± 2103 (units not stated) and 14 607 ± 2265 (units not stated), respectively. The investigators concluded that single dose acetylcysteine was ineffective in the prevention of delayed α-amanitin hepatotoxicity. Survival rates for both groups were nearly identical.

2. Arecoline

Arecoline is the principal alkaloid of betel nut which is chewed by millions of people in India, the Far East, the South Pacific and East Africa. It has cholinergic actions and possesses mutagenic and carcinogenic (oral cancer) potential which may be enhanced by the presence of food or drink.[9] In an animal study, mice were given arecoline 40 mg/kg intraperitoneally for 1, 5 and 15 days or 170 μg/L *ad libitum* in drinking water.[10] An estimated 1mg of arecoline was consumed daily by each mouse for 1, 5, and 15 days. Acetylcysteine 830 μg/L (200 mg/kg) was also added to the drinking water for days 5 to 15. The bone marrow cells were used to measure mutagenicity.

Both routes of arecoline administration produced significant ($p < 0.05$) chromosomal aberrations, cell cycle delay and sister chromatid exchanges. Acetylcysteine reduced the frequency of these changes when arecoline was given orally. The investigators observed that when acetylcysteine was administered alone it was capable of inducing sister chromatid exchanges indicating its potential ability to induce DNA damage which has also been observed by others.[11]

3. Arsenic

Since arsenicals appear to bind with sulfhydryl-containing enzyme systems, acetylcysteine may provide an alternative sulfhydryl source that would bind arsenic, thereby sparing cell membranes and enzyme systems.[12,13] An animal study[12] with 4 groups of 5 mice that were given lethal doses of subcutaneous arsenite (25 mg/kg) was performed to evaluate the efficacy of acetylcysteine. 15 or 30 minutes after the arsenite injection, penicillamine 50 mg/kg, dimercaprol 5 mg/kg or acetylcysteine 100 mg/kg was administered intraperitoneally.

For another group of animals, the doses of the test drugs were doubled and given 30 minutes after arsenic or at 15, 45 and 75 minutes after the arsenic dose. Acetylcysteine prolonged survival time at 15 minutes for the higher doses ($p < 0.01$), and 30 minutes for the lower doses ($p < 0.05$). 30 minutes after arsenite administration, the lower chelator doses and the multiple dose regimen demonstrated no significant differences among the 3 drugs. However, at the higher dose regimen acetylcysteine compared favourably ($p < 0.05$) with dimercaprol in prolonging survival. 15 minutes after the arsenite administration acetylcysteine was more effective ($p < 0.05$) at the lower dosage regimen, but no significant differences were observed among the 3 drugs at the higher dose regimen or with multiple doses.

In another animal study, Henderson et al.[13] studied the efficacy of acetylcysteine in the treatment of copper, sodium arsenite, thallium and cadmium poisoning compared with chelating agents. Groups of albino mice were given intraperitoneal injections of acetylcysteine 200 mg/kg or dimercaprol 10 mg/kg 30 to 60 minutes after administration of the heavy metal. Sodium arsenite was administered subcutaneously as a single dose of 2 to 20 mg/kg. In the arsenite group, survival time was lengthened by dimercaprol or acetylcysteine, but the lethal dose for 50% (LD_{50}) of mice was not changed by either treatment. Mortality was reduced after dimercaprol and somewhat less after acetylcysteine.

Acetylcysteine was administered intravenously to a 32-year-old man who ingested sodium arsenate 900mg 5 hours prior to evaluation in a healthcare facility.[14] Intravenous fluids, dimercaprol and vasopressors were administered, but the patient's condition continued to deteriorate. At 27 hours after the ingestion, acetylcysteine was given intrave-

nously at 70 mg/kg every 4 hours. Within 24 hours, his laboratory tests and clinical condition improved. On day 4 the patient was switched to penicillamine therapy because the patient could not tolerate the oral acetylcysteine. No adverse effects were noted from acetylcysteine and long term effects from the arsenate were not observed.

4. Boron

Banner et al.[15] investigated acetylcysteine therapy in groups of 5 to 6 rats intoxicated with chromium, lead or boron. For boron, rats were gavaged for 3 days with boric acid and received a total dose of 2 g/kg of boric acid. They were given acetylcysteine 500 mg/kg intraperitoneally or succimer (2,3-dimercaptosuccinic acid) 32.8 mg/kg intramuscularly starting 1 hour after the final boric acid dose. Total urine output was increased by both drugs ($p < 0.02$) and boric acid excretion was increased during both drug treatments ($p < 0.01$). A rechallenge 2 weeks later with acetylcysteine 500 mg/kg produced a marked increase in boric acid excretion ($p = 0.005$) with no increase in urine volume. Acetylcysteine appeared to increase the renal excretion of boric acid and may reverse the oliguria associated with the toxicity. The mechanism of action is unknown.

5. Cadmium

Henderson et al.[13] studied the efficacy of acetylcysteine in the treatment of copper, sodium arsenite, thallium and cadmium poisoning compared with chelating agents. Mice were given intraperitoneal doses of acetylcysteine 200 mg/kg or dimercaprol 10 mg/kg, 30 to 60 minutes after administration of the heavy metal. Cadmium chloride was administered subcutaneously at the LD_{50} of mice. In the cadmium group, neither treatment changed mortality rates. A 4-fold increase ($p < 0.05$) in urinary cadmium excretion was noted by Ottenwalder and Simon[16] after male rats were given acetylcysteine 100 mg/kg subsequent to sublethal doses of cadmium chloride, all by intraperitoneal injection.

A cell culture study[17] examined cytoprotection from cadmium toxicity afforded by acetylcysteine. Although intracellular glutathione levels were increased nearly 2-fold ($p < 0.05$), inhibition of this increase by buthionine sulfoximine did not abolish the protection by acetylcysteine. Protection against cadmium toxicity by acetylcysteine appears to be independent of glutathione; moreover, it lowered ($p < 0.05$) the uptake of cadmium into cells which may be responsible for the cytoprotection.

To investigate whether oxidative stress may contribute to cadmium toxicity, 6 groups of rats were given subcutaneous injections of cadmium chloride for up to 22 weeks.[18] Five treatment groups received these agents: buthionine sulfoxime (glutathione depleter), aminotriazole (inhibitor of catalase), acetylcysteine (antioxidant), tocopheral (vitamin E) [antioxidant] and Stronger Neo-Minophagen C which contains glycyrrhizin, glycine and cysteine (a Japanese drug used for treating hepatic disorders that has antioxidant properties).

In this study, glutathione depletion and catalase inhibition enhanced cadmium toxicity, thereby indicating a role for oxidant stress. Given early in the course of cadmium exposure, the 3 antioxidants prevented hepatic and renal toxicity in this model of long term cadmium exposure. The protection from cadmium-induced nephrotoxicity in rats may also be related to continued treatment with acetylcysteine during cadmium exposure.[19] The discontinuation of acetylcysteine in this model during continued cadmium exposure resulted in quick progression of nephrotoxicity.

6. Carbon Monoxide

A 26-year-old man who was assumed to be poisoned with carbon monoxide, exhibited loss of consciousness, cerebral oedema and seizures for 5 days despite supportive care and supplemental oxygenation.[20] On the fifth day he received intravenous acetylcysteine 150 mg/kg over 15 minutes followed by 50 mg/kg over 4 hours, and 100 mg/kg over 16 hours. He also received allopurinol 100 mg/day via gastric tube. During the next 3 weeks

he made a full recovery. The authors speculated that acetylcysteine and allopurinol protected ischaemic nervous system tissue from oxidative damage during the hypoxic/reperfusion injury phase of carbon monoxide toxicity.

7. Carbon Tetrachloride

Carbon tetrachloride (CCl_4) is converted to a toxic trichloromethyl free radical (CCl_3) resulting in lipid peroxidation and damage to cell membranes. The free radical may also undergo anaerobic conversion to carbon monoxide, chloroform or aerobic metabolism to trichloromethanol, a precursor of phosgene, with hydrolysis to carbon monoxide.[21] In an animal study,[22] rats (5 per group) were given acetylcysteine 2 g/kg orally 30 minutes before, and 6 or 10 hours after radiolabelled carbon tetrachloride 5 ml/kg in a 5 or 20% solution intraperitoneally.

Acetylcysteine administered prior to carbon tetrachloride administration partially decreased the binding of the reactive metabolite at 1 and 3 hours and decreased the concentration of carbon tetrachloride reaching the liver at 3 hours. The extent of histologically evident necrosis was decreased by acetylcysteine administration. Acetylcysteine alone slightly increased lipid peroxidation, but decreased carbon tetrachloride-promoted lipid peroxidation slightly or significantly at 1 and 3 hours post poisoning. This suggests that acetylcysteine may offer some early and late hepatoprotective effects.

The potential protective effects of acetylcysteine against the toxic effects of carbon tetrachloride are suggested by a report of 19 patients poisoned by carbon tetrachloride from 1981 to 1984, whose diagnoses were confirmed by laboratory analysis.[23] A total of 13 patients received acetylcysteine intravenously according to a standard intravenous dose regimen for paracetamol (acetaminophen) poisoning. Of the 13 patients, 7 showed mild hepatic injury, 1 had moderate hepatic injury, and 1 had severe hepatorenal damage. Of the 6 patients not treated with acetylcysteine, 3 had hepatorenal failure and 1 died suggesting acetylcysteine may minimise hepatorenal failure. One patient experienced a mild anaphylactoid reaction (rash) after acetylcysteine administration.

Mathieson et al.[24] reported a case of a 61-year-old man who ingested 250ml of carbon tetrachloride and survived. After gastric lavage, intravenous acetylcysteine was initiated 4 hours post ingestion with a loading dose of 150 mg/kg over 15 minutes followed by 50 mg/kg over 4 hours, then 100 mg/kg over 16 hours. Despite high blood concentrations of carbon tetrachloride (31.5 mg/L), the patient experienced minimal symptoms of diarrhoea, mild dehydration, and transient oliguria. No adverse reactions from acetylcysteine were noted. The patient survived, but he experienced elevated plasma AST levels which peaked at 1000 IU/L on the fourth day post ingestion, and an elevated prothrombin time ratio peak of 3 on the second day after ingestion of the carbon tetrachloride. The mechanism of action of acetylcysteine in the treatment of carbon tetrachloride poisoning is uncertain. It may serve as a free radical scavenger or may maintain intracellular glutathione stores.[22,24]

8. Caustic Alkali

In attempts to minimise stricture formation following caustic alkali injury, acetylcysteine and cysteine have been investigated for their potential to interfere with collagen synthesis. Caustic alkali burns of the oesophagus were produced in anaesthetised rats by irrigation with sodium hydroxide 50% *in situ* for 2 minutes.[25] Acetylcysteine 20% 0.5ml or prednisone 1 mg/kg was injected intraperitoneally on a daily basis in 31 and 27 animals, respectively, for the duration of the study. Another 39 rats received no treatment and served as controls.

Histological examination revealed that acetylcysteine nearly halved the rate of stricture formation (45% of animals) compared with controls (80%), and was similar to the prednisone-treated group (52%). In the animals with evidence of strictures, severe stenosis developed in 40% of controls, 14% of acetylcysteine-treated animals, and 14% with prednisone treatment. More animals died

early in the first 2 weeks with acetylcysteine (16%) or no treatment (19%) compared with those receiving prednisone (7%). Acetylcysteine and prednisone exhibited similar efficacy in reducing the development of strictures and stenosis in this animal model. In humans, cysteine was used as an adjunctive irrigant to reduce corneal ulcers in 13 patients whose eyes were burned with caustic alkali.[26] The use of acetylcysteine has not been reported in humans injured by caustic alkali ingestion.

9. Chromium

Since acetylcysteine is believed to have significant antioxidant efficacy, it may serve a role in the treatment of chromium toxicity. Chelation therapy was investigated by Banner et al.[15] in groups of 5 to 6 rats intoxicated with chromium, lead or boron. For the chromate tests, rats intoxicated with potassium dichromate (50 mg/kg) were given acetylcysteine (500 mg/kg), sodium calcium edetate 67.4 mg/kg or saline at 1, 24, and 48 hours after intoxication. Average urinary concentration of chromium did not increase, but urine volume and total chromium excretion were increased on all 3 days of the study period ($p < 0.01$) following acetylcysteine administration. Sodium calcium edetate was also effective ($p < 0.05$), but to a lesser extent. Acetylcysteine appears to chelate and increase the renal excretion of chromium and may reverse the oliguria associated with toxicity. The mechanism of action is unknown.

A 25-year-old man presented to the emergency department 20 hours after ingesting 60ml of a 28% sodium dichromate and chromate solution.[27] Symptoms included abdominal pain, haematochezia, haematemesis, dehydration and orthostasis. Serum chromium concentration was 8067 µg/L. Other laboratory studies revealed haematocrit 62%, pH 7.20, partial carbon dioxide pressure (pCO_2) 26mm Hg, blood urea nitrogen (BUN) 35 mg/dl, serum creatinine level 4.1 mg/dl, AST level 252 U/L, and bilirubin level 1.9 mg/dl. Endoscopy showed severe erosive gastritis and duodenitis. Anuria developed and haemodialysis was started 9 hours after admission and continued intermittently for 14 days during which serum chromium concentrations did not decrease appreciably.

Intravenous acetylcysteine 140 mg/kg every 4 hours was started 12 hours after admission and continued for 48 hours. Renal and hepatic function initially worsened, but by day 15 urine output and hepatic function were normal. Renal function improved gradually thereafter and no haemolysis was observed.

Endo and Watanabe[28] found that the incidence of congenital malformations in mice exposed to chromium trioxide was greater ($p < 0.025$) with acetylcysteine treatment (11.6%) compared with controls (5.2%). Again, the underlying mechanism is unknown.

10. Cisplatin

The mechanism of cisplatin nephrotoxicity is not well known, but it may be related to the total dose and duration of therapy. Sulfhydryl-containing compounds, such as acetylcysteine, may theoretically prevent cisplatin nephrotoxicity, because cisplatin appears to bind irreversibly to certain sulfhydryl-containing enzymes. Glutathione prevents this effect by binding cisplatin, and acetylcysteine may act to replenish glutathione.[29,30]

To investigate the potential effects of acetylcysteine on cisplatin nephrotoxicity, rats were given cisplatin 0.6 mg/100g intraperitoneally concomitantly with acetylcysteine 100 mg/100g subcutaneously, cisplatin and acetylcysteine mixed in one solution and injected intraperitoneally, cisplatin 0.3 or 0.6 mg/100g intraperitoneally only, or acetylcysteine 100 mg/100g subcutaneously only.[29] Acetylcysteine concomitantly or in solution with cisplatin prevented the nephrotoxic (proteinuria and oliguria) effects of cisplatin despite a slight elevation of BUN. Cisplatin concentrations in the kidney were decreased and its urinary excretion increased. The authors hypothesised that renal protective effects of acetylcysteine could result from the formation of a cisplatin-acetylcysteine complex which would be unsuitable for renal tubular reabsorption.

Cisplatin-induced nephrotoxicity may be caused by generation of reactive oxygen species.[30] Cisplatin was found to cause cytotoxicity in bladder cancer cells by the production of reactive oxygen species which was exacerbated by the depletion of intracellular glutathione.[31] Cell culture studies suggest that toxicities induced by cisplatin and glutathione depletion can be blunted by acetylcysteine.[32] Elevated glutathione levels were observed by incubation of acetylcysteine in cancer bladder cells, which suggests that the protective effect of acetylcysteine may be mediated by its ability to raise glutathione levels. Acetylcysteine was also shown to be able to scavenge cisplatin-induced reactive oxygen species. The investigators concluded that in cisplatin-induced injury acetylcysteine scavenges free radicals and augments glutathione levels.

In another cell culture study using human glioma cells, cisplatin toxicity could be reduced by various antioxidants including acetylcysteine; however, glutathione depletion or free radical formation was not associated with cytotoxicity.[33] These researchers hypothesised that cisplatin toxicity is mediated by a pro-oxidant that is subject to inhibition by antioxidants such as acetylcysteine and is independent of free radical formation in this cell line.

A 38-year-old woman diagnosed with large cell lymphoma of the small intestine was inadvertently given a total cisplatin dose of 640mg intravenously over 4 days.[34] Two days after the completion of the drug course, the patient developed acute pancreatitis, hepatic and oliguric renal failure. On the eighth day after the cisplatin treatment, acetylcysteine was given in an attempt to minimise cisplatin nephrotoxicity. Acetylcysteine 140 mg/kg followed by 70 mg/kg every 4 hours for 4 days (route not specified) was initiated. On the second day of acetylcysteine therapy, the patient's BUN and creatinine peaked at 103 and 9.7 mg/dl, respectively, and then declined. Four days after initiation of acetylcysteine, the patient's urine output increased to 3 L/day with a BUN and serum creatinine of 71 and 6.4 mg/dl, respectively. The patient died from sepsis, disseminated intravascular coagulation, and severe leucopenia which were unlikely to be caused by acetylcysteine. The improvement in the patient's renal function suggests some potential benefits of acetylcysteine in the treatment of cisplatin renal toxicity, but its role is impossible to discern in this case.

11. Clozapine

Clozapine is associated with a 0.8 % incidence of agranulocytosis.[35-37] The mechanism of the agranulocytosis has not been determined. Clozapine does not appear to exhibit direct toxicity to polymorphonuclear leucocytes, but it is metabolised to demethylclozapine and clozapine *N*-oxide which form a reactive intermediate. Myeloperoxidase, a major enzyme in polymorphonuclear leucocytes (neutrophils, eosinophils, basophils), can bioactivate clozapine to a radical cation and nitrenium ion.[35,36]

Mononuclear and polymorphonuclear leucocytes were isolated from the blood of healthy volunteers to determine whether the reactive metabolite was cytotoxic by generating the metabolites *in situ*.[37] Clozapine and its stable metabolites were not cytotoxic; however, other metabolites, with the exception of clozapine N-oxide, exhibited cytotoxicity. Bioactivation of clozapine was accompanied by the formation of C6-glutathionyl clozapine, and both C6- and C9-glutathionyl clozapine without and with the addition of exogenous glutathione. Addition of glutathione, acetylcysteine and ascorbic acid (vitamin C) reduced cytotoxicity for both cell types to background values.

12. Copper

In an animal study, Henderson et al.[13] studied the efficacy of acetylcysteine in the treatment of copper, sodium arsenite, thallium and cadmium poisoning compared with chelating agents. Groups of mice were given intraperitoneal doses of acetylcysteine 200 mg/kg, dimercaprol 10 mg/kg or penicillamine 50 mg/kg at 30 to 60 minutes after administration of the heavy metal. Cupric sulfate was administered subcutaneously at a LD_{50} of mice. In

the copper group, mortality was nearly halved ($p < 0.05$) with acetylcysteine or dimercaprol treatment, but pencillamine had a negligible effect.

13. Cotrimoxazole (Trimethoprim-Sulfamethoxazole)

The high frequency of hypersensitivity reactions observed in HIV-positive individuals who received cotrimoxazole (trimethoprim-sulfamethoxazole) may be because of systemic glutathione deficiency and a decreased ability to scavenge reactive sulfamethoxazole metabolites. In a clinical study[38] when cotrimoxazole was initiated as primary *Pneumocystis carinii* pneumonia prophylaxis, 238 patients were randomised to receive or not receive acetylcysteine 3g 1 hour before each dose of cotrimoxazole (trimethoprim 80mg with sulfamethoxazole 400mg) twice daily. Cotrimoxazole was discontinued in 45 patients within 2 months because of fever, rash or pruritus. There was no difference in the occurrence of hypersensitivity reactions in 25 out of 102 patients (25%) who received cotrimoxazole alone, and in 20 out of 96 patients (21%) who were also receiving acetylcysteine. Another study reported similar findings with a daily dose of acetylcysteine 800mg. Moreover, there was no detectable change in plasma glutathione levels.[39]

14. Cyanide

The events preceding cyanide-induced cell death were studied to determine whether cyanide produces DNA damage *in vitro*, the nature of the DNA damage and whether the damage is time and dose dependent.[40] Freshly isolated rat thymocytes and nonlymphoid cells from baby hamster kidney cells (BHK-21) were exposed to 1.25 to 10 mmol/L potassium cyanide for varying periods of time. The cells were evaluated for viability, lactate dehydrogenase leakage and DNA strand breaks (fragmentation). The protective effects of zinc sulfate, acetylcysteine, and diltiazem were evaluated by simultaneous introduction with potassium cyanide.

For the thymocytes, potassium cyanide 5 mmol/L for 6 hours significantly reduced cell viability and increased DNA fragmentation. Internucleosomal DNA fragmentation was blunted when equimolar doses of zinc sulfate, acetylcysteine and diltiazem were added. Simultaneous treatment with zinc, diltiazem and acetylcysteine were equipotent in preventing the cytotoxicity, but diltiazem and acetylcysteine did not attenuate the DNA damage as effectively as zinc.

15. Cyclophosphamide

Cyclophosphamide, a derivative of nitrogen mustard, is used in cancer chemotherapy. It is metabolically activated by cytochrome P450 (CYP) by hydroxylation at C-4, primarily by isoenzymes 2C11 and 2C6.[41] Metabolites such as 4-hydroxycyclophosphamide and aldophosphamide are further converted to acrolein and phosphoramide mustard. Since acrolein may deactivate CYP by covalently binding the thiols of CYP, free sulfhydryl-containing groups may protect against the acrolein-induced injury. Other studies have indicated that the effect is not caused by direct inactivation by acrolein.[42] A previous *in vitro* study demonstrated that acetylcysteine may provide lymphocyte protection from nitrogen mustard.[43]

The effects of cyclophosphamide and acetylcysteine on hepatic CYP were studied in male rats (180 to 200g) that were assigned randomly to 6 groups.[44] Animals in group I were given saline intraperitoneally and sacrificed after 7 days. Groups II, III and IV were given a single dose of cyclophosphamide 200 mg/kg and sacrificed on days 1, 4, and 7, respectively. Group V was given cyclophosphamide and acetylcysteine with acetylcysteine 200 mg/kg given 0.5 hours before and after the cyclophosphamide dose. The animals were sacrificed 7 days later. The animals in group VI received acetylcysteine 400 mg/kg only and were sacrificed on day 7. Assays were performed for protein level, P450 content, microsomal androstenedione hydroxylase, nicotinamide adenine dinucleotide phosphate (NADPH) CYP reductase, aminopyrine and erythromycin demethylase activity.

Cyclophosphamide had no effect *in vivo* on CYP content or erythromycin demethylase activity. Aminopyrine demethylase was elevated on day 4 and NADPH CYP reductase was increased after day 1 with no change at day 4. Seven days after cyclophosphamide administration, all variables decreased. One and 4 days after cyclophosphamide, there were no changes in the activity of CYP 2A1/2, 3A2 and 2C11 isoenzymes; CYP 2B1 was increased on day 1 only. There were no adverse changes in study variables when acetylcysteine was given, but its use was associated with elevated aminopyrine demethylase, CYP 2A1/2, 3A2 and 2C11 activity when compared with saline only. *In vitro* acrolein or some other metabolite capable of interacting with acetylcysteine reduced CYP content, NADPH CYP reductase, aminopyrine demethylase, erythromycin demethylase, CYP 2A1/2, 3A2 and 2C11 activities. This study supported the hypothesis that acetylcysteine acts as a free sulfhydryl donor in cyclophosphamide-induced cytochrome toxicity and may preserve CYP activity.[45]

16. Cyclosporin

The effect of acetylcysteine on ameliorating cyclosporin-induced renal toxicity was studied in rats.[46] Animals were treated with oral cyclosporin 25 or 50 mg/kg alone or in combination with intraperitoneal acetylcysteine in dosages of 10, 20 and 40 mg/kg daily for 3 weeks. After 3 weeks, the rats were sacrificed 24 hours following the last dose. Treatment with acetylcysteine ameliorated several indicators of cyclosporin-induced structural and functional renal damage. Acetylcysteine produced a dose-dependent reduction in BUN and serum creatinine levels. Indices of oxygen-derived free radical damage (lipid peroxidation, conjugated dienes, and glutathione depletion) as well as histopathological changes (tubular vacuolation, tubular necrosis, interstitial fibrosis, and parietal cell hyperplasia) were reduced by acetylcysteine. Treatment with acetylcysteine did not affect blood cyclosporin concentrations. The mechanism of the protective effect is not clear; however, cyclosporin-induced damage may be related to oxidative stress and the antioxidant effects of acetylcysteine may be useful in reducing cyclosporin-induced renal toxicity.

17. Daunorubicin

The efficacy of antineoplastic drugs such as daunorubin and doxorubicin is often limited by the development of irreversible cardiac toxicity which may be caused by the formation of reactive oxygen species. In an experiment in which acetylcysteine was used as an antioxidant to delineate the mechanism of daunorubicin toxicity, pretreatment with acetylcysteine did not prevent daunorubicin-induced cell apoptosis in isolated rat cardiac myocytes.[47]

18. Doxorubicin

To determine the effectiveness of acetylcysteine in the prevention of doxorubicin-associated cardiac toxicity, 24 patients with various tumour types were given doxorubicin 75 mg/m^2 intravenously every 4 weeks alone or pretreated with acetylcysteine 5.5 g/m^2 orally 1 hour prior to doxorubicin administration.[48] A total of 24 drug-treated patients were matched to 30 control patients. Electrocardiograms were obtained prior to treatment and ejection fractions were measured at rest and after exercise. These variables were measured again when the patients received total doses of doxorubicin of 300 to 350 mg/m^2 and 500 to 550 mg/m^2. Patients were excluded if they were hypertensive, had a medical history of heart disease or had received over 600 rad of cardiac irradiation.

Adverse effects observed during the study were primarily attributed to doxorubicin. Diarrhoea was only noted in patients receiving acetylcysteine and an erythematous flare developed at venipuncture sites in 3 patients receiving this agent. Hair loss was marginally observed more often in patients receiving acetylcysteine. Nausea was less severe in patients receiving this compound, but 5 patients refused further treatment with acetylcysteine because of nausea. Many patients were thought to have developed a conditioned nausea response,

whereby the odour of acetylcysteine was associated with doxorubicin-induced nausea. Occasionally vomiting would occur in patients after receiving acetylcysteine, but acetylcysteine was retained at least 1 hour in 96 of 130 cycles (74%).

The rate of progression of cardiac injury was similar in the control and treatment groups and the number of patients who eventually developed congestive heart failure was the same in both groups. The investigators hypothesised that doxorubicin may produce a defect in free radical defences which spans several days and which requires more than a single dose of acetylcysteine for efficacy.

Studies *in vitro* and *in vivo* have demonstrated that a reduced level of glutathione is an important factor in the development of doxorubicin cardiotoxicity[49,50] and cytotoxicity.[51] Furthermore, acetylcysteine administration has been shown to provide protection against this cardiotoxicity and cytotoxicity.[49-51]

19. Alcohol (Ethanol)

Sulfhydryl compounds have been shown to reduce injury to gastric mucosa[52] and acetylcysteine may provide protection via its sulfhydryl component. Other investigators have found that intraperitoneal acetylcysteine actually increased the degree of gastric injury induced by alcohol (ethanol).[53] To resolve these contradictory findings, rats were given 1ml of 100% alcohol orally and assigned to 1 of 4 treatments: acetylcysteine 1.2 g/kg (20%) buffered to pH 7.0 with sodium hydroxide orally, intraperitoneal injection of acetylcysteine 1.2 g/kg (20%) and saline given orally or intraperitoneally.[54] The animals were sacrificed within 5 minutes of alcohol administration.

At necropsy mucosal injury patterns were consistent among the saline-treated animals. Oral pretreatment with acetylcysteine protected the gastric mucosa, but intraperitoneal acetylcysteine promoted injury. The authors claimed the protective effect was due to the ability of acetylcysteine to induce glutathione when given orally. The enhanced injuries when acetylcysteine was given intraperitoneally seemed to be related to irritation of the peritoneum which caused third-space fluid losses resulting in hypovolaemic shock.

When acetylcysteine is neutralised with sodium hydroxide, a high sodium content results and hypertonic saline has been shown to prevent gastric injury.[55] Since the contribution of the hypertonic sodium is an important confounding variable, *in vitro* studies were performed to test this observation.[56] Female rats were given 100% alcohol orally and the stomachs were examined immediately. In several experimental phases rats were given sodium acetylcysteine, sodium acetylserine (not a sulfhydryl donor), sodium acetate and sodium chloride. Gastric protective effects appear to be related to the sodium content of the agent used for protection (sodium acetylcysteine, sodium acetylserine, sodium chloride). The role of acetylcysteine in gastric protection is not apparently related to the presence of a sulfhydryl group and therefore is not mediated by promotion of glutathione production. Neither prostaglandins nor dilution play a role in cytoprotection.

In rats and humans alcohol has been shown to cause hypertension.[57,58] Elevated cytosolic calcium in vascular smooth muscle has been suggested as the mediator of this effect. It is unclear whether acetaldehyde, a metabolic by product of alcohol, plays a role in the elevated cytosolic free calcium seen in patients or rats developing alcohol-induced hypertension. As a consequence of its carboxyl moiety, acetaldehyde is very reactive and can bind to amino and sulfhydryl groups present on many proteins. If acetylcysteine binds acetaldehyde, it might prevent its damaging effects on proteins.

In an *in vivo* study,[59] rats were given alcohol 5% or water orally for 14 weeks. Treatment groups were given oral alcohol 5% plus acetylcysteine 1% for 4 weeks followed by alcohol 5% and acetylcysteine 2% for 10 weeks, or alcohol 5% for 7 weeks followed by acetylcysteine 2% for 7 weeks. Systolic blood pressure and cytosolic calcium were higher ($p < 0.001$) in the alcohol group. Acetylcysteine given concomitantly with alcohol lowered ($p < 0.001$) both the systolic pressure and cytosolic

calcium level. Sequential administration of acetylcysteine for 7 weeks after 7 weeks of alcohol pretreatment also lowered ($p < 0.05$) these variables. Blood acetaldehyde concentration was highest in the group receiving only alcohol, but this increase was attenuated by acetylcysteine.

Acetaldehyde may alter calcium channel homeostasis by binding to the sulfhydryl groups of calcium channel proteins. This binding disrupts the calcium channel leading to increased vascular tension and blood pressure. Glutathione protects against the toxic effects of acetaldehyde, but it becomes depleted with chronic alcohol ingestion. Acetylcysteine may act as a glutathione surrogate and diminish the hypertension and calcium surge that follows chronic alcohol ingestion.

20. Gold

Although gold therapy is helpful in the treatment of rheumatoid arthritis, serious adverse effects may occur which can result in thrombocytopenia, granulocytopenia and pancytopenia in approximately 3% of patients. Numerous approaches have been used to manage these reactions with varying success and acetylcysteine has been proposed as an alternative.

The heavy metal complexing potential of acetylcysteine was explored in an *in vitro* and clinical study by Lorber et al.[60] In the *in vitro* study, acetylcysteine at a final concentration of 6 μg/L was incubated with human serum which was previously incubated with silver nitrate, ^{198}gold sodium thiomalate, or ^{203}mercury neohydrin. Serum protein was removed and the supernatant showed that acetylcysteine apparently complexes gold, mercury, and silver. In the clinical study, the complexing potential of acetylcysteine was investigated in patients receiving gold injections for the treatment of rheumatoid arthritis. Multiple 50mg doses of ^{198}gold sodium thiomalate (approximately one-half of which is gold) were injected to maintain serum gold concentrations between 300 and 500 μg/L for a cumulative dose of 0.5 to 11g. Daily urinary gold excretion was monitored for 7 days. At the end of the sixth day, acetylcysteine 3g was administered intravenously over 6 hours after 50mg of ^{198}gold sodium thiomalate was given to 23 study participants.

Between days 6 and 7, the 17 control patients showed a 15% decline in gold excretion whereas, those receiving acetylcysteine demonstrated a 54% increase ($p < 0.01$) in gold excretion. This difference was unrelated to the cumulative dosage of gold. No adverse effects of acetylcysteine were encountered. The authors also reported successful acetylcysteine treatment of severe bone marrow suppression due to gold therapy in 2 patients. Intravenous acetylcysteine 3 to 6 g/day given for 7 days, increased serum sulfhydryl content (approximately 100%) and urinary gold excretion. Improvement was seen after 3 days with restoration of normal white cell count and platelets within 2 weeks. The authors suggested that acetylcysteine may be an effective treatment for gold intoxication.

Twelve patients, aged 20 to 69 years, who experienced blood dyscrasias as a complication of gold therapy were given acetylcysteine.[61] Thrombocytopenia was found in 4 patients, granulocytopenia in 2, and pancytopenia in 5. One patient had granulocytopenia and thrombocytopenia. The reactions occurred within the first 6 months of treatment with an average total dose of gold of 555mg. Time from the last injection of gold to recognition of the blood dyscrasia ranged from 0 to 35 days and time from the last gold dose to acetylcysteine therapy varied from 1 to 150 days.

A 20% acetylcysteine solution was filtered and diluted to an unspecified concentration for intravenous use. The daily dose of acetylcysteine ranged from 20 to 130 mg/kg. Patients with thrombocytopenia and granulocytopenia recovered. One patient with pancytopenia was given acetylcysteine within 4 days of the last gold injection and achieved near normal cell line levels. Two pancytopenic patients died. Daily urinary gold excretion measured in 9 patients nearly doubled and correlated with a 50% increase in serum sulfhydryl groups. All 8 patients given intravenous acetylcysteine within 20 days of their last gold injection recovered.

The adverse effects of gold therapy may be mediated by an immunological mechanism or via a toxic effect of the metal. Heavy metal toxicity affecting the blood may be mediated by blockage of enzyme reactive sulfhydryl groups. Elimination of the gold is less important than reversing the inhibition of the essential enzyme groups. Acetylcysteine can increase gold excretion,[61] and it may reverse enzyme inhibition through the action of acetylcysteine-donated sulfhydryl groups displacing the gold. Although acetylcysteine may be able to chelate gold and enhance its urinary elimination in animals,[16,60] it may also reverse the enzyme inhibition which occurs in gold-induced haematological toxicity.[62]

21. Lead

Chelation therapy with acetylcysteine was investigated in rats intoxicated with chromium, lead or boron by Banner et al.[15] Urine samples were analysed for urinary toxin, amount, and volume. Acetylcysteine was not significantly different than normal saline in increasing lead excretion, but it was effective for chromium and boric acid. A 2-fold increase ($p < 0.0005$) in urinary lead excretion and a 34% increase ($p < 0.0005$) in faecal lead elimination was noted by Ottenwalder and Simon[16] after male rats were given acetylcysteine 100 mg/kg subsequent to sublethal doses of lead given as $Pb(NO_3)_2$, all by intraperitoneal injection.

An animal study[63] investigated the role of acetylcysteine or succimer in reducing blood lead concentrations and indicators of oxidative stress from lead in red blood cells. Rats were fed lead acetate 2000 ppm in their drinking water for 5 weeks which was replaced with acetylcysteine 800 mg/kg/day or succimer 90 mg/kg/day in their drinking water for 1 week. Blood lead concentrations (μg/dl) were 35 ± 4 in lead-treated control animals and were reduced to 2.5 ± 1 with succimer and 25 ± 3 with acetylcysteine. Treatment with acetylcysteine or succimer reversed lead-induced lipid perioxidation and decreased glutathione content of red blood cells indicating relief from lead-induced oxidative stress.

Intracellular δ-5-aminolevulinic acid is a heme precursor that accumulates in lead poisoning and has been shown to induce free radical generation that may cause damage to proteins and DNA. Chinese hamster ovary cells which were incubated in solutions of δ-5-aminolevulinic acid (1 to 5 mmol/L) and lead acetate 100 μg/L for 4, 12, and 24 hours were treated with acetylcysteine (1 mmol/L) or 2 other agents (superoxide dismutase or the antioxidant enzyme catalase).[64] Oxidative damage to DNA was determined by measuring the increase in a chemical marker. Exposure of the cells to increasing δ-5-aminolevulinic acid concentrations resulted in a linear increase ($p < 0.05$) in oxidative damage over the study time. Treatment with acetylcysteine returned the level of oxidative injury to control levels which suggested a possible protective role.

22. Mercury

Acetylcysteine has been studied as a chelator of mercury. Acetylcysteine was administered orally to mice in their drinking water (10 mg/ml) at the time of or 48 hours after intraperitoneal injection of radiolabelled methylmercury chloride or mercury chloride (inorganic mercury).[65] Urinary or faecal elimination of the inorganic mercury was not affected by acetylcysteine. Nevertheless, acetylcysteine produced significant tissue redistribution and accelerated methylmercury elimination in urine and redistribution from tissues.

The lack of effect on inorganic mercury is consistent with observations with other divalent metals. A study of healthy volunteers investigated the change in plasma and urine concentrations of calcium, magnesium, iron, zinc and copper following oral administration of acetylcysteine 200mg 3 times a day for 2 weeks. No significant changes in the concentration or excretion of these trace metals were observed.[66] A report by Ottenwalder and Simon[16] indicated that acetylcysteine does not increase mercury elimination in male rats following intraperitoneal injections of mercury chloride and acetylcysteine.

Others have found that inorganic mercury levels may be decreased with acetylcysteine treatment. Rats were exposed to mercury vapours (30 mg/m^3) for 1 or 2 hours which is known to produce lung tissue injury by denaturing proteins or inactivating enzymes such as superoxide dismutase.[67] Animals treated with acetylcysteine received daily intraperitoneal injections of 300mg for 6 days following the mercury exposure. In the animals exposed for 2 hours to mercury vapours, acetylcysteine treatment increased survival time and rate. The changes in lung superoxide dismutase activity were not consistent with treatment or duration of exposure. Mercury concentrations were decreased in blood and lung following acetylcysteine administration.

The action of acetylcysteine to enhance the elimination of methylmercury may be selective for a particular form of mercury, the route of mercury exposure or other unknown factors. A study in rats found that the magnitude and site of uptake of mercuric ions in the kidney may be affected by acetylcysteine.[68,69]

23. Methylmercury

Organic mercury can be teratogenic and embryotoxic and is a common environmental pollutant.[70] There are contradictory results of the effect of acetylcysteine on the development of congenital malformations following exposure to methylmercury. Acetylcysteine was given intravenously and orally to pregnant mice pretreated with methylmercury chloride 25 mg/kg or a long term daily dose of 3 or 6 mg/kg during organogenesis.[71] Palatoschisis was partially blocked and appeared to be related to the dose of acetylcysteine. Embryotoxicity induced by long term maternal exposure was completely prevented by multidose acetylcysteine. Acetylcysteine showed a protective effect given at or after the time of methylmercury chloride administration.

Endo and Watanabe[28] investigated the protective effects of acetylcysteine on the teratogenicity of several heavy metals in mice. Acetylcysteine was contained in the diets of the mice for 4 weeks before and throughout gestation. A single intraperitoneal injection of methylmercury chloride (8 mg/kg), chromium trioxide (15 mg/kg) and cadmium chloride (2 mg/kg) was given on the ninth day of gestation. On the seventeenth day of gestation, the animals were sacrificed and the fetuses examined for malformations. The incidence of congenital malformations with acetylcysteine treatment was 2 to 3 times higher than control values. For methylmercury, malformations occurred in 24.5% of animals treated with acetylcysteine ($p < 0.025$) compared with a rate of 13.2% for controls. The underlying mechanism for this observed increase is unknown.

Lower plasma and placental concentrations of methylmercury have been observed following acetylcysteine administration in animals.[72] Another study supported the general ability of acetylcysteine to lower methylmercury concentrations.[65] Acetylcysteine was administered orally to mice in their drinking water (10 mg/ml) at the time of, or 48 hours after intraperitoneal injection of radiolabelled methylmercury chloride or mercury chloride (inorganic mercury). Mice that received acetylcysteine excreted 87% and 47 to 54% of the methylmercury dose compared with 4 to 10% of the control group when acetylcysteine was given immediately or 48 hours after methylmercury administration, respectively. Acetylcysteine also mobilised methylmercury from brain, kidney and liver tissue. No change in tissue levels of glutathione was observed in the treated versus nontreated animals. Acetylcysteine accelerated methylmercury elimination in urine and redistribution from tissues, however, clearance of inorganic mercury was not changed by acetylcysteine in this animal study.

A 20-year-old man ingested haloperidol, benzatropine and a fungicide containing methylmercury for which he received gastric decontamination with gastric lavage and activated charcoal within 2 hours of ingestion.[73] On the basis of high blood methylmercury concentrations (1930 and 1007 μg/L at 2 and 24 hours after ingestion, respectively), haemodialysis was begun with the infusion

of acetylcysteine into the blood as it entered the dialyser to achieve a concentration of 1 mmol/L. Urinary organic mercury elimination rate increased nearly 40-fold during and 84-fold after acetylcysteine dialysis compared with elimination during initial treatment with pencillamine.

24. Nitrite

Since acetylcysteine may function as an antioxidant and methaemoglobinaemia results from the oxidation of iron in haemoglobin from the ferrous to the ferric form, acetylcysteine may be able to reduce drug-induced methaemoglobinaemia.

Blood samples from 5 healthy volunteers were obtained and incubated with phosphate-buffered saline and sodium nitrite, or acetylcysteine and sodium nitrite.[74] The samples were tested for methaemoglobin at 0, 30, 90, 150, 210, 270 and 330 minutes. The control specimens had methaemoglobin levels under 0.3%. Peak methaemoglobin levels occurred at 90 minutes and were 65.1% of control for the phosphate-buffered saline and sodium nitrite samples, and 62.7% for the acetylcysteine and sodium nitrite samples. From 90 to 330 minutes methaemoglobin declined at a rate of 10.7 ± 1.0% per hour for the acetylcysteine and sodium nitrite samples, whereas it declined at 2.9 ± 2.3% per hour ($p = 0.002$) for phosphate-buffered saline and sodium nitrite. Acetylcysteine appears to enhance the reduction of methaemoglobin *in vitro*.

Acetylcysteine may have several mechanisms of action, which include direct reduction of the heme molecule, metabolic shunting of the inducing agent into pathways that do not produce an oxidative agent, and direct reduction of the oxidising agent. One potential advantage of acetylcysteine over the typical treatment of methaemoglobinaemia, that is methylthioninium chloride (methylene blue) is whether acetylcysteine acts in patients with glucose-6-phosphate dehydrogenase deficiency. Patients deficient in this enzyme may not have the requisite NADPH for methylthioninium chloride action, thereby rendering this agent ineffective.[75] In an *in vitro* model of glucose-6-phosphate dehydrogenase deficiency, acetylcysteine was shown to reduce methaemoglobin to haemoglobin.[76] Acetylcysteine may enter cells directly from plasma and can reduce the methaemoglobin directly or react with cytosolic glutamate and glycine to form glutathione, which can reduce the methaemoglobin.

In a trial with healthy volunteers, intravenous acetylcysteine 150 mg/kg produced no improvement in subtoxic methaemoglobinaemia compared with a control infusion of 5% dextrose in water within 130 minutes.[77] Further studies are needed to determine whether acetylcysteine can replace or supplement methylthioninium chloride in the treatment of methaemoglobinaemia.

25. Nitrofurantoin

Acetylcysteine was tested with 7 other agents in isolated perfused rat livers to determine a potential treatment strategy for nitrofurantoin-induced hepatotoxicity. Liver damage is thought to be caused by a nitrofurantoin superoxide radical that is normally reduced by glutathione. When glutathione is depleted beyond a critical level, protein thiols become vulnerable to attack by nitrofurantoin-induced reactive oxygen species, potentially causing cell death. In an *in vitro* study, acetylcysteine was hypothesised to protect the liver by maintaining tissue levels of glutathione.[78] Rat livers were perfused with blank perfusate or acetylcysteine, then perfused with nitrofurantoin. The treatment group livers were co-perfused with acetylcysteine 0.25 mmol/L. Tissue levels of glutathione and protein thiols were used as markers of progression to toxicity, and lactate dehydrogenase leakage into the perfusate was used as a marker of irreversible cell death. Acetylcysteine was found to delay, but not significantly prevent, hepatotoxicity. There was a diminished decline in glutathione tissue levels, but gradual deterioration of the liver continued. Infusion of acetylcysteine 0.1 mmol/L was also ineffective with acetylcysteine 0.5 mmol/L characterised as being toxic, but details of the toxicity were not described.

26. Paracetamol (Acetaminophen)

The problem of paracetamol poisoning has been described in adults[79,80] and children.[81,82] Moreover, the role of acetylcysteine in the therapy of acute paracetamol poisoning is widely accepted worldwide.[83-85] Since the first reports of paracetamol-induced hepatotoxicity were published in 1966,[86,87] significant advances have been made and applied to patient care. These include: elucidation of a putative mechanism of hepatotoxicity that involves a reactive metabolite, acetyl-*p*-benzoquinone imine, formed by the CYP oxidase system, particularly CYP2E1 and 3A4, following intracellular depletion of glutathione,[88-91] demonstration of the efficacy of an antidote, acetylcysteine, to alter the evolution of hepatotoxicity,[92,93] development of clinical treatment nomograms based on serum paracetamol concentrations and time after acute ingestion for the assessment of risk for hepatotoxicity and for initiation of therapy with acetylcysteine,[94-96] characterisation of the effectiveness of acetylcysteine in a large series of patients poisoned with paracetamol and ostensibly reducing mortality and morbidity when administered optimally within 10 hours of the ingestion of paracetamol,[94-97] recognition that late administration of acetylcysteine may minimise hepatorenal toxicity and associated complications by alternative mechanisms,[97-100] and identification of high-risk patients with predisposing conditions, e.g. poor nutritional status, use of enzyme-inducing drugs, and long term abuse of alcohol, who may require special assessment and more aggressive treatment.[82,101,102]

Despite these advances in a relatively short period of time, several major issues such as the mechanism of action of acetylcysteine, the value of acetylcysteine for delayed treatment of or chronic toxicity from paracetamol overdosage, and the optimal regimen for acetylcysteine administration are still under investigation.

The mechanism of action of acetylcysteine in the early phases (pre-injury) of paracetamol poisoning may involve several independent and complementary actions. Acetylcysteine can produce cysteine, which is a metabolic precursor of glutathione that detoxifies acetyl-*p*-benzoquinone imine when glutathione stores are adequate.[103,104] It may also act as a surrogate for glutathione by virtue of its sulfhydryl content (fig. 1).[105] Furthermore, acetylcysteine may increase intracellular sulfate, which serves as a substrate for the sulfate conjugation of paracetamol to nontoxic metabolites.[92,106] There is evidence that paracetamol overdose also depletes cellular sulfate stores which presumably leads to increased formation of acetyl-*p*-benzoquinone imine by limiting alternative metabolic pathways.[107,108] Lastly, acetylcysteine may promote chemical reduction of acetyl-*p*-benzoquinone imine back to paracetamol instead of proceeding to react with cellular constituents.[109] All of these pre-injury actions minimise formation of the toxic metabolite, acetyl-*p*-benzoquinone imine, and thereby decrease cellular injury.

Although acetylcysteine optimally prevents hepatotoxicity when initiated within 10 hours of an acute ingestion,[96,110] it may prove beneficial in some patients after hepatic injury has already occurred (post injury). Several clinical studies of paracetamol poisonings, albeit with small patient numbers, suggested that acetylcysteine use in patients with fulminant hepatic failure or patients starting acetylcysteine treatment 15 hours after paracetamol ingestion may improve clinically (i.e. improvement in cerebral oedema or circulatory collapse) and have better outcomes than similar patients not treated with acetylcysteine.[95-97,99,100,110]

In patients with liver injury unrelated to paracetamol toxicity, general improvement in hepatic and renal function have been demonstrated following acetylcysteine use.[111] Furthermore, acetylcysteine may provide protection as an antioxidant to reduce oxygen free radicals formed by hepatic necrosis.[112] It may also restore intracellular systems to proteolyse arylated proteins that may result from interaction with acetyl-*p*-benzoquinone imine.[113] After cellular injury acetylcysteine may improve the microcirculation to injured tissue thereby improving the function of the affected organ.[114] The improved microcirculation may result from stimu-

Table II. Acetylcysteine regimens for treatment of acute paracetamol (acetaminophen) poisoning

Regimen	Loading dose	Maintenance dose	Total dose
20h IV	150 mg/kg in 200ml D5W over 15 min	After loading dose infusion: 50 mg/kg in 500ml D5W over 4h, then 100 mg/kg in 1L of D5W over 16h	300 mg/kg
52h IV	140 mg/kg as 3% solution in D5W over 1h	4h after start of loading dose: 70 mg/kg as 3% solution in D5W over 1h for 12 doses	980 mg/kg
72h oral	140 mg/kg as 5% solution	4h after start of loading dose: 70 mg/kg as 5% solution for 17 doses	1330 mg/kg

D5W = 5% dextrose in water for injection; **h** = hours; **IV** = intravenous; **min** = minutes.

lation of local nitric oxide production which mediates vasorelaxation.[115]

These post-injury actions suggest that administration of acetylcysteine after the occurrence of hepatorenal injury may prove beneficial in some patients. Some investigators have recommended that acetylcysteine therapy be continued until the international normalised ratio is below 2 and encephalopathy is resolved.[79] Better definitions of a 'late acetylcysteine regimen' and patient selection criteria are needed.

The toxicity of long term supertherapeutic doses of paracetamol is not well defined, but hepatotoxicity has been reported.[95,96,116] Although the value of acetylcysteine in these situations is often unknown because of the delayed recognition of a patient's risk for toxicity, the post-injury actions of acetylcysteine may also prove to be beneficial in some patients.

Several empiric dosage regimens for the treatment of acute paracetamol poisoning are currently in use (table II).[95,96,116] Outside of the US, one of the intravenous regimens is typically employed.[84,85,95,102,117] An oral regimen has been used in the US since the mid-1970s as an investigational regimen and as a US Food and Drug Administration–approved indication since 1985.[94,96] Since only an oral and inhalational formulation is available in the US, it has been administered orally via a gastric tube, or filtered and given intravenously.[118]

Most clinical studies of paracetamol toxicity define a negative outcome measurement of hepatotoxicity as a serum transaminase level (i.e. ALT, AST) exceeding 1000 U/L.[93,95,96,110] A comparison (fig. 2) of the regimens with this measurement indicates that patients given the 20-hour regimen have greater prevalence of hepatotoxicity when therapy is delayed beyond 10 hours of the paracetamol overdose.[110] Several of the adverse effects of acetylcysteine therapy are associated with the route of administration. The intravenous regimens are associated with anaphylactoid reactions such as flushing, urticaria, angioedema, and bronchospasm in an apparently small number of patients.[95,98,110,118-120] A clinical guideline[120] to manage these reactions has been tested and includes using diphenhydramine and slowing the infusion rate.[119,120] The oral regimen may produce rashes in hypersensitive individuals and diarrhoea, but nausea and vomiting are common problems because of the foul odour and taste of acetylcysteine.[96,120] Vomiting may necessitate repeating the dose of acetylcysteine and the concurrent or prophylactic use of metoclopramide.[121] A meta-analysis of the clinical outcomes of paracetamol indicates that the intravenous route of acetylcysteine administration may be preferable for most patients.[122] Acetylcysteine can effectively treat paracetamol poisoning, but no randomised, clinical study has compared the route and duration of therapy despite some apparent advantages of each.

27. Pennyroyal Oil

Pennyroyal oil, a volatile oil extracted from the leaves of the *Mentha pulegium* and *Hedeoma pulegioides*, is promoted as an aid to regulate menstruation and as an abortifacient, and its use has been associated with hepatotoxicity. Buechel et al.[123] published a case of a 20-year-old woman who had ingested pennyroyal tea 3 times daily during the 2 weeks intermittently prior to her admission. After the first week the patient took a gelatin capsule packed with pennyroyal leaves which re-

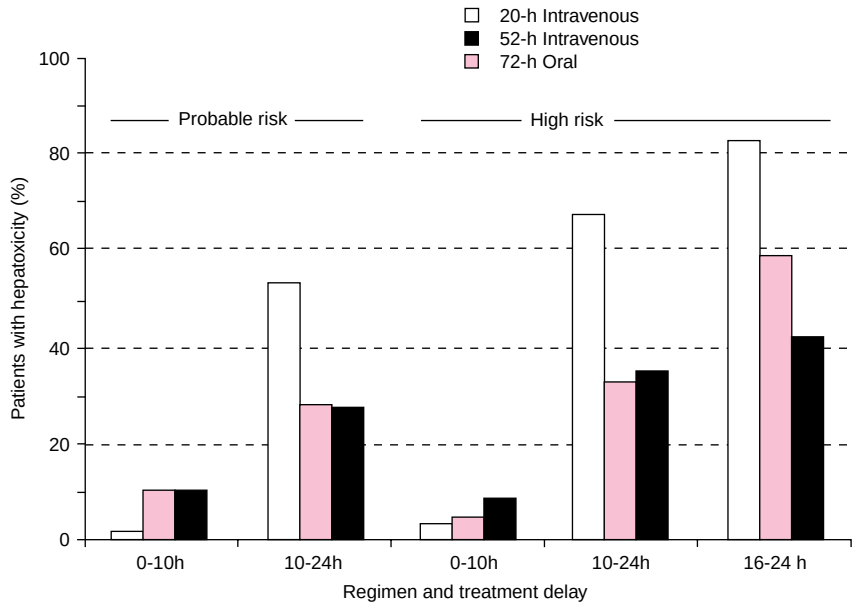

Fig. 2. Comparison of paracetamol (acetaminophen)-induced hepatotoxicity in patients treated with different acetylcysteine regimens initiated at different intervals after paracetamol overdose. Risk categorisation was based on serum paracetamol concentration after time of ingestion as reported in Smilkstein et al.[110]

sulted in menstrual spotting later that day. Two days prior to admission the patient took 2 more pennyroyal-filled capsules and on the day of admission swallowed 15ml of pennyroyal oil. Within 2 hours of the capsule and oil ingestion, the patient felt 'high,' vomited once and passed out. Two hours and 15 minutes later upon arrival to the emergency department the patient was lethargic and responded only to painful stimuli.

After gastric decontamination with gastric lavage, activated charcoal and a cathartic, acetylcysteine 140 mg/kg followed by 70 mg/kg every 4 hours for 17 doses was given by nasogastric tube. Within 1 hour of the treatment the patient became more alert. The patient was discharged 96 hours after the last ingestion. An evaluation 2 weeks later revealed that laboratory studies remained within normal limits. The authors postulated that acetylcysteine may be beneficial because of its ability to act as a glutathione surrogate and bind toxic constituents or metabolites of pennyroyal.

A series of pennyroyal ingestions reported in the literature and 4 cases reported to a poison centre were reviewed.[124] Two cases in the series received acetylcysteine, with one of the cases previously reported by Beuchel et al.[123] The other case involved a 22-month-old female infant who ingested an unknown amount of pennyroyal oil from a 30ml bottle. The patient arrived in the emergency department within 15 minutes of the ingestion. Besides a blood pressure of 104/55mm Hg, respirations of 30 beats/min and temperature of 36.3°C, the patient's physical examination was normal. Gastric lavage, activated charcoal and sorbital were administered within 30 minutes of the ingestion. Immediately thereafter, acetylcysteine 190 mg/kg was given orally followed by 70 mg/kg every 4 hours for 17 doses. The patient's course was unremarkable and she was soon sent home. Three serum samples drawn during the child's hospitalisation were positive for menthofuran, a toxic metabolite of pulegone that is found in pennyroyal. Menthofuran is produced by CYP and appears to be a hepato-

toxin by binding to intrahepatic cellular proteins. Pulegone also forms metabolites that deplete glutathione, but menthofuran modestly depletes glutathione.[124] Acetylcysteine may protect hepatic cells from pennyroyal toxicity and may be effective in the later stages of cell injury.

28. Phenytoin

The use of acetylcysteine to treat drug-induced hypersensitivity syndrome and toxic epidermal necrolysis was described in 2 cases.[125] A 47-year-old woman with temporal lobe glioblastoma multiforme was diagnosed with a hypersensitivity reaction to phenytoin (fever, rash, conjunctivitis, enanthem, strawberry tongue, and hepatosplenomegaly) 1 month after initiation of phenytoin 100mg 3 times a day. Her therapy included dexamethasone, famotidine, cisplatin, carmustine, and radiation. Infection was excluded. Phenytoin therapy was stopped and valproic acid (sodium valproate) substituted. The patient also received 2g of acetylcysteine every 6 hours after which she immediately improved clinically. The authors suggested that acetylcysteine reacts with phenytoin metabolites and replenishes intracellular cysteine levels needed for the production of the antioxidant glutathione. Furthermore, *in vitro* acetylcysteine has been found to inhibit the production of tumour necrosis factor-α and interleukin-1β implicated in the pathogenesis of toxic epidermal necrolysis and possibly other toxic drug reactions. It was impossible to determine whether the improvement could have occurred spontaneously in this patient.

In the other case,[125] a patient who developed phenytoin-induced toxic epidermal necrolysis was successfully treated with intravenous acetylcysteine, *S*-adenosyl-*L*-methionine (a glutathione precursor), and pentoxifylline. Improvement was attributed to pentoxifylline, although it is possible that acetylcysteine and *S*-adenosyl-*L*-methionine were more therapeutically important than originally thought. The authors speculated that acetylcysteine might be effective in treating hypersensitivity syndrome and toxic epidermal necrolysis by replenishing cells with antioxidant capacity and inhibiting cytokine-mediated immune reactions.

A study in rodents suggested that the readily oxidised disulfide form of acetylcysteine can act as a potent immunomodulator which can enhance or reduce contact sensitivity or delayed-type hypersensitivity reactions depending upon the experimental conditions.[126]

29. Phosgene

Phosgene-induced lung injury is thought to result from endogenous production of reactive oxygen metabolites after levels exceed inactivation by glutathione. Acetylcysteine was investigated for its possible protective effects on pulmonary oedema formation in isolated perfused rabbit lungs after phosgene exposure.[127] Rabbits in the control group were exposed to a cumulative dosage of 1500 ppm/min of phosgene, which causes reproducible dose-related lung injury. In the treatment group, a total of 130mg of acetylcysteine (40 mg/kg) was given as an intratracheal bolus at 45 to 60 minutes post-phosgene exposure. At the end of the experiment (150 min), intratracheal acetylcysteine significantly lowered pulmonary artery pressure ($p < 0.001$), lung weight gain ($p < 0.05$), and arachidonic acid metabolites ($p < 0.01$) which may be markers of pulmonary injury. The measure of lipid peroxidation was not significantly different than that in the untreated controls, but the glutathione redox state was preserved at normal levels in the acetylcysteine group.

The effectiveness of acetylcysteine was attributed to its ability to maintain the glutathione redox state, possible direct antioxidant effects of acetylcysteine, and intratracheal administration of acetylcysteine that delivered the drug directly to the alveolar surface, which is the likely site of injury and site of action of acetylcysteine.

30. Ricin

Ricin, a cytotoxic plant protein, affects the 28S RNA of the 60S ribosomal subunit to inhibit protein synthesis which produces apoptotic death in several cell lines. Oxidative stress has also been

postulated to be a common mediator of apoptosis. Human myeloid leukaemia cells were used to evaluate the ability of acetylcysteine to affect ricin-induced cytotoxicity and intracellular glutathione levels.[128] Cells were treated with or without acetylcysteine (5 to 20 mmol/L) for 1 hour then incubated with varying ricin levels (0.001 to 10 μg/L) in the presence or absence of acetylcysteine. Treatment with acetylcysteine inhibited ricin-induced cytotoxicity and DNA fragmentation, but it had no effect on the protein synthesis inhibitory activity of ricin. Cellular content of glutathione and other nonprotein thiols were found to decrease after ricin treatment which was consistent with the appearance of apoptotic cells. Acetylcysteine prevented glutathione depletion. Glutathione biosynthesis inhibitors were also tested and they decreased cellular glutathione levels, but ricin-induced apoptosis was not produced under these conditions.

Acetylcysteine appeared to be effective in protecting these cells from apoptosis. The investigators proposed that inhibition of glutathione depletion is only one of the mechanisms by which acetylcysteine is able to protect cells from the apoptotic effects of ricin.

31. Sulfasalazine

A 37-year-old woman with spondylarthropathy developed a life-threatening adverse reaction to sulfasalazine which was thought to be reversed by sulfasalazine withdrawal and intravenous acetylcysteine.[129] Three weeks after starting sulfasalazine (daily doses up to 1.5g), the patient developed fatigue, fever, and erythematous cutaneous lesions at which time the sulfasalazine was stopped. Her clinical condition did not improve and the patient was hospitalised 2 days later. Infection was ruled out and she was given paracetamol 0.5 to 2.0g daily for 5 days for fever of unknown origin. By the tenth day of hospitalisation, the patient had a diffuse skin rash, high grade fever, a mononucleosis-like syndrome, disseminated intravascular coagulation, and hepatocellular necrosis with portal inflammation. Paracetamol was stopped and intravenous acetylcysteine was started with the patient receiving a total dose of 24g over 3 days. Concurrently, the patient improved dramatically with complete defervescence and progressive normalisation of hepatic and coagulation tests. She left the hospital on the seventeenth day and a follow-up evaluation 2 weeks later showed complete resolution of clinical symptoms and normalisation of laboratory tests.

Although the pathogenesis of the adverse reaction is unclear, an immune-mediated response induced by reactive sulfasalazine metabolites is hypothesised. These destructive metabolites are thought to be partially detoxified by sulfhydryl compounds such as glutathione; acetylcysteine may replenish glutathione stores. *In vitro*, acetylcysteine has also been reported to reverse sulfonamide-related adverse effects.[130] Coincidental spontaneous resolution and the contribution of paracetamol cannot be ruled out in this case, but excessive doses of paracetamol were not used. No adverse effects of acetylcysteine were noted.

32. Thallium

Since thallium binds sulfhydryl groups, the use of acetylcysteine was considered to be a potential antidote for thallium poisoning. Henderson et al.[13] studied the efficacy of acetylcysteine in the treatment of copper, sodium arsenite, thallium and cadmium poisoning compared with chelating agents. Intraperitoneal doses of acetylcysteine 200 mg/kg or dimercaprol 10 mg/kg were given to groups of mice, 30 to 60 minutes after administration of the heavy metal. Thallium acetate was administered subcutaneously at the LD_{50} of mice. In the thallium group, dimercaprol or acetylcysteine were not effective in reducing mortality.

The efficacy of Prussian blue and acetylcysteine were compared in female mice that were injected subcutaneously with thallium acetate 70 mg/kg (LD_{90}) or 85 mg/kg ($>LD_{100}$).[131] For each of these 2 doses, 4 treatment groups were used: control, Prussian blue, acetylcysteine, and Prussian blue with acetylcysteine. Survival at 120 hours was the outcome measurement. The mice were treated every 8 hours for 3 days with the first treatment given

immediately after injection with thallium. Prussian blue 50 mg/kg was given by oral gavage and acetylcysteine 200 mg/kg was given by intraperitoneal injection. For thallium doses of 70 mg/kg survival at 120 hours was 10% for controls, 50% for Prussian blue ($p = 0.014$), 35% for acetylcysteine ($p = 0.13$), and 60% for Prussian blue plus acetylcysteine ($p = 0.002$). Increasing the acetylcysteine dose to 1 g/kg did not improve survival. At the higher dose of thallium, there was no change in survival with any treatment. Overall, adding acetylcysteine to Prussian blue did not improve survival.

In a study of female rats that were injected with thallium 2 mg/g measurements of nephrotoxicity and thallium levels in renal cortex and medulla were determined.[132] In renal tissues glutathione levels were not decreased by thallium and the increase of glutathione level by acetylcysteine pretreatment did not influence thallium nephrotoxicity.

33. Zidovudine

The role of zinc and acetylcysteine in reversing zidovudine-induced bone marrow toxicity was tested by exposing murine bone marrow cells to 5 concentrations of zidovudine (0.1, 1, 5, 10 and 50 μmol/L) either alone (control) or in the presence of zinc acetate or acetylcysteine.[133] The cell survival rate was determined by the colony-forming assay of erythroid and granulocytic-macrocytic lineage. A concentration-dependent inhibition of colony formation was produced with zidovudine causing an inhibitory concentration for 50% of cells (IC_{50}) of 3.0 μmol/L in the colony-forming assay of erythroid and 4.3 μmol/L in the colony-forming assay of erythroid and granulocytic-macrocytic lineage. Simultaneous addition of zinc acetate 100 μmol/L or acetylcysteine 100 μmol/L protected progenitor cells from zidovudine-induced toxicity at several concentrations of zidovudine for both agents. Zinc acetate increased the IC_{50} value approximately 3-fold (from 3.0 to 9.5 μmol/L) in the colony-forming assay of erythroid, and 7-fold (from 4.3 to 28.8 μmol/L) in the colony-forming assay of erythroid and granulocytic-macrocytic lineage. Acetylcysteine increased the IC_{50} values by 2- and 4-fold to 6.6 and 15.4 μmol/L, respectively.

The mechanism of zidovudine toxicity is not well understood, but it is possibly due to the formation of a toxic azido radical of zidovudine. A protective effect may be produced by scavenging the toxic radical by the sulfhydryls of acetylcysteine, or zinc-induced biosynthesis of metallothionein, a protein rich in cysteine residues. In this study, murine bone marrow cells incubated in zinc acetate showed a 42% increase in metallothionein levels. Although there is no direct evidence that acetylcysteine and metallothionein are responsible for inactivating the toxic metabolites of zidovudine, these cell culture studies indicate that zinc or acetylcysteine may be beneficial in reducing zidovudine-induced myelosuppression.

34. Conclusion

Of the 45 potential uses of acetylcysteine that have been studied for the treatment of poisonings or adverse drug reactions (table III), 14 of the toxic effects have little support for its use, while promising results have been demonstrated for 27 toxicities. Currently, treatment of acute paracetamol poisoning is the only widely accepted clinical indication for acetylcysteine as treatment for poisoning or adverse drug reactions. With other applications it is often difficult to determine the benefit of therapy with acetylcysteine because of the nature of the toxicity being treated, use of other therapy, the presence of comorbid conditions, and the small number of patients studied. Nevertheless, the diverse nature of the investigations summarised in this review suggests that there is considerable interest in acetylcysteine as a research tool and pharmacological agent.[134]

With increased understanding of the mechanisms of action of acetylcysteine, the pathogenesis of adverse drug reactions, the pathophysiology of drug and chemical poisoning, the interaction of toxins with mechanisms of cellular apoptosis (programmed cell death), and the body's response to cellular injury,[1-5,134,135] the role of acetylcysteine

Table III. Summary of evidence for acetylcysteine use in cases of poisoning and adverse drug reactions by type of investigation[a]

Agent	Toxicity	Nature of evidence			
		in vitro	*in vivo*	case reports	clinical studies
α-Amanitin	Hepatic		–	U	
Arecoline	Mutagenesis	+			
Arsenic	General		+	+	
Boric acid	Excess concentrations		+		
Cadmium	Cytotoxicity	+			
Cadmium	Lethality		–		
Cadmium	Hepatorenal		+		
Cadmium	Excess concentrations		+		
Carbon monoxide	Neurological			U	
Carbon tetrachloride	Hepatorenal		+	+	
Caustic alkali	Stricture formation		+		
Caustic alkali	Lethality		–		
Chromium	Excess concentrations		+		
Chromium	Teratogenicity		–		
Chromium	Hepatorenal			U	
Cisplatin	Renal		+	U	
Clozapine	Agranulocytosis	+			
Copper	Lethality		+		
Cotrimoxazole (trimethoprim-sulfamoxazole)	Hypersensitivity				–
Cyanide	DNA fragmentation	+			
Cyclophosphamide	Enzyme inhibition		+		
Cyclosporin	Renal		+		
Daunorubicin	Cytotoxicity	–			
Doxorubicin	Cardiac			–	
Doxorubicin	Cytotoxicity	+			
Alcohol (ethanol)	Gastritis		U		
Alcohol (ethanol)	Hypertension		+		
Gold	Haematologic			+	
Gold	Excess concentrations	+		+	
Lead	Cytotoxicity	+			
Lead	Excess concentrations		±		
Mercury	Excess concentrations		±		
Methylmercury	Excess concentrations		+	U	
Methylmercury	Embryotoxicity		±		
Nitrite	Methaemoglobinaemia	+			–
Nitrofurantoin	Hepatic	–			
Paracetamol (acetaminophen)	Hepatic	+	+	+	+
Pennyroyal oil	Hepatic			+	
Phenytoin	Hypersensitivity			U	
Phosgene	Pulmonary		+		
Ricin	Cytotoxicity	+			
Sulfasalazine	General			U	
Thallium	Lethality		–		
Thallium	Renal		–		
Zidovudine	Haematopoietic	+			

a *In vivo* studies do not include those with human participants. Presence or absence of a beneficial effect does not necessarily imply therapeutic value nor advocacy for use in humans.

+ = beneficial effect was observed; **–** = no benefit was determined; ± = contradictory or mixed evidence of benefit; **U** = benefit was undeterminable.

will become better defined than its current empirical use in many clinical situations.

References

1. Halliwell B. Introduction: free radicals and human disease – trick or treat? In: Thomas CE, Balaraman K, editors. Oxygen radicals and the disease process. Amsterdam: Harwood Academic Publishers, 1997: 1-14
2. Bast A, Haenen RMM, Doelman CJA. Oxidants and antioxidants: state of the art. Am J Med 1991: 91 Suppl. 3c: 2-13
3. Ruffman R, Wendel A. GSH rescue by N-acetylcysteine. Klin Wochenschr 1991; 69: 857-62
4. Flanagan RJ. The role of acetylcysteine in clinical toxicology. Med Toxicol 1987; 2: 93-104
5. Flanagan RJ, Meredith TJ. Use of *N*-acetylcysteine in clinical toxicology. Am J Med 1991: 91 Suppl. 3c: 131-9
6. Coccini T, Randine MG, Baiardi P, et al. Hepatic glutathione depletion induced by α-amanitin poisoning: study in laboratory animals [abstract]. 19th International Congress of the European Association of Poisons Centres and Clinical Toxicologists: 1999 Jun 22-25; Dublin
7. Locatelli C, Butera R, Gandini C, et al. Intravenous N-acetyl-L-cysteine in the treatment of amanita phalloides poisoning [abstract]. 19th International Congress of the European Association of Poisons Centres and Clinical Toxicologists: 1999 Jun 22-25; Dublin
8. Schneider SM, Vanscoy GJ, Michelson EA. Failure of N-acetylcysteine to reduce alpha amanitin toxicity [abstract]. Vet Human Toxicol 1989; 31: 359
9. Nelson BS, Heischober B. Betel nut: a common drug used by naturalized citizens from India, Far East Asia, and the South Pacific Islands. Ann Emerg Med 1999; 34: 238-43
10. Chatterjee A, Deb S. Genotoxic effect of arecoline given either by the peritoneal or oral route in murine bone marrow cells and the influence of N-acetylcysteine. Cancer Lett 1999; 139: 23-31
11. Oikawa S, Yamada K, Yamashita N, et al. N-acetylcysteine, a cancer chemopreventive agent, causes oxidative damage to cellular and isolated DNA. Carcinogenesis 1999; 20: 1485-90
12. Shum S, Skarbovig J, Habersang R. Acute lethal arsenite poisoning in mice: effect of treatment with n-acetylcysteine, d-penicillamine and dimercaprol on survival time. Vet Human Toxicol 1981; 23 Suppl. 1: 39-42
13. Henderson P, Hale TW, Shum S. N-acetylcysteine therapy of acute heavy metal poisoning in mice. Vet Human Toxicol 1985; 27: 522-5
14. Martin DS, Willis SE, Cline DM. N-acetylcysteine in the treatment of human arsenic poisoning. J Am Board Fam Pract 1990; 3: 293-5
15. Banner Jr W, Koch M, Capin DM, et al. Experimental chelation therapy in chromium, lead, and boron intoxication with N-acetylcysteine and other compounds. Toxicol Appl Pharmacol 1986; 83: 142-7
16. Ottenwalder H, Simon P. Differential effect of N-acetylcysteine on excretion of the metals Hg, Cd, Pb, and Au [letter]. Arch Toxicol 1987; 60: 401-2
17. Wispriyono B, Matsuoka M, Igisu H, et al. Protection from cadmium cytotoxicity by N-acetylcysteine in LLC-PK1 cells. J Pharmacol Exp Ther 1998; 287: 344-51
18. Shaikh ZA, Vu TT, Zaman K. Oxidative stress as a mechanism of chronic cadmium-induced hepatotoxicity and renal toxicity and protection by antioxidants. Toxicol Appl Pharmacol. 1999; 154: 256-63
19. Shaikh ZA, Zaman K, Tang W, et al. Treatment of chronic cadmium nephrotoxicity by N-acetyl cysteine. Toxicol Lett 1999; 104 (1-2): 137-42
20. Howard RJMW, Blake DR, Pall H, et al. Allopurinol/N-acetylcysteine for carbon monoxide poisoning [letter]. Lancet 1987; II: 628-9
21. Fleming LE, Hodgson M, Ambre J, et al. Carbon tetrachloride toxicity: Agency for Toxic Substances and Disease Registry. Am Fam Physician 1992; 46: 1199-207
22. Valles EG, de Castro CR, Castro JA. N-acetylcysteine is an early but also a late preventive agent against carbon tetrachloride-induced liver necrosis. Toxicol Lett 1994; 71: 87-95
23. Ruprah M, Mant TG, Flanagan RJ. Acute carbon tetrachloride poisoning in 19 patients: implications for diagnosis and treatment. Lancet 1985; I: 1027-9
24. Mathieson PW, Williams G, MacSweeney JE. Survival after massive ingestion of carbon tetrachloride treated by intravenous infusion of acetylcysteine. Hum Toxicol 1985; 4: 627-31
25. Liu AJ, Richardson MA. Effects of N-acetylcysteine on experimentally induced esophageal lye injury. Ann Otol Rhinol Laryngol 1985; 94: 477-82
26. Brown SI, Hook CW. Treatment of corneal destruction with collagenase inhibitors. Trans Am Acad Ophthalmol Otolaryngol 1971: 75: 1199-207
27. Vasallo S, Howland MA. Severe dichromate poisoning: survival after therapy with intravenous N-acetylcysteine and hemodialysis [abstract]. Vet Human Toxicol 1988; 30: 347
28. Endo A, Watanabe T. Analysis of protective activity of N-acetylcysteine against teratogenicity of heavy metals. Reprod Toxicol 1988; 2: 141-4
29. Appenroth D, Winnefeld K, Heinz S, et al. Beneficial effect of acetylcysteine on cisplatin nephrotoxicity in rats. J Appl Toxicol 1993; 13: 189-98
30. Sugihara K, Nakano S, Gemba M. Effect of cisplatin on in vitro production of lipid peroxides in rat kidney cortex. Jpn J Pharmacol 1987; 44: 71-6
31. Miyajima A, Nakashima J, Yoshioka K, et al. Role of reactive oxygen species in cis-dichlorodiammineplatinum-induced cytotoxicity on bladder cancer cells. Br J Cancer 1997; 76: 206-10
32. Miyajima A, Nakashima J, Tachibana M, et al. N-acetylcysteine modifies cis-dichlorodiammineplatinum-induced effects in bladder cancer cells. Jpn J Cancer Res 1999; 90: 565-70
33. Roller A, Weller M. Antioxidants specifically inhibit cisplatin cytotoxicity of human malignant glioma cells. Anticancer Res 1998; 18 (6A): 4493-8
34. Sheikh-Hamad D, Timmins K, Jalali Z. Cisplatin-induced renal toxicity: possible reversal by N-acetylcysteine treatment. J Am Soc Nephrol 1997; 8: 1640-5
35. Gerson SL, Arce C, Meltzer HY. N-desmethylclozapine: a clozapine metabolite that suppresses haemopoiesis. Br J Haematol 1994; 86: 555-61
36. Pirmohamed M, Park K. Mechanism of clozapine-induced agranulocytosis: current status of research and implications for drug development. CNS Drugs 1997; 7: 139-58
37. Williams DP, Pirmohamed M, Naisbitt DJ, et al. Neutrophil cytotoxicity of the chemically reactive metabolite(s) of clozapine: possible role in agranulocytosis. J Pharmacol Exp Ther 1997; 283: 1375-82
38. Walmsley SL, Khorasheh S, Singer J, et al. A randomized trial of N-acetylcysteine for prevention of trimethoprim-sulfamethoxazole hypersensitivity reactions in Pneumocystis carinii pneumonia prophylaxis. J Acquir Immune Defic Syndr Hum Retrovirol 1998; 19: 498-505

39. Akerlund B, Tynell E, Bratt G, et al. N-acetylcysteine treatment and the risk of toxic reactions to trimethoprim-sulphamethoxazole in primary Pneumocystis carinii prophylaxis in HIV-infected patients. J Infect 1997; 35 (2): 143-7
40. Bhattacharya R, Rao PV. Cyanide induced DNA fragmentation in mammalian cell cultures. Toxicol 1997; 124: 207-15
41. Clarke L, Waxman DJ. Oxidative metabolism of cyclophosphamide: identification of the hepatic monooxygenase catalysts of drug activation. Cancer Res 1989; 49: 2344-50
42. Le Balnc GA, Wasman DJ. Mechanisms of cyclophosphamide action on hepatic P-450 expression. Cancer Res 1984; 44: 4615-21
43. Weltin D, Aupeix K, Iltis C, et al. N-acetylcysteine protects lymphocytes from nitrogen mustard-induced apoptosis. Biochem Pharmacol 1996; 51: 1123-9
44. Berrigan MJ, Marinello AJ, Pavelic Z, et al. Protective role of thiols in cyclophosphamide-induced urotoxicity and depression of hepatic drug metabolism. Cancer Res 1982; 42: 3688-95
45. McClure MT, Stupans I. Investigation of the mechanism by which cyclophosphamide alters cytochrome P450 in male rats. Biochem Pharmacol 1992; 43: 2655-8
46. Tariq M, Morais C, Sobki S, et al. N-acetylcysteine attenuates cyclosporin-induced nephrotoxicity in rats. Nephrol Dial Transplant 1999; 14: 923-9
47. Sawyer DB, Fukazawa R, Arstall MA, et al. Daunorubicin-induced apoptosis in rat cardiac myocytes is inhibited by dexrazoxane. Circ Res 1999; 84: 257-65
48. Meyers C, Bonow R, Palmeri S, et al. A randomized controlled trial assessing the prevention of doxorubicin cardiomyopathy in N-acetylcysteine. Semin Oncol 1983; 10: 53-5
49. Villani F, Galimberti M, Monti E, et al. Effect of GSH and N-acetylcysteine on in vitro and in vivo cardiac toxicity of doxorubin. Free Radic Res Commun 1990; 11: 145-51
50. Doroshow JH, Locker GY, Irfrim I, et al. Prevention of doxorubicin cardiac toxicity in the mouse by N-acetylcysteine. Clin Invest 1981; 68: 1053-64
51. Mallery SR, Clark YM, Ness GM, et al. Thiol redox modulation of doxorubicin mediated cytotoxicity in cultured AIDS-related Kaposi's sarcoma cells. J Cell Biochem 1999; 73: 259-77
52. Szabo S, Trier JS, Frankel P. Sulfhydryl compounds may mediate gastric cytoprotection. Science 1981; 214: 200-2
53. Lu SC, Kuhlenham J, Robert A, et al. Role of glutathione status in protection against ethanol-induced gastric lesions. Pharmacol 1989; 38: 57-60
54. Lopez RA, Tornwall MS, Henagan JM, et al. N-acetyl-cysteine: protective agent or promoter of gastric damage? Proc Soc Exp Biol Med 1991; 197: 273-8
55. Wallace JL. Increased resistance of the rat gastric mucosa to hemorrhagic damage after exposure to an irritant: role of the "mucoid cap" and prostaglandin synthesis. Surgery 1990; 108: 467-74
56. Barreto JC, Smith GS, Tornwall MS, et al. Protective action of oral N-acetylcysteine against gastric injury: role of hypertonic saline. Am J Physiol 1993; 264: G422-6
57. Puddy IB, Beilen LJ, Vandongen R, et al. Evidence for a direct effect of alcohol consumption on blood pressure in normotensive men: a randomized controlled trial. Hypertension 1985; 7: 707-13
58. Vasdev S, Gupta IP, Sampson CA, et al. Ethanol induced hypertension in rats: reversibility and role of intracellular cytosolic calcium. Artery 1993; 20: 19-43
59. Vasdev S, Mian T, Longerich L, et al. N-acetylcysteine attenuates ethanol induced hypertension in rats. Artery 1995; 21: 312-36
60. Lorber A, Baumgartner WA, Bovy RA, et al. Clinical application for heavy metal-complexing potential of N-acetylcysteine. J Clin Pharmacol 1973; 13: 332-6
61. Godfrey NF, Peter A, Simon TM, et al. Intravenous N-acetylcysteine treatment of hematologic reactions to chrysotherapy. Rheumatology 1982; 9: 519-26
62. Vreugdenhill G, Swaak AJG. Effects of oral N-acetylcysteine on gold levels in rheumatoid arthritis [letter]. Br J Rheumatol 1990; 29: 404-5
63. Gurer H, Ozgunes H, Neal R, et al. Antioxidant effects of N-acetylcysteine and succimer in red blood cells from lead-exposed rats. Toxicol 1998; 128: 181-9
64. Yusof M, Yildiz D, Ercal N. N-acetyl-L-cysteine protects against delta-aminolevulinic acid-induced 8-hydroxydeoxyguanosine formation. Toxicol Lett 1999: 106: 41-7
65. Ballatori N, Lieberman MW, Wang W. N-acetylcysteine as an antidote in methylmercury poisoning. Environ Health Perspect 1998; 106: 267-71
66. Hjortsø E, Fomsgaard JS, Fogh-Andersen N. Does N-acetylcysteine increase the excretion of trace metals (calcium, magnesium, iron, zinc and copper) when given orally? Eur J Clin Pharmacol 1990; 39: 29-31
67. Livardjani F, Lediga M, Koppa P, et al. Lung and blood superoxide dismutase activity in mercury vapor exposed rats: effect of N-acetylcysteine treatment. Toxicol 1991; 66: 289-95
68. Zalups RK, Barfuss DW. Participation of mercuric conjugates of cysteine, homocysteine, and N-acetylcysteine in mechanisms involved in the renal tubular uptake of inorganic mercury. J Am Soc Nephrol 1998; 9: 551-61
69. Zalups RK. Basolateral uptake of mercuric conjugates of N-acetylcysteine and cysteine in the kidney involves the organic anion transport system. J Toxicol Environ Health 1998: 55: 13-29
70. Lu FC. Mercury as a food contaminant. WHO Chron 1974; 28: 8-11
71. Slott VL, Hales BF. Effect of gluthione depletion by buthione sulfoximine on rat embryonic development *in vitro*. Biochem Pharmacol 1987; 36: 683-8
72. Thomas DJ, Smith JC. Effects of coadministered low-molecular-weight thiol compounds on short-term distribution of methyl mercury in the rat. Toxicol Appl Pharmacol 1982; 62: 104-10
73. Lund ME, Banner Jr W, Clarkson TW, et al. Treatment of acute methylmercury ingestion by hemodialysis with N-acetylcysteine (Mucomyst) infusion and 2,3 dimercaptopropane sulfonate. Clin Toxicol 1984; 22: 31-49
74. Wright RO, Magnani B, Shannon MW, et al. N-acetylcysteine reduces methemoglobin *in vitro*. Ann Emerg Med 1996; 28: 499-503
75. Rosen PJ, Johnson C, McGehee WG, et al. Failure of methylene blue treatment in toxic methemoglobinemia. Ann Intern Med 1971; 75: 93-6
76. Wright RO, Woolf AD, Shannon MW, et al. N-acetylcysteine reduces methemoglobin in an *in-vitro* model of glucose-6-phosphate dehydrogenase deficiency. Acad Emerg Med 1998; 5: 225-9
77. Tanen D, LoVecchio F, Curry S. N-acetylcysteine is not effective in rapidly reducing methemoglobinemia [abstract]. J Toxicol Clin Toxicol 1999; 37: 642-3
78. Shen W, Hoener B. Mitigation of nitrofurantoin-induced toxicity in the perfused rat liver. Human Exp Toxicol 1996; 15 (5): 428-34

79. Makin AJ, Wendon J, Williams R. A 7-year experience of severe acetaminophen-induced hepatotoxicity (1987-1993). Gastroenterology 1995; 109: 1907-16
80. Schiodt FV, Rochling FA, Casey DL, et al. Acetaminophen toxicity in an urban county hospital. N Engl J Med 1997; 337: 1112-7
81. Rivera-Penera T, Gugig R, Davis J, et al. Outcome of acetaminophen overdose in pediatric patients and factors contributing to liver toxicity. J Pediatr 1997; 130: 300-4
82. Heubi JE, Barbacci MB, Zimmerman HJ. Therapeutic misadventures with acetaminophen: hepatotoxicity after multiple doses in children. J Pediatr 1998; 132: 22-7
83. Janes JM, Routledge PA. Recent developments in the management of paracetamol (acetaminophen) poisoning. Drug Saf 1992; 7: 170-7
84. Brotodihardjo AE, Batey RG, Farrell GC, et al. Hepatotoxicity from paracetamol self-poisoning in western Sydney: a continuing challenge. Med J Aust 1992; 157: 382-5
85. Chan TY, Chan AY, Critchley JA. Paracetamol poisoning and hepatotoxicity in Chinese – the Prince of Wales Hospital (Hong Kong) experience. Singapore Med J 1993; 34: 299-302
86. Davidson DGD, Eastham WN. Acute liver necrosis following overdose of paracetamol. BMJ 1966; 2: 497-9
87. Thomson JS, Prescott LF. Liver damage and impaired glucose tolerance after paracetamol overdosage. BMJ 1966; 2: 506-7
88. Jollow DJ, Mitchell JR, Potter WZ, et al. Acetaminophen-induced hepatic necrosis. II: role of covalent binding in vivo. J Pharmacol Exp Ther 1973; 187: 195-202
89. Dahlin DC, Miwa GT, Lu AYH, et al. N-acetyl-p-benzoquinone imine: a cytochrome P-450-mediated oxidation product of acetaminophen. Proc Natl Acad Sci U S A 1984: 81: 1327-31
90. Thummel KE, Lee CA, Kunze KL, et al. Oxidation of acetaminophen to N-acetyl-p-benzoquinone imine by human CYP3A4. Biochem Pharmacol 1993; 45: 1563-9
91. Lee SST, Buters JTM, Pineau T, et al. Role of CYP2E1 in the hepatotoxicity of acetaminophen. J Biol Chem 1996; 271: 12063-7
92. Miners JO, Drew R, Birkett DJ. Mechanism of action of paracetamol protective agents in mice in vivo. Biochem Pharmacol 1984; 33: 2995-3000
93. Prescott LF. Paracetamol overdosage: pharmacological considerations and clinical management. Drugs 1983; 25: 290-314
94. Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. Pediatrics 1975; 55: 871-6
95. Prescott LF, Illingworth RN, Critchley JAJH, et al. Intravenous acetylcysteine: the treatment of choice for paracetamol poisoning. BMJ 1979; 2: 1097-100
96. Smilkstein MJ, Knapp GL, Kulig KW, et al. Efficacy of oral *N*-acetylcysteine in the treatment of acetaminophen overdose: Analysis of the national multicenter study (1976-1985). N Engl J Med 1988; 319: 1557-62
97. Keays R, Harrison PM, Wendon JA, et al. Intravenous acetylcysteine in paracetamol-induced fulminant hepatic failure: a prospective controlled trial. BMJ 1991; 303: 1026-9
98. Jones AL. Mechanism of action and value of N-acetylcysteine in the treatment of early and late acetaminophen poisoning: a critical review. J Toxicol Clin Toxicol 1998; 36: 277-85
99. Harrison PM, Keays R, Bray GP, et al. Improved outcome of paracetamol induced fulminant hepatic failure by late administration of acetylcysteine. Lancet 1990; 335: 1572-3
100. Rey C, Ajzenberg N, Tchernia G, et al. Insuffisance hepatocellulaire aigue au paracetamol: faut-il prolonger la duree traitement par la N-acetyl cysteine. Arch Pediatr 1995; 2: 662-6
101. Makin AJ, Williams R. Acetaminophen-induced hepatotoxicity: predisposing factors and treatments. Adv Intern Med 1997; 42: 453-83
102. Routledge P, Vale JA, Bateman DN, et al. Paracetamol (acetaminophen) poisoning: no need to change current guidelines to accident departments. BMJ 1998; 317: 1609-10
103. Lauterburg BH, Corcoran GB, Mitchell JR. Mechanism of action of N-acetylcysteine in the protection against the hepatotoxicity of acetaminophen in rats in vivo. J Clin Invest 1983; 71: 980-91
104. Mitchell JR, Jollow DJ, Potter WZ, et al. Acetaminophen-induced hepatic necrosis: IV: protective role of glutathione. J Pharmacol Exp Ther 1973; 187: 211-7
105. Mitchell JR, Thorgeirsson SS, Potter WZ, et al. Acetaminophen-induced hepatic injury: protective role of glutathione in man and rationale for therapy. Clin Pharmacol Ther 1974; 16: 676-84
106. Slattery JT, Wilson JM, Kalhorn TF, et al. Dose-dependent pharmacokinetics of acetaminophen: evidence for glutathione depletion in humans. Clin Pharmacol Ther 1987; 41: 413-8
107. Galinsky RE, Levy G. Effect of N-acetylcysteine on the pharmacokinetics of acetaminophen in rats. Life Sci 1979; 25: 693-700
108. Lin JH, Levy G. Renal clearance of inorganic sulfate in rats: effect of acetaminophen-induced depletion of endogenous sulfate. J Pharm Sci 1983; 72: 213-7
109. Corcoran GB, Mitchell JR, Vaishnav YN, et al. Evidence that acetaminophen and N-hydroxyacetaminophen form a common arylating intermediate, N-acetyl-p-benzoquinoneimine. Mol Pharmacol 1980; 18: 536-42
110. Smilkstein MJ, Bronstein AC, Linden C, et al. Acetaminophen overdose: a 48 hour intravenous N-acetylcysteine treatment protocol. Ann Emerg Med 1991; 20: 1058-63
111. Holt S, Goodier D, Marley R, et al. Improvement in renal function in hepatorenal syndrome with N-acetylcysteine. Lancet 1999; 353: 294-5
112. Jaeschke H, Mitchell JR. Mitochondria and xanthine oxidase both generate reactive oxygen species in isolated perfused rat liver after hypoxic injury. Biochem Biophys Res Commun 1989; 160: 140-7
113. Bruno MK, Cohen SD, Khairallah EA. Antidotal effectiveness of N-acetylcysteine in reversing acetaminophen-induced hepatotoxicity: enhancement of the proteolysis of arylated proteins. Biochem Pharmacol 1988; 37: 4319-25
114. Devlin J, Ellis AE, McPeake J, et al. N-acetylcysteine improves indocyanine green extraction and oxygen transport during hepatic dysfunction. Crit Care Med 1997; 25: 236-42
115. Lopez BL, Snyder JW, Birenbaum DS, et al. N-acetylcysteine enhances endothelium-dependent vasorelaxation in the isolated rat mesenteric artery. Ann Emerg Med 1998; 32: 405-10
116. Perry HE, Shannon MW. Efficacy of oral versus intravenous N-acetylcysteine in acetaminophen overdose: results of an open-label, clinical trial. J Pediatr 1998; 132: 149-52
117. Dhawan A, Sorrell MF. Acetaminophen overdose: Need to consider intravenous preparation of N-acetylcysteine in the United States. Am J Gastroenterol 1998; 91: 1476
118. Yip L, Dart RC, Hurlbut KM. Intravenous administration of oral N-acetylcysteine. Crit Care Med 1998; 26: 40-3
119. Chan TYK, Critchley JAJH. Adverse reactions to intravenous N-acetylcysteine in Chinese patients with paracetamol (acetaminophen) poisoning. Hum Exp Toxicol 1994; 13: 542-4
120. Bailey B, McGuigan MA. Management of anaphylactoid reactions to intravenous N-acetylcysteine. Ann Emerg Med 1998; 31: 710-5

121. Wright RO, Anderson AC, Lesko SL, et al. Effect of metoclopramide dose on preventing emesis after oral administration of N-acetylcysteine for acetaminophen overdose. J Toxicol Clin Toxicol 1999; 37: 35-42
122. Buckley NA, Whyte IM, O'Connell DL, et al. Oral or intravenous N-acetylcysteine: which is the treatment of choice for acetaminophen (paracetamol) poisoning? J Toxicol Clin Toxicol 1999; 37: 759-67
123. Buechel DW, Haverlah VC, Gardner ME. Pennyroyal oil ingestion: report of a case. J Am Osteopath Assoc 1983; 82: 793-4
124. Anderson IB, Mullen WH, Meeker JE, et al. Pennyroyal toxicity: measurement of toxic metabolite levels in two cases and review of the literature. Ann Intern Med 1996; 124: 726-34
125. Redondo P, de Felipe I, de la Pena A, et al. Drug-induced hypersensitivity syndrome and toxic epidermal necrolysis. Treatment with N-acetylcysteine. Br J Dermatol 1997; 136 (4): 645-6
126. Sarnstrand B, Jansson AH, Matuseviciene G, et al. N,N'-diacetyl-L-cystine – the disulfide dimer of N-acetylcysteine - is a potent modulator of contact sensitivity/delayed type hypersensitivity reactions in rodents. J Pharmacol Exp Ther 1999: 288: 1174-84
127. Sciuto AM, Strickland PT, Kennedy TP, et al. Protective effects of N-acetylcysteine treatment after phosgene exposure in rabbits. Am J Respir Crit Care Med 1995; 151 (Pt 1): 768-72
128. Oda T, Iwaoka J, Komatsu N, et al. Involvement of N-acetylcysteine-sensitive pathways in ricin-induced apoptotic cell death in U937 cells. Biosci Biotechnol Biochem 1999; 63: 341-8
129. Gabay C, De Bandt M, Palazzo E. Sulphasalazine-related life-threatening side effects: is N-acetylcysteine of therapeutic value? Clin Exp Rheumatol 1993; 11 (4): 417-20
130. Rieder MJ, Uetrecht J, Cannon NH, et al. Sulfonamide hypersensitivity reactions: reversal of hydroxylamine toxicity by N-acetylcysteine in lymphocytes of patients and normal volunteers [abstract]. Pediatr Res 1988; 23: 263A
131. Meggs WJ, Cahill-Morasco R, Shih RD, et al. Effects of Prussian blue and N-acetylcysteine on thallium toxicity in mice. J Toxicol Clin Toxicol 1997; 35 (2): 163-6
132. Appenroth D, Winnefeld K. Is thallium-induced nephrotoxicity in rats connected with riboflavin and/or GSH?: reconsideration of hypotheses on the mechanism of thallium toxicity. J Appl Toxicol 1999; 19: 61-6
133. Gogu SR, Agrawal KC. The protective role of zinc and N-acetylcysteine in modulating zidovudine induced hematopoietic toxicity. Life Sci 1996; 59: 1323-9
134. Cotgreave IA. *N*-acetylcysteine: pharmacological considerations and experimental and clinical applications. Adv Pharmacol 1997; 38: 205-27
135. Saikumar P, Dong Z, Mikhailov V, et al. Apoptosis: definition, mechanisms, and relevance to disease. Am J Med 1999; 107: 489-506

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