minocycline hydrochloride, and prochlorperazine edisilate during simulated Y-site administration.

1. Trissel LA, Martinez JF. Compatibility of amifostine with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1995; **52:** 2208–12.

Adverse Effects, Treatment, and Precautions

Amifostine may cause a transient reduction, usually in systolic, or, less frequently, in diastolic blood pressure. However, more pronounced reductions in blood pressure may occur and transient loss of consciousness has been reported very rarely. To minimise hypotension, patients should be adequately hydrated before treatment begins and should be in a supine position. Amifostine is contra-indicated in patients who are hypotensive or dehydrated. Patients taking antihypertensive drugs should discontinue treatment 24 hours before starting amifostine. Arterial blood pressure must be monitored during the amifostine infusion and if systolic blood pressure decreases significantly, the infusion must stop. It may be continued if blood pressure returns to normal within 5 minutes.

Nausea and vomiting are frequently reported and concurrent antiemetic therapy is recommended.

Amifostine reduces serum-calcium concentrations, although clinical hypocalcaemia has occurred only very rarely in patients who received multiple doses of amifostine within 24 hours. Serum-calcium concentrations should be monitored in patients at risk of hypocalcaemia.

Other adverse effects include flushing, chills, somnolence, hiccups, and sneezing. Hypersensitivity reactions and anaphylactoid reactions have been reported. Skin rashes may occur and there have been reports of more severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, in some cases resulting in fatality.

Administration of amifostine over a longer period than the recommended 15 minutes is associated with a higher incidence of adverse effects.

Effects on the skin. Amifostine has been associated with severe skin reactions, including Stevens-Johnson syndrome[1,2] and toxic epidermal necrolysis,[1,2] and fatalities have occurred.[2] The reactions appear to be more common in patients receiving radiotherapy.[2]

1. Lale Atahan I, *et al*. Two cases of Stevens-Johnson syndrome: toxic epidermal necrolysis possibly induced by amifostine during radiotherapy. *Br J Dermatol* 2000; **143:** 1072–3.
2. Boccia R, *et al*. Assessment and management of cutaneous reactions with amifostine administration: findings of the ethyol (amifostine) cutaneous treatment advisory panel (ECTAP). *Int J Radiat Oncol Biol Phys* 2004; **60:** 302–9.

Pharmacokinetics

Amifostine is rapidly cleared from the plasma after intravenous administration and is dephosphorylated by alkaline phosphatase to the active metabolite WR-1065, a free thiol compound. The elimination half-life of amifostine after a 15-minute infusion is less than 10 minutes. About 6% or less of a dose is excreted in the urine.

Uses and Administration

Amifostine, an aminothiol compound, is a cytoprotective agent. It is converted in the body to its active metabolite WR-1065, which protects noncancerous cells against the toxic effects of antineoplastics and ionising radiation. It is used in patients with advanced ovarian cancer to reduce neutropenia-related infection associated with cyclophosphamide and cisplatin therapy and, in patients with advanced solid tumours of non-germ cell origin, to reduce the cumulative renal toxicity associated with repeated cisplatin use. It is also used to reduce the incidence of xerostomia (dry mouth) in patients undergoing radiation therapy for head and neck cancer. Amifostine is under investigation in ameliorating the adverse effects of other antineoplastics and in the treatment of myelodysplasia.

In chemotherapy, amifostine is given by intravenous infusion over 15 minutes starting no more than 30 minutes before the antineoplastic therapy. The dose in adults is 910 mg/m^2 once daily. Subsequent doses should be reduced to 740 mg/m^2 in patients unable to tolerate the full dose. A dose of 740 mg/m^2 is also recommended for the reduction of renal toxicity of cisplatin if doses of cisplatin of less than 100 mg/m^2 are used.

In the prevention of xerostomia, amifostine is given in a dose of 200 mg/m^2 daily as a 3-minute intravenous infusion started 15 to 30 minutes before radiotherapy.

Cytoprotection. WR-1065, the active metabolite of amifostine, readily enters non-malignant cells where it deactivates cytotoxics such as alkylating and platinum-containing antineoplastics and protects against the effects of ionising radiation.[1-3] The cytoprotective effects of amifostine are reported to be selective for normal cells and not to interfere with the cytotoxic effects of antineoplastics and radiation on malignant cells. Several factors contribute to this selectivity, including the lower alkaline phosphatase content of malignant cells compared with normal cells, and the lower pH of malignant tissues, both of which decrease the formation and uptake of WR-1065 by malignant cells.[2,3]

Benefit has been reported with amifostine in various malignancies and the American Society of Clinical Oncology currently recommends[4] that its use may be considered in patients receiving cisplatin- or alkylating agent-based chemotherapy, and in patients receiving radiation therapy in the head and neck region. Although it is usually given intravenously, there is some evidence[5,6] that the subcutaneous route may be effective and may be associated with fewer adverse effects.

1. Foster-Nora JA, Siden R. Amifostine for protection from antineoplastic drug toxicity. *Am J Health-Syst Pharm* 1997; **54:** 787–800.
2. Mabro M, *et al*. A risk-benefit assessment of amifostine in cytoprotection. *Drug Safety* 1999; **21:** 367–87.
3. Culy CR, Spencer CM. Amifostine: an update on its clinical status as a cytoprotectant in patients with cancer receiving chemotherapy or radiotherapy and its potential therapeutic application in myelodysplastic syndrome. *Drugs* 2001; **61:** 641–84.
4. Schuchter LM, *et al*. 2002 update of recommendations for the use of chemotherapy and radiotherapy protectants: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2002; **20:** 2895–903. Also available at: http://www.jco.org/cgi/reprint/20/12/2895.pdf (accessed 4/10/05)
5. Koukourakis MI, *et al*. Subcutaneous administration of amifostine during fractionated radiotherapy: a randomized phase II study. *J Clin Oncol* 2000; **18:** 2226–33.
6. Bonner HS, Shaw LM. New dosing regimens for amifostine: a pilot study to compare the relative bioavailability of oral and subcutaneous administration with intravenous infusion. *J Clin Pharmacol* 2002; **42:** 166–74.

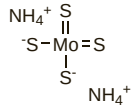
Preparations

USP 31: Amifostine for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Erifostine; Ethyol†; ***Austral.:*** Ethyol; ***Belg.:*** Ethyol; ***Braz.:*** Ethyol; ***Chile:*** Ethyol; ***Cz.:*** Ethyol; ***Denm.:*** Ethyol; ***Fin.:*** Ethyol; ***Fr.:*** Ethyol; ***Ger.:*** Ethyol; ***Gr.:*** Ethyol; ***Hong Kong:*** Ethyol†; ***Hung.:*** Ethyol†; ***India:*** Amiphos; ***Israel:*** Ethyol; ***Ital.:*** Ethyol; ***Malaysia:*** Ethyol†; ***Mex.:*** Ethyol; ***Neth.:*** Ethyol; ***NZ:*** Ethyol; ***Philipp.:*** Ethyol; ***Pol.:*** Ethyol; ***Port.:*** Ethyol; ***S.Afr.:*** Ethyol; ***Singapore:*** Ethyol†; ***Spain:*** Ethyol; ***Swed.:*** Ethyol; ***Switz.:*** Ethyol; ***Thai.:*** Cytofos; Ethyol; ***Turk.:*** Ethyol; ***UK:*** Ethyol†; ***USA:*** Ethyol; ***Venez.:*** Ethyol.

Ammonium Tetrathiomolybdate

Tetratiomolibdato de amonio.
$(NH_4)_2MoS_4$ = 260.3.
CAS — 15060-55-6.



Profile

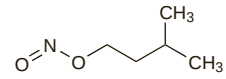
Ammonium tetrathiomolybdate is a chelator that aids the elimination of copper from the body. It is under investigation in the treatment of Wilson's disease.

Wilson's disease. Ammonium tetrathiomolybdate forms a complex with protein and copper. When it is taken with food it blocks the intestinal absorption of copper, and when given between meals it combines with albumin- and caeruloplasmin-bound copper. Ammonium tetrathiomolybdate is under investigation for the initial reduction of copper levels in patients with Wilson's disease (p.1459); it may be particularly suitable for patients with neurological symptoms.[1] Bone marrow depression[1,2] and raised liver enzymes[1] have been reported; both have responded to temporary withdrawal or dose reduction.

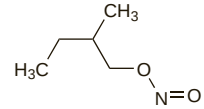
1. Brewer GJ, *et al*. Treatment of Wilson disease with ammonium tetrathiomolybdate III: initial therapy in a total of 55 neurologically affected patients and follow-up with zinc therapy. *Arch Neurol* 2003; **60:** 379–85.
2. Harper PL, Walshe JM. Reversible pancytopenia secondary to treatment with tetrathiomolybdate. *Br J Haematol* 1986; **64:** 851–3.

Amyl Nitrite

Amyli Nitris; Amylis Nitris; Amylium Nitrosum; Amylnitrit; Amyylinitriitti; Azotito de Amilo; Isoamyl Nitrite; Isopentyl Nitrite; Nitrito de amilo; Pentanolis Nitris.
$C_5H_{11}NO_2$ = 117.1.
ATC — V03AB22.
ATC Vet — QV03AB22.



and



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of amyl nitrite:
60 second trip; Aimes; Aimies; Ames; Amys; Boppers; Hard on; Pearls; Poppers; Sixty second trip; Snappers; Whiffenpoppers.

Pharmacopoeias. In *Jpn* and *US*.
USP 31 (Amyl Nitrite). A mixture of the nitrite esters of 3-methyl-1-butanol and 2-methyl-1-butanol. A clear, yellowish liquid having a peculiar, ethereal, fruity odour. It is very flammable. It is volatile even at low temperatures. B.p. about 96°. Practically insoluble in water; miscible with alcohol and with ether. Store in a cool place in airtight containers. Protect from light.

Stability. Amyl nitrite is liable to decompose with evolution of nitrogen, particularly if it has become acid in reaction.

Adverse Effects, Treatment, and Precautions

Amyl nitrite inhalation commonly causes flushing, headache, and dizziness; nausea and vomiting, hypotension, restlessness, and tachycardia may also occur. Overdosage may result in cyanosis, syncope, dyspnoea, and muscular weakness, due to vasodilatation and methaemoglobinaemia. Methylthioninium chloride may be required for severe methaemoglobinaemia but should not be used if cyanide poisoning is suspected since cyanide may be displaced.

Amyl nitrite may increase intra-ocular and intracranial pressure and should be used with caution in patients with glaucoma, recent head trauma, or cerebral haemorrhage.

Abuse. Volatile nitrites (commonly known as 'poppers'), including amyl, butyl, or isobutyl nitrite, have been abused in the belief that they expand creativity, stimulate music appreciation, promote a sense of abandon in dancing, and intensify sexual experience.[1,2]

Inhalation causes headache, tachycardia, syncope, acute psychosis, increased intra-ocular pressure, transient hemiparesis, methaemoglobinaemia, coma, and, rarely, sudden death. Haemolytic anaemia has also been reported;[3-5] in some subjects, Heinz body formation has been detected.[3] Methaemoglobinaemia may be severe,[6] and has also been reported after ingestion of volatile nitrites.[7-10] Symptoms are similar to those of hypoxia[9] and may be reversed by methylthioninium chloride.[6-10]

Amyl nitrite inhalation has led to severe and extensive contact dermatitis around the face with secondary spread elsewhere on the body.[11]

1. Sigell LT, *et al*. Popping and snorting volatile nitrites: a current fad for getting high. *Am J Psychiatry* 1978; **135:** 1216–18.
2. Lockwood B. Poppers: volatile nitrite inhalants. *Pharm J* 1996; **257:** 154–5.
3. Romeril KR, Concannon AJ. Heinz body haemolytic anaemia after sniffing volatile nitrites. *Med J Aust* 1981; **1:** 302–3.
4. Brandes JC, *et al*. Amyl nitrite-induced hemolytic anemia. *Am J Med* 1989; **86:** 252–4.
5. Graves TD, Mitchell S. Acute haemolytic anaemia after inhalation of amyl nitrite. *J R Soc Med* 2003; **96:** 594–5.
6. Modarai B, *et al*. Methylene blue: a treatment for severe methaemoglobinaemia secondary to misuse of amyl nitrite. *Emerg Med J* 2002; **19:** 270–1.
7. Laaban JP, *et al*. Amyl nitrite poppers and methemoglobulinemia. *Ann Intern Med* 1985; **103:** 804–5.
8. Osterloh J, Olson K. Toxicities of alkyl nitrites. *Ann Intern Med* 1986; **104:** 727.
9. Pierce JMT, Nielsen MS. Acute acquired methaemoglobinaemia after amyl nitrite poisoning. *BMJ* 1989; **298:** 1566.
10. Forsyth RJ, Moulden A. Methaemoglobinaemia after ingestion of amyl nitrite. *Arch Dis Child* 1991; **66:** 152.
11. Bos JD, *et al*. Allergic contact dermatitis to amyl nitrite ('poppers'). *Contact Dermatitis* 1985; **12:** 109.

Handling and storage. Amyl nitrite is very flammable and must not be used where it may be ignited.

Uses and Administration

Amyl nitrite is rapidly absorbed on inhalation and has been used in the immediate treatment of patients with definite cyanide poisoning (p.2045) to induce the formation of methaemoglobin, which combines with the cyanide to form non-toxic cyanmethaemoglobin. The value of such treatment has been questioned since only low levels of methaemoglobin are formed, but other mechanisms may also be important. A suggested procedure has