Treatment of leukaemia. References[1-5] to and a review[6] of adverse effects in patients receiving arsenic trioxide for the treatment of acute promyelocytic leukaemia, including a report of sudden death occurring in 3 patients in a dose-finding study.[5]

1. Huang SY, *et al.* Acute and chronic arsenic poisoning associated with treatment of acute promyelocytic leukaemia. *Br J Haematol* 1998; **103:** 1092–5.
2. Huang CH, *et al.* Complete atrioventricular block after arsenic trioxide treatment in an acute promyelocytic leukemic patient. *Pacing Clin Electrophysiol* 1999; **22:** 965–7.
3. Camacho LH, *et al.* Leukocytosis and the retinoic acid syndrome in patients with acute promyelocytic leukemia treated with arsenic trioxide. *J Clin Oncol* 2000; **18:** 2620–5.
4. Ohnishi K, *et al.* Prolongation of the QT interval and ventricular tachycardia in patients treated with arsenic trioxide for acute promyelocytic leukemia. *Ann Intern Med* 2000; **133:** 881–5.
5. Westervelt P, *et al.* Sudden death among patients with acute promyelocytic leukemia treated with arsenic trioxide. *Blood* 2001; **98:** 266–71.
6. Rust DM, Soignet SL. Risk/benefit profile of arsenic trioxide. *Oncologist* 2001; **6** (suppl 2): 29–32.

Treatment of Adverse Effects

Acute poisoning due to the ingestion of arsenic compounds should be treated by immediate gastric lavage if the patient presents within 1 hour and has not already vomited. Activated charcoal has been used to reduce absorption but is unlikely to be of benefit unless a significant amount of arsenic has been ingested. Intravenous replacement of fluids and electrolytes should be undertaken as necessary to correct dehydration and electrolyte imbalance; pressor agents may be required.

Chelation therapy should start immediately the cause of arsenic poisoning is suspected. The therapy of choice for acute poisoning is unithiol (p.1468) given intravenously in cases of gastrointestinal toxicity. Dimercaprol (p.1444) given intramuscularly is the second choice therapy if unithiol is unavailable. Oral therapy with unithiol or succimer (p.1466) should be substituted when gastrointestinal disturbances are no longer a problem. Oral penicillamine (p.1456) has also been used, including in conjunction with dimercaprol in severely ill patients, but its use in arsenic poisoning has been superseded by unithiol and succimer.

Patients suffering from chronic arsenic poisoning should be removed from the source of contamination as soon as possible. Initiation of oral chelation therapy with unithiol or succimer will depend on the patient's clinical condition and laboratory results of arsenic in urine, hair, and nails.

Chelation therapy should be continued until arsenic concentrations in urine have fallen to acceptable levels, although the therapeutic end-points of chelation therapy are poorly defined.

If renal failure occurs haemodialysis may be required.

Poisoning. The treatment of 3 patients who had ingested massive doses of arsenic has been described.[1,2] An adult survived after ingesting 54 g of arsenic trioxide:[1] in addition to standard supportive measures, attempts to remove the arsenic from his gastrointestinal tract included lavage, endoscopic removal, manual removal after gastrotomy, and cleansing enemas, plus chelation therapy. Of 2 siblings who ingested solubilised inorganic arsenic in a pesticide solution,[2] one child (aged 4 months) was estimated to have ingested 428 mg/kg arsenic and died despite aggressive attempts at removal of the arsenic, including chelation therapy, extracorporeal membrane oxygenation, exchange transfusion, and haemodialysis. The other child, aged 2 years, was estimated to have ingested 14.6 mg/kg arsenic, and survived following standard chelation therapy.

1. Dueñas-Laita A, *et al.* Acute arsenic poisoning. *Lancet* 2005; **365:** 1982.
2. Lai MW, *et al.* Acute arsenic poisoning in two siblings. *Pediatrics* 2005; **116:** 249–57.

Precautions

Patients receiving arsenic trioxide for acute promyelocytic leukaemia should have their ECG, blood sugar, electrolytes, blood count, and coagulation monitored at least twice weekly during induction and at least weekly during consolidation. More frequent monitoring may be needed in clinically unstable patients. Arsenic trioxide should be used with caution in renal impairment since renal excretion is the main route of elimination.

Pharmacokinetics

Water-soluble arsenic acids and their salts are more rapidly absorbed from the gastrointestinal tract than poorly soluble arsenicals such as arsenic trioxide. The absorption of arsenic trioxide is dependent upon the physical form of the compound and coarsely powdered material may be eliminated in the faeces before significant dissolution and absorption can occur. Soluble arsenic salts may also be absorbed following inhalation and through skin.

Once absorbed, arsenic is stored mainly in the liver, kidneys, heart, and lungs, with smaller amounts in the muscles and nervous tissue. About 2 weeks after ingestion, arsenic is deposited in the hair and nails and remains fixed to the keratin for years. It is also deposited in the bones and skin.

Although pentavalent arsenic is reduced to some degree *in vivo* to the more toxic trivalent form, trivalent arsenic is slowly and extensively oxidised to pentavalent arsenic. Both forms are methylated and excreted in the urine, mainly as dimethylarsinic acid, with smaller amounts appearing as monomethylarsonic acid and inorganic arsenic compounds. Although about 60% of a dose may be eliminated in the urine within 8 days, small amounts may continue to be excreted for several weeks after a single dose. Less significant amounts of arsenic are excreted in the faeces and sweat and via the lungs and skin. It is also distributed into breast milk and readily crosses the placenta.

Uses and Administration

Arsenic trioxide is used for induction of remission and consolidation in acute promyelocytic leukaemia (see below). It is given as an intravenous infusion over 1 to 2 hours to patients who are refractory to, or who have relapsed from, conventional therapy with retinoids and antineoplastics; if acute vasomotor reactions occur, the rate of infusion may be slowed and up to 4 hours may be taken. For induction, a dose of 150 micrograms/kg is given once daily until remission occurs; no more than 50 doses should be given (in the USA, the maximum number of induction doses allowed is 60). Treatment for consolidation must begin 3 to 4 weeks after completion of induction (or 3 to 6 weeks in the USA). The dose for consolidation is 150 micrograms/kg once daily given for 25 doses spread over a period of up to 5 weeks; the regimen suggested in the UK is to give the daily dose for 5 days each week followed by 2 days without dosing.

Arsenic trioxide is used in certain Asian herbal remedies. Arsenic anhydride has also been used.

Arsenic trioxide has been widely used as a constituent of weedkillers and sheepdips and as a rodenticide.

Arsenic trioxide and arsenic triiodide were formerly used internally as solutions or externally as ointments in the treatment of various skin diseases, but such use is generally no longer recommended. Externally, arsenic trioxide has a caustic action.

Homoeopathy. Arsenic trioxide has been used in homoeopathic medicines under the following names: Arsenious trioxide; Arsenici trioxidum; Arsenicum album; Acidum arsenicosum; Ars. alb.

Acute myeloid leukaemias. The use of arsenic trioxide in the management of patients with acute promyelocytic leukaemia (p.652) has been reviewed.[1-4] Remission was achieved in patients who had relapsed despite conventional therapy with retinoids and antineoplastics.[5,6] Arsenic trioxide is also being investigated for postremission therapy and in conjunction with transplantation.[4] Treatment was also successful in newly-diagnosed patients but severe liver toxicity occurred in some cases.[5]

For references to adverse effects occurring in patients receiving arsenic trioxide for acute promyelocytic leukaemia, see under Adverse Effects, above.

1. Soignet SL. Clinical experience of arsenic trioxide in relapsed acute promyelocytic leukemia. *Oncologist* 2001; **6** (suppl 2): 11–6.
2. Murgo AJ. Clinical trials of arsenic trioxide in hematologic and solid tumors: overview of the National Cancer Institute Cooperative Research and Development Studies. *Oncologist* 2001; **6** (suppl 2): 22–8.
3. Slack JL, *et al.* Advances in the management of acute promyelocytic leukemia and other hematologic malignancies with arsenic trioxide. *Oncologist* 2002; **7** (suppl 1): 1–13.
4. Douer D, Tallman MS. Arsenic trioxide: new clinical experience with an old medication in hematologic malignancies. *J Clin Oncol* 2005; **23:** 2396–2410.
5. Niu C, *et al.* Studies on treatment of acute promyelocytic leukemia with arsenic trioxide: remission induction, follow-up, and molecular monitoring in 11 newly diagnosed and 47 relapsed acute promyelocytic leukemia patients. *Blood* 1999; **94:** 3315–24.
6. Soignet SL, *et al.* United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. *J Clin Oncol* 2001; **19:** 3852–60.

Multiple myeloma. Arsenic trioxide is under investigation for the treatment of relapsed or refractory multiple myeloma (p.658).

References.

1. Munshi NC. Arsenic trioxide: an emerging therapy for multiple myeloma. *Oncologist* 2001; **6** (suppl 2): 17–21.
2. Munshi NC, *et al.* Clinical activity of arsenic trioxide for the treatment of multiple myeloma. *Leukemia* 2002; **16:** 1835–7.
3. Bahlis NJ, *et al.* Feasibility and correlates of arsenic trioxide combined with ascorbic acid-mediated depletion of intracellular glutathione for the treatment of relapsed/refractory multiple myeloma. *Clin Cancer Res* 2002; **8:** 3658–68.
4. Berenson JR, Yeh HS. Arsenic compounds in the treatment of multiple myeloma: a new role for a historical remedy. *Clin Lymphoma Myeloma* 2006; **7:** 192–8.

Myelodysplastic syndromes. The use of arsenic trioxide for the treatment of myelodysplastic syndromes (p.654) is also under investigation.

References.

1. List A, *et al.* Opportunities for Trisenox (arsenic trioxide) in the treatment of myelodysplastic syndromes. *Leukemia* 2003; **17:** 1499–1507.
2. Vey N. Arsenic trioxide for the treatment of myelodysplastic syndromes. *Expert Opin Pharmacother* 2004; **5:** 613–21.
3. Schiller GJ, *et al.* Phase II multicenter study of arsenic trioxide in patients with myelodysplastic syndromes. *J Clin Oncol* 2006; **24:** 2456–64.
4. Vey N, *et al.* Arsenic trioxide in patients with myelodysplastic syndromes: a phase II multicenter study. *J Clin Oncol* 2006; **24:** 2465–71.
5. Sekeres MA. New data with arsenic trioxide in leukemias and myelodysplastic syndromes. *Clin Lymphoma Myeloma* 2007; **8** (suppl 1): S7–S12.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Trisenox; ***Belg.:*** Trisenox; ***Cz.:*** Trisenox; ***Fr.:*** Trisenox; ***Gr.:*** Trisenox; ***Ital.:*** Trisenox; ***Jpn:*** Trisenox; ***Neth.:*** Trisenox; ***Spain:*** Trisenox; ***UK:*** Trisenox; ***USA:*** Trisenox.

Multi-ingredient: ***Ital.:*** Pasta Arsenicale.

Arsine

Arsenic Trihydride; Arsina; Hydrogen Arsenide.

AsH_3 = 77.95.

CAS — 7784-42-1.

Profile

Arsine is a heavy colourless gas with a garlic-like odour, which has no clinical uses but is an environmental or occupational hazard. It is highly toxic and causes severe haemolysis which may result in acute renal failure. It is potentially toxic below the odour threshold of 0.5 ppm and dangerously toxic after exposure to as little as 3 ppm; there may be a latent period of up to 24 hours following exposure before symptoms develop. Symptoms of arsine gas poisoning include generalised weakness, muscle cramps, thirst, headache, abdominal pain, nausea, vomiting, anorexia, jaundice, bronze skin coloration, haemolytic anaemia, haematuria, oliguria, and anuria. Pulmonary oedema, ECG abnormalities, and neurological disorders have also been reported. Treatment involves exchange transfusions and haemodialysis; dimercaprol and other chelating agents have been used but are of no value in the acute stage and do not prevent haemolysis.

◊ References.

1. Fowler BA, Weissberg JB. Arsine poisoning. *N Engl J Med* 1974; **291:** 1171–4.
2. Hesdorffer CS, *et al.* Arsine gas poisoning: the importance of exchange transfusions in severe cases. *Br J Ind Med* 1986; **43:** 353–5.
3. Rael LT, *et al.* The effects of sulfur, thiol, and thiol inhibitor compounds on arsine-induced toxicity in the human erythrocyte membrane. *Toxicol Sci* 2000; **55:** 468–77.

Asafetida

Asafétida; Asafoetida; Asant; Devil's Dung; Gum Asafetida.

Pharmacopoeias. In *Chin.*

Profile

Asafetida is an oleo-gum resin obtained from various species of *Ferula* (Umbelliferae). It has been used as a carminative and antispasmodic. It was also formerly used as an expectorant. It is used in cooking and is an ingredient of certain foods.

◊ References.

1. Kelly KJ, *et al.* Methemoglobinemia in an infant treated with the folk remedy glycerited asafoetida. *Pediatrics* 1984; **73:** 717–19.

Preparations

Proprietary Preparations (details are given in Part 3)
S.Afr.: Duiwelsdrekdruppels.

Multi-ingredient: ***India:*** Tummy Ease; ***S.Afr.:*** Entressdruppels HM; Stuidruppels; ***Thai.:*** Flatulence; ***UK:*** Daily Tension & Strain Relief.

Asarabacca

Ásaro europeo; Hazelwort; Rhizoma Asari; Wild Nard.

NOTE. Asarabacca has also been used as a common name for *Aristolochia clematitis* (see Aristolochia, p.2260).

Profile

Asarabacca is the dried rhizome, roots, and leaves of *Asarum europaeum* (Aristolochiaceae), which is an ingredient of snuffs. It is also an irritant emetic and has been used in rodent poisons. Asarabacca is an ingredient of preparations given for respiratory disorders.

Homoeopathy. Asarabacca has been used in homoeopathic medicines under the following names: Asarum; Asarum europaeum; Asar. eur.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Escarol†.

Asbestos

Amianto; Asbesto.

Profile

The name asbestos is applied to several naturally occurring and widely distributed fibrous mineral silicates of the serpentine and amphibole groups. They include amosite (brown asbestos), anthophyllite, chrysotile (white asbestos), and crocidolite (blue asbestos).

Asbestos has properties of heat resistance, insulation, and reinforcement and has been used extensively for heat or electrical insulation, fire protection, in friction materials, and in the construction industry in a wide variety of materials including cement, pipes, and tiles.

When inhaled, asbestos fibres can cause asbestosis (pulmonary fibrosis), lung cancer, and mesothelioma of the pleura and peri-