Bronchography (examination of the bronchial tree) has been performed with oily or aqueous media, such as iopydol or iopydone, instilled through a catheter or bronchoscope to coat the airways; however, other visualisation techniques are generally preferred.

For **hysterosalpingography** (visualisation of the uterus and fallopian tubes) ultrasound and endoscopic techniques are generally used, and microbubble contrast media such as galactose may be used to improve ultrasound images. If radiography is performed, water-soluble iodinated contrast media may be used.

For **lymphography** or **lymphangiography** (visualisation of the lymphatic system) a high radiodensity is required and the contrast medium must be retained within the lymphatic system for long enough to be visualised, requiring particulate, water-insoluble media, or very large molecules. Iodised oil has been most widely used, but adverse effects and limited distribution within the lymphatic system restrict its use.

Adverse effects of contrast media. Although contrast media are generally considered to be very safe, with most adverse effects being mild and transient, more severe and even life-threatening reactions are possible, and the risk of adverse effects may influence the choice of contrast medium or imaging technique in a particular patient.

Iodinated radiographic contrast media all have a similar range of adverse effects (see under Amidotrizoic Acid, p.1475) but the incidence and severity varies. Many of the adverse effects are related to the osmolality of the preparation, and the incidence tends to be lower with those that have low osmolality. Osmolality depends on the number of particles present in the solution; for a given iodine content, this is highest for the ionic monomers and lowest for nonionic dimers, and this is reflected in the incidence of adverse effects. Hypersensitivity reactions also tend to be less frequent with nonionic media (see under Amidotrizoic Acid, p.1476), although these reactions are not directly related to osmolality. However, low-osmolality media tend to be more expensive; while nonionics and dimers are preferred, ionic monomers may still have a role in patients at low risk of adverse effects. Ionic contrast media may also carry a lower risk of thromboembolism (see Effects on the Blood, p.1476).

Magnetic resonance contrast media tend to be safer than iodinated contrast media, although similar general effects may occur. Ionic and nonionic media are available, but this tends to have little influence on the incidence of adverse effects. All gadolinium chelates have similar adverse effects (see under Gadopentetic Acid, p.1479); there is a theoretical risk of gadolinium toxicity due to instability of the chelates and most preparations also contain free chelating agent to reduce this risk. The adverse effects of superparamagnetic iron compounds are described under ferumoxides (p.1478) and ferumoxsil (p.1478).

Ultrasound contrast media are generally safe; minor and transient adverse effects have been reported, but may be due to the procedure rather than to the contrast medium used.

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1. Thomsen HS, Bush WH. Adverse effects of contrast media: incidence, prevention and management. *Drug Safety* 1998; **19:** 313–24.
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5. Christiansen C. X-ray contrast media—an overview. *Toxicology* 2005; **209:** 185–7.
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8. Meth MJ, Maibach HI. Current understanding of contrast media reactions and implications for clinical management. *Drug Safety* 2006; **29:** 133–41.
9. European Society of Urogenital Radiology. ESUR guidelines on contrast media (February 2007). Available at: http://www.esur.org/fileadmin/Guidelines/ESUR_2007_Guideline_6_Kern_Ubersicht.pdf (accessed 14/07/08)

Adipiodone *(BAN, rINN)*

Adipiodon; Adipiodona; Adipiodoni; Adipiodonum; Iodipamide. 3,3′-Adipoyldiaminobis(2,4,6-tri-iodobenzoic acid).

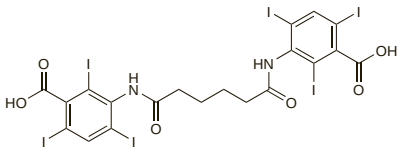
Адипиодон

$C_{20}H_{14}I_6N_2O_6$ = 1139.8.

CAS — 606-17-7.

ATC — V08AC04.

ATC Vet — QV08AC04.



Description. Adipiodone contains about 66.8% of I.

Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Iodipamide). A white, practically odourless, crystalline powder. Very slightly soluble in water, in chloroform, and in ether; slightly soluble in alcohol. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Meglumine Adipiodone *(rINNM)*

Adipiodona de meglumina; Adipiodone Méglumine; Adipiodone Meglumine *(BANM)*; Dimeglumine Iodipamide; Iodipamide Meglumine; Meglumine Iodipamide; Meglumini Adipiodonum. The di(*N*-methylglucamine) salt of adipiodone.

Меглумина Адипиодон

$C_{20}H_{14}I_6N_2O_6.(C_7H_{17}NO_5)_2$ = 1530.2.

CAS — 3521-84-4.

ATC — V08AC04.

ATC Vet — QV08AC04.

Description. Meglumine adipiodone contains about 49.8% of I.

Pharmacopoeias. *US* includes only as an injection.

Incompatibility. Incompatibilities have been reported between meglumine adipiodone and some antihistamines.

Adverse Effects, Treatment, and Precautions

See under the amidotrizoates, p.1475. Rapid injection may increase the incidence of adverse effects.

Adipiodone may show some uricosuric activity.

Effects on the liver. Of 149 patients given the recommended dose of adipiodone, 13 developed elevated serum aspartate aminotransferase (SGOT) values; of 126 who received twice the dose, 23 developed elevated values.[1] Hepatotoxicity has also been reported[2-4] on isolated occasions in patients given meglumine adipiodone.

1. Scholz FJ, *et al.* Hepatotoxicity in cholangiography. *JAMA* 1974; **229:** 1724.
2. Stillman AE. Hepatotoxic reaction to iodipamide meglumine injection. *JAMA* 1974; **228:** 1420–1.
3. Sutherland LR, *et al.* Meglumine iodipamide (Cholografin) hepatotoxicity. *Ann Intern Med* 1977; **86:** 437–9.
4. Imoto S. Meglumine hepatotoxicity. *Ann Intern Med* 1978; **88:** 129.

Pharmacokinetics

Meglumine adipiodone is rapidly distributed in extracellular fluid after intravenous injection and is reported to be extensively bound to plasma proteins. It appears in the bile ducts within about 10 to 15 minutes after injection, with peak opacity at about 20 to 30 minutes, and reaches the gallbladder by about 1 hour, peak opacification occurring after about 2 hours. About 80 to 95% is excreted unchanged in the faeces; small amounts are excreted unchanged in urine. A terminal half-life of about 2 hours has been reported.

Uses and Administration

Adipiodone is an ionic dimeric iodinated radiographic contrast medium (see p.1474); it is taken up by the liver and excreted in bile, and is used in cholangiography and cholecystography.

Adipiodone is given intravenously as a solution containing 52% of the meglumine salt. The usual dose is about 10 g of meglumine adipiodone, given by slow intravenous injection over about 10 minutes.

A solution of meglumine adipiodone with meglumine diatrizoate is given by intra-uterine instillation for hysterosalpingography.

Preparations

BP 2008: Meglumine Iodipamide Injection;
USP 31: Iodipamide Meglumine Injection.

Proprietary Preparations (details are given in Part 3)

USA: Cholografin.

Multi-ingredient: ***USA:*** Sinografin.

Amidotrizoic Acid *(BAN, rINNM)*

Acide amidotrizoïque; Ácido amidotrizoico; Acidum amidotrizoicum; Acidum Diatrizoicum; Amidotritsoiinihappo; Amidotrizoesav; Amidotrizoinė rūgštis; Amidotrizoinsyra; Diatritsoiinihappo; Diatrizoic Acid *(USAN)*; Diatrizoinsyra; Kyselina amidotrizoová; NSC-262168. 3,5-Diacetamido-2,4,6-tri-iodobenzoic acid.

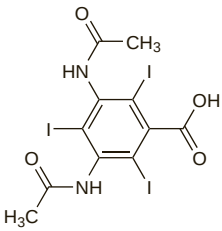
Амидотризоевая Кислота

$C_{11}H_9I_3N_2O_4.2H_2O$ = 649.9.

CAS — 117-96-4 (anhydrous amidotrizoic acid); 50978-11-5 (amidotrizoic acid dihydrate).

ATC — V08AA01.

ATC Vet — QV08AA01.



Description. Amidotrizoic acid contains about 62% of I calculated on the anhydrous substance.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Amidotrizoic Acid Dihydrate). A white or almost white, crystalline powder. Very slightly soluble in water and in alcohol; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 31 (Diatrizoic Acid). It is anhydrous or contains two molecules of water of hydration. A white, odourless, powder. Very slightly soluble in water and in alcohol; soluble in dimethylformamide and in alkali hydroxide solutions.

Meglumine Amidotrizoate *(BANM, rINNM)*

Amidotrizoate de Méglumine; Amidotrizoato de meglumina; Diatrizoate Meglumine; Meglumine Diatrizoate; Meglumini Amidotrizoas; Methylglucamine Diatrizoate. *N*-Methylglucamine 3,5-diacetamido-2,4,6-tri-iodobenzoate.

Меглумина Амидотризоат

$C_{11}H_9I_3N_2O_4.C_7H_{17}NO_5$ = 809.1.

CAS — 131-49-7.

ATC — V08AA01.

ATC Vet — QV08AA01.

Description. Meglumine amidotrizoate contains about 47.1% of I.

Pharmacopoeias. In *US.*

USP 31 (Diatrizoate Meglumine). A white, odourless, powder. Freely soluble in water. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Sodium Amidotrizoate *(BANM, rINN)*

Amidotrizoate de Sodium; Amidotrizoato de sodio; Diatrizoate Sodium; Natrii amidotrizoas; Natrio amidotrizoatas; Natriumamidotritsoaatti; Natriumamidotrizoat; Nátrium-amidotrizoát; Natrium-amidotrizoát; NSC-61815; Sodium, amidotrizoate de; Sodium Diatrizoate; Sodu amidotrizoat. Sodium 3,5-diacetamido-2,4,6-tri-iodobenzoate.

Натрия Амидотризоат

$C_{11}H_8I_3N_2NaO_4$ = 635.9.

CAS — 737-31-5.

ATC — V08AA01.

ATC Vet — QV08AA01.

Description. Sodium amidotrizoate contains about 59.9% of I calculated on the anhydrous substance.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*
Chin. includes the injection.

Ph. Eur. 6.2 (Sodium Amidotrizoate). A white or almost white powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in acetone. A 50% solution in water has a pH of 7.5 to 9.5. Protect from light.

USP 31 (Diatrizoate Sodium). A white, odourless, powder. Soluble in water; slightly soluble in alcohol; practically insoluble in acetone and in ether.

Incompatibility. Incompatibilities of sodium amidotrizoate with some antihistamines have been reported.

Adverse Effects and Treatment

Amidotrizoates and other iodinated contrast media may cause adverse effects due to direct toxicity, which tends to be dose-related and predictable, but use often leads to unpredictable or anaphylactoid reactions. Most reactions occur within 5 to 10 minutes and are mild and transient; however, severe, life-threatening reactions may also occur, and delayed reactions have been reported.

Direct toxic effects of iodinated contrast media are related to the osmolality of the solutions used and are most common with the amidotrizoates and other ionic monomeric compounds, which have a high osmolality. The route, the speed with which it is given, and the volume, concentration, and viscosity of the solution, also affect the incidence of adverse effects. For ionic media, the cation is also important: meglumine salts are generally better tolerated, but sodium salts have a lower viscosity and may produce fewer arrhythmias, and preparations containing a mixture of the salts are therefore often used. Anaphylactoid reactions are also more common with high-osmolality, ionic contrast media.

The most frequent direct adverse reaction to iodinated contrast media is flushing or a sensation of heat and caused by vasodilatation in response to the osmolality of the solution. Pain at the injection site is also common and extravasation may lead to tissue damage or thrombophlebitis.

General symptoms such as nausea, vomiting, headache, and dizziness may be related to patient anxiety or similar factors, or may be due to a mild anaphylactoid reaction. Urticaria, pruritus, pallor, sweating, a metallic taste, weakness, coughing, rhinitis, sneezing, lachrymation, and visual disturbances may also occur. Cardiovascular effects may also be due to direct toxicity, notably after intracoronary injection, or anaphylactoid response; they include hypotension, tachycardia, bradycardia, transient ECG abnormalities, and haemodynamic disturbances. More severe anaphylactoid reactions may lead to dyspnoea, bronchospasm, angioedema, severe urticaria, and eventually to profound hypotension, pulmonary oedema, respiratory arrest, ventricular fibrillation, circulatory failure, and cardiac arrest; fatalities have occurred.

CNS effects may result from direct toxicity, particularly after intrathecal use of ionic media or use in patients with a compromised blood-brain barrier, and can lead to severe neurotoxicity. Convulsions are more common in patients with epilepsy or brain tumours, but may also result from anaphylactoid reactions; paraesthesia, paralysis, and coma have also been reported.

Acute renal failure is an established adverse effect of contrast media, particularly in patients with predisposing factors such as dehydration (see Effects on the Kidneys, and Precautions, below). It appears to be related to the osmolality of the solution and is usually reversible, but deaths have occurred.

Iodinated contrast media also have direct effects on the blood, inhibiting blood coagulation and platelet aggregation. However, thromboembolism may also occur (see below). Disseminated intravascular coagulation and thrombocytopenia have also been reported.

Hyperthyroidism has been reported with use of iodinated contrast media, particularly in patients with goitre, and thyroid storm may be precipitated in patients with thyrotoxicosis. This is probably due to the small amounts of iodine present as a contaminant or released by any breakdown of the medium in the body. For the effects of iodine on the thyroid gland, see p.2169.

Mild diarrhoea may follow the oral or rectal use of amidotrizoates for gastrointestinal examinations. Aspiration of oral solutions has caused fatal pulmonary oedema.

Adverse effects are treated symptomatically; adequate resuscitative facilities should be available when radiographic procedures are undertaken, and patients should be kept under observation for a suitable period after the procedure.

Effects on the blood. Iodinated contrast media affect blood coagulation to differing degrees.[1,2] Amidotrizoates and other ionic contrast media have inhibitory effects on blood coagulation and platelet aggregation, whereas nonionic media lack these effects. In procedures such as angiography, which are associated with a risk of thromboembolism, there may therefore be an advantage in using ionic media. However, the better overall tolerability of nonionic media means that they are still generally preferred to ionic media for angiography, particularly in patients at high risk of non-thromboembolic adverse effects.

Other effects on the blood that have been reported with amidotrizoates and other iodinated contrast media include disseminated intravascular coagulation,[3,4] haemolysis,[5] thrombocytopenia,[6,7] and thrombotic microangiopathy.[8]

1. Husted SE, Kanstrup H. Thrombotic complications in coronary angioplasty—ionic versus non-ionic low-osmolar contrast media. *Acta Radiol* 1998; **39:** 340–3.
2. Esplugas E, *et al.* Comparative tolerability of contrast media used for coronary interventions. *Drug Safety* 2002; **25:** 1079–98.
3. Lucas LM, *et al.* Case report: multisystem failure following intravenous iopamidol. *Clin Radiol* 1992; **45:** 276–7.
4. Shigyo M, *et al.* A rare case of disseminated intravascular coagulation caused by the nonionic contrast medium iohexol. *J Urol (Baltimore)* 1995; **153:** 1901–3.
5. Catterall JR, *et al.* Intravascular haemolysis with acute renal failure after angiocardiography. *BMJ* 1981; **282:** 779–80.
6. Shojania AM. Immune-mediated thrombocytopenia due to an iodinated contrast medium (diatrizoate). *Can Med Assoc J* 1985; **133:** 123.
7. Ural AU, *et al.* Thrombocytopenia following intravenous iopamidol. *Eur J Clin Pharmacol* 1998; **54:** 575–6.
8. Fairley S, Ihle BU. Thrombotic microangiopathy and acute renal failure associated with arteriography. *BMJ* 1986; **293:** 922–3.

Effects on the kidneys. Contrast nephropathy or contrast-induced nephrotoxicity is a well-established adverse effect of iodinated contrast media.[1-9] Estimates of the incidence vary depending on the type and amount of contrast medium used, the definition of nephropathy, and the population of patients being studied, but is about 1 to 6% overall. In the majority of patients who develop contrast-medium-induced renal impairment the condition develops within about 24 hours of the procedure, is asymptomatic, and resolves completely within about 10 days. However, the condition may occasionally be severe, producing oliguria and renal failure that requires dialysis; fatalities have occurred.

The mechanism of nephrotoxicity is not certain, but is thought to involve both medullary hypoxia due to reduced renal blood flow, and direct toxicity. The osmolality of the contrast medium solution appears to be an important factor and most studies have shown that high-osmolality media increase the risk compared with low-osmolality media. There is also some evidence that use of media that are iso-osmolar with plasma may reduce the risk even further. The volume of contrast solution used is also important, and risk increases with higher volumes. The use of ionic or nonionic media appears to have less influence, except that nonionic media generally have a lower osmolality and may therefore be preferred.

The most important patient characteristic that increases the risk of nephrotoxicity is pre-existing renal impairment, especially in patients with diabetes mellitus. Other risk factors include conditions where there is reduced renal blood flow, such as heart failure and dehydration. Old age, repeated exposure (over a short period of time), multiple myeloma, and use with other nephrotoxic drugs, are also risk factors.

Various methods have been tried to prevent contrast medium-induced nephropathy.[1,3-12] All patients should be assessed for risk factors and those at high risk should be given a small volume of a low-osmolality or iso-osmolar nonionic medium if possible. Hydration before and after the procedure is of established benefit and is recommended in all patients, although the optimum route and fluid to use remains unclear. Oral hydration may be adequate in low risk patients, but most patients are given sodium chloride 0.45% or 0.9% intravenously. Sodium bicarbonate may be an alternative; a study[13] in patients with pre-existing stable renal impairment suggested that it was more effective than sodium chloride. However, a retrospective study[14] found an increased risk of nephropathy in patients given sodium bicarbonate compared with those who had no prophylaxis, and further studies are needed to confirm its role.

Antoxidants have been suggested as a way of reducing the direct toxicity of contrast media. Acetylcysteine is widely used,[15] but evidence of benefit is conflicting. Some studies have produced promising results, but others have been less positive and, although reviews and meta-analyses have shown benefit[16,17] or a trend towards benefit,[18-20] most have concluded[15,17-21] that the wide variation between the studies included means that the efficacy of acetylcysteine remains uncertain. Later randomised studies have also reported conflicting results.[22,23] An observational study[24] found that there was no difference in the incidence of contrast nephropathy before and after the introduction of acetylcysteine prophylaxis, while a follow-up study[25] found that acetylcysteine had no effect on overall outcomes over 9 months. However, some authors[4,7,15] recommend the use of acetylcysteine in particularly high-risk patients. Ascorbic acid has also been tried and showed benefit in one study,[26] and promising results have been reported with trimetazidine, an anti-anginal drug with antoxidant properties,[27] but further confirmation is needed.

Other approaches have generally produced disappointing results.[1,3-7,10] The use of diuretics may increase the risk of nephropathy and is not recommended. Vasodilators have been tried, including atrial natriuretic peptide, calcium-channel blockers, low-dose dopamine, and alprostadil, but benefit has not been established and they are not generally used. Although positive results have been reported[28] with fenoldopam, which has preferential effects on renal blood flow, a large randomised study[29] failed to confirm any benefit. Studies with theophylline have produced conflicting results, although a meta-analysis[30] concluded that it might be of benefit. Use of dialysis to remove contrast medium from the circulation has also been suggested; some benefit has also been found with haemofiltration started before the procedure,[31] but not with haemodialysis immediately after the procedure.[32]

1. Esplugas E, *et al.* Comparative tolerability of contrast media used for coronary interventions. *Drug Safety* 2002; **25:** 1079–98.
2. Rudnick MR, Goldfarb S. Pathogenesis of contrast-induced nephropathy: experimental and clinical observations with an emphasis on the role of osmolality. *Rev Cardiovasc Med* 2003; **4** (suppl 5): S28–S33.
3. Cox CD, Tsikouris JP. Preventing contrast nephropathy: what is the best strategy? A review of the literature. *J Clin Pharmacol* 2004; **44:** 327–37.
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9. Pannu N, *et al.* Prophylaxis strategies for contrast-induced nephropathy. *JAMA* 2006; **295:** 2765–79.
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11. Barrett BJ, Parfrey PS. Preventing nephropathy induced by contrast medium. *N Engl J Med* 2006; **354:** 379–86.
12. Kelly AM, *et al.* Meta-analysis: effectiveness of drugs for preventing contrast-induced nephropathy. *Ann Intern Med* 2008; **148:** 284–94.
13. Merten GJ, *et al.* Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. *JAMA* 2004; **291:** 2328–34.
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15. Fishbane S, *et al.* N-acetylcysteine in the prevention of radiocontrast-induced nephropathy. *J Am Soc Nephrol* 2004; **15:** 251–60.
16. Birck R, *et al.* Acetylcysteine for prevention of contrast nephropathy: meta-analysis. *Lancet* 2003; **362:** 598–603.
17. Bagshaw SM, Ghali WA. Acetylcysteine for prevention of contrast-induced nephropathy after intravascular angiography: a systematic review and meta-analysis. *BMC Med* 2004; **2:** 38.
18. Pannu N, *et al.* Systematic review of the impact of N-acetylcysteine on contrast nephropathy. *Kidney Int* 2004; **65:** 1366–74.
19. Nallamothu BK, *et al.* Is acetylcysteine effective in preventing contrast-related nephropathy? A meta-analysis. *Am J Med* 2004; **117:** 938–47.
20. Zagler A, *et al.* N-acetylcysteine and contrast-induced nephropathy: a meta-analysis of 13 randomized trials. *Am Heart J* 2006; **151:** 140–5.
21. Kshirsagar AV, *et al.* N-acetylcysteine for the prevention of radiocontrast induced nephropathy: a meta-analysis of prospective controlled trials. *J Am Soc Nephrol* 2004; **15:** 761–9.
22. Coyle LC, *et al.* Acetylcysteine In Diabetes (AID): a randomized study of acetylcysteine for the prevention of contrast nephropathy in diabetics. *Am Heart J* 2006; **151:** 1032.e9–1032.e12.
23. Marenzi G, *et al.* N-acetylcysteine and contrast-induced nephropathy in primary angioplasty. *N Engl J Med* 2006; **354:** 2773–82.
24. Shah SJ, Hsu C-Y. Has acetylcysteine use changed the incidence of contrast nephropathy in hospitalized patients? A before-after study. *Am J Med* 2004; **117:** 948–52.
25. Miner SES, *et al.* N-acetylcysteine reduces contrast-associated nephropathy but not clinical events during long-term follow-up. *Am Heart J* 2004; **148:** 690–5.
26. Spargias K, *et al.* Ascorbic acid prevents contrast-mediated nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. *Circulation* 2004; **110:** 2837–42.
27. Onbasili AO, *et al.* Trimetazidine in the prevention of contrast-induced nephropathy after coronary procedures. *Heart* 2007; **93:** 698–702.
28. Chu VL, Cheng JWM. Fenoldopam in the prevention of contrast media-induced acute renal failure. *Ann Pharmacother* 2001; **35:** 1278–82. Correction. *ibid.*; 1677.
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32. Vogt B, *et al.* Prophylactic hemodialysis after radiocontrast media in patients with renal insufficiency is potentially harmful. *Am J Med* 2001; **111:** 692–8.

Hypersensitivity. Anaphylactoid reactions to iodinated contrast media are more common with the ionic agents than the nonionic media of lower osmolality. Patients at increased risk are those with a history of asthma or allergy, drug hypersensitivity, adrenal suppression, heart disease, previous reaction to a contrast medium, and those receiving beta blockers or interleukin-2 therapy. In such patients, nonionic media are preferred. Stopping treatment with beta blockers should be considered in patients with other risk factors.

Pretreatment with corticosteroids may be considered for preventing anaphylactoid reactions in high-risk patients, and an antihistamine may be given. However, reactions may still occur and the value of premedication remains controversial.

References.

1. Canter LM. Anaphylactoid reactions to radiocontrast media. *Allergy Asthma Proc* 2005; **26:** 199–203.
2. Idée J-M, *et al.* Allergy-like reactions to iodinated contrast agents: a critical analysis. *Fundam Clin Pharmacol* 2005; **19:** 263–81.
3. Morcos SK. Acute serious and fatal reactions to contrast media: our current understanding. *Br J Radiol* 2005; **78:** 686–93.
4. Tramèr MR, *et al.* Pharmacological prevention of serious anaphylactic reactions due to iodinated contrast media: systematic review. Abridged version: *BMJ* 2006; **333:** 675–8. Full version: http://www.bmj.com/cgi/reprint/333/7570/675 (accessed 05/09/08)

Precautions

The risk of anaphylactoid reactions with amidotrizoates and other iodinated contrast media is increased in patients with asthma or a history of allergies and they should be used with great caution in such patients; they should not be used in patients with a previous reaction to contrast media or iodine. Test doses have been given but are not generally recommended since they do not predict hypersensitivity with certainty and may cause severe or fatal reactions. Pretreatment with corticosteroids may be considered in patients considered at high risk of reactions, but the value of this is uncertain (see Hypersensitivity, above). An antihistamine may be given with the corticosteroid.

Iodinated contrast media should be used with caution in patients with severe hepatic or renal impairment, diabetics with renal impairment, and others who may be at increased risk of renal failure. Dehydration should be avoided, and any fluid or electrolyte

imbalance should be corrected before contrast media are given. Particular care is needed in patients with multiple myeloma since dehydration resulting from use of contrast media may cause precipitation of protein in the renal tubules, leading to anuria and fatal renal failure.

Caution is also necessary in patients with severe hypertension, advanced cardiac disease, phaeochromocytoma, sickle-cell disease, or hyperthyroidism or epilepsy, and in debilitated, severely ill, very old, or very young patients.

Amidotrizoates and other hypertonic contrast media are neurotoxic and should not be given intrathecally; patients with subarachnoid haemorrhage may be at risk with any intravascular use. Intravascular contrast media should also be used with caution in any patient with occlusive vascular disease. Iodinated contrast media should not be used for hysterosalpingography in the presence of infection or inflammation of the pelvic cavity, nor during menstruation or in pregnancy (although any abdominal radiography should be avoided during pregnancy because of the risks of radiation to the fetus).

Iodine-containing contrast media may interfere with thyroid function tests. There may also be interference with blood coagulation tests and certain urine tests.

Breast feeding. No adverse effects have been seen in breast-feeding infants whose mothers were receiving amidotrizoates and the American Academy of Pediatrics considers[1] that they are therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/03/06)

Neonates. Although amidotrizoates may be used in the management of some forms of intestinal obstruction (see below), meglumine amidotrizoate was considered[1] a possible contributory factor in the deaths of 2 infants who developed bowel necrosis, perforation, and peritonitis after its use for meconium ileus.

1. Leonidas JC, *et al*. Possible adverse effects of methylglucamine diatrizoate compounds on the bowel of newborn infants with meconium ileus. *Radiology* 1976; **121:** 693–6.

Pharmacokinetics

Amidotrizoates are very poorly absorbed from the gastrointestinal tract. Amidotrizoates in the circulation are not significantly bound to plasma proteins. If renal function is not impaired, unchanged amidotrizoate is rapidly excreted by glomerular filtration; over 95% of an intravascular dose is reported to be excreted in urine within 24 hours, and about 1 to 2% of a dose may be excreted in faeces. Trace amounts may be detected in other body fluids including tears and saliva. Faecal excretion may increase to 10 to 50% in severe renal impairment. The half-life of amidotrizoates has been reported to be 30 to 60 minutes, which can increase to 20 to 140 hours in severe renal impairment. They are removed by haemodialysis and peritoneal dialysis.

The amidotrizoates cross the placenta and are distributed into breast milk.

Uses and Administration

The amidotrizoates are ionic monomeric iodinated radiographic contrast media (p.1474). Both the sodium and the meglumine salt have been widely used in diagnostic radiography; however, adverse effects may be reduced by using a mixture of both salts, and this is often preferred. Preparations are available containing a wide range of strengths. Mixtures containing sodium amidotrizoate 10% w/v with meglumine amidotrizoate 66% w/v, or sodium amidotrizoate 4% with meglumine amidotrizoate 26%, are commonly used. For use alone, preparations containing sodium amidotrizoate 25 to 50% w/v, or meglumine amidotrizoate 60% w/v, may be appropriate.

The amidotrizoates are used in an extensive range of procedures, although in many cases lower osmolality contrast media are now preferred. The dose and route depend on the procedure and the degree and extent of contrast required. They are given intravenously for urography, for venography, and in computed tomography; for urography, they have also been given by intramuscular or subcutaneous injection, but these routes are not generally recommended. They may be given intra-arterially for angiography, by intra-articular injection for arthrography, or by intra-osseous injection for imaging of the vasculature of the bones. For other procedures they may be instilled into body cavities, or injected into the gallbladder, biliary ducts, or spleen. Amidotrizoates have also been given orally or rectally for imaging of the gastrointestinal tract.

Solutions of amidotrizoates have also been given as an enema in the treatment of uncomplicated meconium ileus.

Calcium amidotrizoate and lysine amidotrizoate have also been used as contrast media.

Gastrointestinal obstruction. Amidotrizoates and other water-soluble contrast media have been given rectally as osmotic agents in the management of gastrointestinal obstruction due to meconium ileus;[1] however, adverse effects have been reported in neonates (see above). They have also been used as an alternative to barium sulfate enemas in the management of intussusception (see below). Amidotrizoates given orally have been used in the management of adhesive small bowel obstruction;[2] they allow identification of patients who require surgery and, although they have not been shown to relieve obstruction, they may reduce length of hospital stay in patients treated without surgery.

1. Murshed R, *et al*. Meconium ileus: a ten-year review of thirty-six patients. *Eur J Pediatr Surg* 1997; **7:** 275–7.
2. Abbas S, *et al*. Oral water soluble contrast for the management of adhesive small bowel obstruction. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 14/07/08).

Preparations

BP 2008: Meglumine Amidotrizoate Injection; Sodium Amidotrizoate Injection;
USP 31: Diatrizoate Meglumine and Diatrizoate Sodium Injection; Diatrizoate Meglumine and Diatrizoate Sodium Solution; Diatrizoate Meglumine Injection; Diatrizoate Sodium Injection; Diatrizoate Sodium Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Angiografina; Densopax; Hypaque 60%†; Hypaque 76%†; MD-76; MD-Gastroview; Plenigraf; Temistac; Tomoray; Triyosom; Urografina; Urovisona; ***Austral.:*** Angiografin†; Gastrografin; MD-60†; MD-76; MD-Gastroview; Urografin; ***Austria:*** Gastrografin; Urografin†; ***Belg.:*** Gastrografin; Urografine†; ***Braz.:*** Hypaque; Hypaque-M; Urografina; ***Canad.:*** Hypaque-M†; Hypaque†; MD-76; ***Chile:*** Angiovist; Hypaque 60%†; Hypaque 76%†; Pielograf†; Reliev; Reliev 76%; ***Cz.:*** Urografin†; ***Denm.:*** Urografin; Urografin Meglumin; ***Fin.:*** Gastrografin; ***Fr.:*** Gastrografine; Radioselectan; ***Ger.:*** Ethibloc; Gastrografin; Gastrolux; Peritrast; Peritrast comp; Peritrast-Infusio 160/32%†; Peritrast-Infusio 180/31%; Peritrast-Oral CT; Peritrast-Oral-GI; Peritrast-RE; Urolux; Urolux Retro; Urovison†; ***Gr.:*** Gastrografin; ***Hung.:*** Gastrografin; Peritrast; ***India:*** Urografin; ***Israel:*** Urografin†; ***Ital.:*** Gastrografin; ***Neth.:*** Angiografin†; Gastrografin; Urografin; Urovison†; ***Norw.:*** Gastrografin; ***NZ:*** Gastrografin; Urografin; ***Port.:*** Gastrografina; Urografina; ***Rus.:*** Hypaque (Гипак)†; Trazograph (Тразограф); Urographin (Урографин); ***S.Afr.:*** Angiografin†; Gastrografin; Urografin; ***Spain:*** Gastrografin; Pielograf; Plenigraf; Radialar 280; Trazograf; Uro Angiografin; Urografin; ***Swed.:*** Gastrografin; Urografin; ***Switz.:*** Gastrografin; Urografin†; ***UK:*** Gastrografin; Hypaque; Urografin 150 and 370; ***USA:*** Cystografin; Gastrografin; Hypaque; Hypaque-M, Hypaque-76; MD-76; MD-Gastroview; Reno-M; Renografin; ***Venez.:*** Hypaque-M†.

Multi-ingredient: ***USA:*** Sinografin.

Barium Sulfate

Barii sulfas; Barii Sulphas; Bario sulfatas; Barium Sulfuricum; Barium Sulphate; Bariumsulfaatti; Bariumsulfat; Bárium-szulfát; Baru siarczan; Baryum (Sulfate de); Baryum, sulfate de; Síran barnatý; Sulfato de bario.

$BaSO_4$ = 233.4.

CAS — 7727-43-7.

ATC Vet — QV08BA02.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet*.

Ph. Eur. 6.2 (Barium Sulphate). A fine, white powder, free from gritty particles. Practically insoluble in water and in organic solvents; very slightly soluble in acids and in solutions of alkali hydroxides.

USP 31 (Barium Sulfate). A fine, white, odourless, bulky powder, free from grittiness. Practically insoluble in water, in organic solvents, and in solutions of acids and of alkalis. pH of a 10% w/w aqueous suspension is between 3.5 and 10.0.

Adverse Effects

Because barium sulfate is almost insoluble it lacks the severe toxicity characteristic of the barium ion; deaths have occurred in patients given the more soluble barium sulfide in error for the sulfate.

Constipation may occur after oral or rectal barium sulfate; impaction, obstruction, and appendicitis have occurred. Surgical removal of faecaliths has sometimes been necessary. Cramping or diarrhoea have also been reported. Venous intravasation has led to the formation of emboli; deaths have occurred. Perforation of the bowel has led to peritonitis, adhesions, granulomas, and a high mortality rate.

ECG abnormalities have occurred during the use of barium sulfate enemas.

Accidental aspiration into the lungs has led to pneumonitis or granuloma formation.

Hypersensitivity. A survey of hypersensitivity reactions to barium preparations found that although barium is inert many of the additives used in formulation have the potential to cause reactions.[1] Of 106 reactions reported or found in the literature, 61% involved the skin and only 8% the respiratory tract; unconsciousness was reported in 8% of cases. In view of the frequency of use of barium preparations, such adverse reactions must be very rare, but radiologists should be aware that they might be somewhat more common than was usually appreciated. A number of severe reactions associated with the use of barium enemas supplied with an inflatable latex cuff may have been due to leaching of components from the latex.[2]

1. Janower ML. Hypersensitivity reactions after barium studies of the upper and lower gastrointestinal tract. *Radiology* 1986; **161:** 139–40.
2. Nightingale SL. Severe adverse reactions to barium enema procedures. *JAMA* 1990; **264**: 2863.

Precautions

Barium sulfate should not be given to patients with intestinal obstruction and care is needed in those with conditions such as pyloric stenosis or lesions that may predispose to obstruction. Adequate hydration should be ensured after the procedure to prevent severe constipation.

It is contra-indicated in patients with gastrointestinal perforation, and should be avoided, particularly when given rectally, in those at risk of perforation, such as patients with acute ulcerative colitis or diverticulitis and after rectal or colonic biopsy, sigmoidoscopy, or radiotherapy.

Uses and Administration

Barium sulfate is used as a radiographic contrast medium (p.1474) for X-ray examination of the gastrointestinal tract involving single- or double-contrast techniques or computed tomography.

The dose of barium sulfate is dependent upon the type of examination and technique used. In the UK typical doses and concentrations used for examination are:

- oesophagus: up to 150 mL of a 50 to 200% w/v suspension given orally
- stomach and duodenum: up to 300 mL of a 30 to 200% w/v suspension given orally
- small intestine: 100 to 300 mL of a 30 to 150% w/v suspension given orally
- colon: 200 mL to 2 litres of a 20 to 130% w/v suspension given as an enema.

A suspension containing 1.6 to 2.2% may be used in gastrointestinal computed tomography.

In the USA, suspensions containing up to 230% w/v barium sulfate may be used; lower concentrations are available for use in computed tomography and usually contain about 1 to 2% w/v.

For double-contrast examination, gas can be introduced into the gastrointestinal tract by using suspensions of barium sulfate containing carbon dioxide; separate gas-producing preparations based on sodium bicarbonate are also available. Air given via a tube may be used as an alternative to carbon dioxide.

◊ Reviews.

1. Nolan DJ, Traill ZC. The current role of the barium examination of the small intestine. *Clin Radiol* 1997; **52:** 809–20.
2. Mendelson RM. The role of the barium enema in the diagnosis of colorectal neoplasia. *Australas Radiol* 1998; **42:** 191–6.
3. de Zwart IM, *et al*. Barium enema and endoscopy for the detection of colorectal neoplasia: sensitivity, specificity, complications and its determinants. *Clin Radiol* 2001; **56:** 401–9.
4. Rubesin SE, Maglinte DD. Double-contrast barium enema technique. *Radiol Clin North Am* 2003; **41:** 365–76.
5. O'Connor SD, Summers RM. Revisiting oral barium sulfate contrast agents. *Acad Radiol* 2007; **14:** 72–80.

Intussusception. Contrast media enemas and ultrasound are both used in the diagnosis of intussusception, a condition in infants where part of the intestine prolapses into the lumen of an adjacent part causing an obstruction.[1,2] However, some consider ultrasound to be superior for diagnosis and reserve enemas for the therapeutic reduction of intussusception. Reduction is achieved as a result of the hydrostatic pressure of the enema pushing the intestine back into its natural position. Although there is extensive experience using barium enemas for reduction some centres prefer to use water-soluble contrast media so as to minimise the risk of chemical peritonitis if perforation of the bowel occurs. Other agents used instead of barium for reduction include air enemas or ultrasound guided saline enemas, both of which avoid or reduce radiographic exposure. Surgery is indicated when enema therapy fails or is considered unsuitable.

1. del-Pozo G, *et al*. Intussusception in children: current concepts in diagnosis and enema reduction. *Radiographics* 1999; **19:** 299–319.
2. Sorantin E, Lindbichler F. Management of intussusception. *Eur Radiol* 2004; **14** (suppl 4): L146–L154.

Preparations

BP 2008: Barium Sulphate for Suspension; Barium Sulphate Oral Suspension;
USP 31: Barium Sulfate for Suspension; Barium Sulfate Paste; Barium Sulfate Suspension; Barium Sulfate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Barigraf; Bario; Bariofarma; Barosperse; E-Z-Cat; Entero VU; Gastropaque; Novopacum; Opti-Up†; Scheribar; Tixobar; Top-Cat; ***Austral.:*** Medebar; Medescan; Tixobar†; ***Austria:*** Barilux; Prontobario; Scannotrast; ***Belg.:*** E-Z-Paque; Micropaque; Microtrast; Polibar; ***Braz.:*** Bariogel; Celobar†; ***Chile:*** Barigraf†; ***Cz.:*** E-Z-Cat; E-Z-HD; E-Z-Paque†; Micropaque; Microtrast; Polibar; Prontobario†; ***Denm.:*** Micropaque; Microtrast; Mixobar; ***Fin.:*** Mixobar; ***Fr.:*** Micropaque; Microtrast; ***Ger.:*** Barilux; Micropaque; Microtrast; ***Gr.:*** Barilux; Micropaque; Unibaryt-R; ***Hung.:*** E-Z-Cat; E-Z-HD; Micropaque; Microtrast; Polibar ACB; Polibar Rapid; ***Israel:*** E-Z-Cat; E-Z-HD; E-Z-Paque; Entero VU; Liquid Polibar Plus; Polibar ACB; ***Ital.:*** Mixobar†; Prontobario; TAC Esofago; ***Neth.:*** Baricol; E-Z-HD; Micropaque; Polibar; ***Norw.:*** Mixobar; ***NZ:*** Medebar†; ***Port.:*** E-Z-Cat; E-Z-HD; Gastrobario; Micropaque; Microtrast; Polibar; ***Spain:*** Barigraf; Bario Dif; Bario Llorente†; Disperbarium; Justebarin†; Micropaque†; ***Swed.:*** Mixobar; ***Switz.:*** CAT-Barium (E-Z-CAT); Microbar-HD (E-Z-HD); Micropaque; Polibar ACB; ***UK:*** Baritop; E-Z-Cat; E-Z-HD; E-Z-Paque; Polibar; Polibar Rapid; ***USA:*** Anatrast; Baricon; Baro-cat; Barobag; Barosperse; Bear-E-Yum; CheeTah; Enecat; Enemark; Enhancer; Entrobar; Epi-C; Flo-Coat; HD 200 Plus; HD 85; Introp aste; Liqui-Coat HD; Liquipake; Medebar; Medescan; Prepcat; Scan C; Tomocat; Tonojug; Tonopaque; ***Venez.:*** Barin; Bariogel†; Bariotin†; Sulfobarina†.