11. Allwood MC. The effectiveness of preservatives in insulin injections. *Pharm J* 1982; **229:** 340.
12. Sunderland VB, Watts DW. Kinetics of the degradation of methyl, ethyl and n-propyl 4-hydroxybenzoate esters in aqueous solution. *Int J Pharmaceutics* 1984; **19:** 1–15.
13. Flora KP, *et al.* The loss of paraben preservatives during freeze drying. *J Pharm Pharmacol* 1980; **32:** 577–80.

Adverse Effects and Precautions

Hypersensitivity reactions occur with the hydroxybenzoates. Generally these are of the delayed type, appearing as contact dermatitis. Immediate reactions with urticaria and bronchospasm have occurred rarely.

Breast cancer. Some researchers[1] have questioned whether *p*-hydroxybenzoic acid esters, the most common preservatives found in body care cosmetic products, could increase the incidence of breast cancer in women. The esters have been shown to be oestrogenic *in vitro* and *in vivo* and have been detected in human breast tumour tissue, although a causal association cannot be confirmed.

1. Harvey PW, Darbre P. Endocrine disrupters and human health: could oestrogenic chemicals in body care cosmetics adversely affect breast cancer incidence in women? *J Appl Toxicol* 2004; **24:** 167–76.

Hypersensitivity. Immediate hypersensitivity reactions such as urticaria and bronchospasm with generalised pruritus, have been reported rarely on injection of preparations containing hydroxybenzoates.[1,2] Delayed contact dermatitis occurs more frequently, usually after use of topical medications, but has also occurred after use of an ester or of *p*-hydroxybenzoic acid in oral preparations.[3] Hypersensitivity reactions have also been reported in patients given local anaesthetics containing hydroxybenzoates[1,4] and cross-reactions with other para-amino compounds including benzocaine, paraphenylenediamine, and sulfonamides have occurred rarely.[5]

The incidence of sensitisation to hydroxybenzoates ranges from 0 to 3.5% but has tended to stay relatively constant over time.[5] A report from the North American Contact Dermatitis Group[6] in 1972 provided an incidence of 3%, while another later review[7] of a large number of patients gave an incidence of 2.2%. The Swiss Contact Dermatitis Research Group reported[8] a sensitisation rate of 1.7% based on a one-year study from 1989 to 1990 in 2295 patients.

Subjects with healthy skin exposed to hydroxybenzoates, for example in cosmetics, are considered to have a much lower incidence of reactions than patients with eczema or skin trauma. Unusually, patients who have reacted to a hydroxybenzoate with a contact dermatitis appear to be able to apply that preservative to another unaffected site and yet not suffer a reaction; this has been termed the 'paraben paradox'.[9]

1. Aldrete JA, Johnson DA. Allergy to local anaesthetics. *JAMA* 1969; **207:** 356–7.
2. Nagel JE, *et al.* Paraben allergy. *JAMA* 1977; **237:** 1594–5.
3. Kaminer Y, *et al.* Delayed hypersensitivity reaction to orally administered methylparaben. *Clin Pharm* 1982; **1:** 469–70.
4. Lederman DA, *et al.* An unusual skin reaction following local anesthetic injection: review of the literature and report of four cases. *Oral Surg* 1980; **49:** 28–33.
5. Sasseville D. Hypersensitivity to preservatives. *Dermatol Ther* 2004; **17:** 251–63.
6. North American Contact Dermatitis Group. Epidemiology of contact dermatitis in North America 1972. *Arch Dermatol* 1973; **108:** 537–40.
7. Moore J. Final report on the safety assessment of methylparaben, ethylparaben, propylparaben, and butylparaben. *J Am Coll Toxicol* 1984; **3:** 147–209.
8. Perrenoud D, *et al.* Frequency of sensitization to 13 common preservatives in Switzerland. *Contact Dermatitis* 1994; **30:** 276–9.
9. Fisher AA. Cortaid cream dermatitis and the "paraben paradox". *J Am Acad Dermatol* 1982; **6:** 116–7.

Neonates. An *in-vitro* study on serum from neonates with hyperbilirubinaemia indicated that methyl hydroxybenzoate at a concentration of 200 micrograms/mL of serum increased the concentration of free unconjugated bilirubin and interfered with the binding of bilirubin to serum proteins. Methyl hydroxybenzoate was present in an injection of gentamicin sulfate at a concentration of 1.3 to 1.8 mg/mL. Neither gentamicin nor propyl hydroxybenzoate had a significant effect on bilirubin.[1]

1. Loria CJ, *et al.* Effect of antibiotic formulations in serum protein: bilirubin interaction of newborn infants. *J Pediatr* 1976; **89:** 479–82.

Pharmacokinetics

Neonates. After intramuscular injection, methyl hydroxybenzoate present in a gentamicin preparation was excreted in the urine of preterm infants to a variable extent and mainly in the conjugated form.[1] *p*-Hydroxybenzoic acid was detected as a metabolite. The injection contained methyl hydroxybenzoate 3.6 mg, propyl hydroxybenzoate 400 micrograms, and gentamicin 80 mg. Propyl hydroxybenzoate was also detected in the urine samples.

1. Hindmarsh KW, *et al.* Urinary excretion of methylparaben and its metabolites in preterm infants. *J Pharm Sci* 1983; **72:** 1039–41.

Uses

The hydroxybenzoate preservatives are alkyl esters of *p*-hydroxybenzoic acid with antibacterial and antifungal properties. They are more active against Gram-positive than against Gram-negative bacteria. They are active over a broad pH range (4 to 8), though are generally more active in acidic solutions. Activity increases with increasing alkyl chain length but aqueous solubility decreases, although this may be overcome by employing the more soluble sodium salts as long as the pH of the preparation is not increased. Activity may also be increased by combining two hydroxybenzoates with short alkyl chains. Another way of increasing activity is to use a hydroxybenzoate with propylene glycol.

Hydroxybenzoates are used as preservatives in pharmaceutical preparations in usual concentrations of up to 0.25%. Methyl hydroxybenzoate and propyl hydroxybenzoate are used together in some preparations. There have been reports of the hydroxybenzoates not being satisfactory preservatives for ophthalmic preparations because of their relative lack of efficacy against some Gram-negative bacteria, particularly *Pseudomonas aeruginosa*. The hydroxybenzoate preservatives are widely used in cosmetics and are also used for food preservation.

Hydroxybenzoates have been used in preparations promoted for the management of skin infections or pruritus.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Nisapulvol; Nisaseptol; Nisasol; ***Malaysia:*** Nisapulvol.

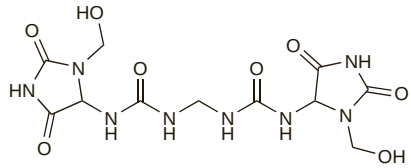
Multi-ingredient: ***Austral.:*** Mycoderm; ***Hong Kong:*** Mycoderm†; ***Malaysia:*** Mycoderm; ***Neth.:*** Trachitol; ***UK:*** Brushtox; ***Venez.:*** Glizigen.

Imidurea

N,N″-Methylenebis{*N′*-[3-(hydroxymethyl)-2,5-dioxo-4-imidazolidinyl]urea}.

$C_{11}H_{16}N_8O_8$ = 388.3.

CAS — 39236-46-9.



Pharmacopoeias. In *USNF*.

USNF 26 (Imidurea). A white odourless powder. Soluble in water and in glycerol; sparingly soluble in propylene glycol; insoluble in most organic solvents. A 1% solution in water has a pH of 6.0 to 7.5. Store in airtight containers.

Profile

Imidurea is used as an antimicrobial preservative in topical pharmaceutical and cosmetic preparations.

Iodoform

Iodoformo. Tri-iodomethane.

CHI_3 = 393.7.

CAS — 75-47-8.

ATC — D09AA13.

ATC Vet — QD09AA13.

Pharmacopoeias. In *Jpn* and *US*.

USP 31 (Iodoform). A lustrous greenish-yellow powder or lustrous crystals. It is slightly volatile at ordinary temperatures and distils slowly with steam. It decomposes at high temperatures emitting vapours of iodine. Practically insoluble in water; sparingly soluble in alcohol, in glycerol, and in olive oil; soluble in boiling alcohol; freely soluble in chloroform and in ether. Store in airtight containers at a temperature not exceeding 40°. Protect from light.

Profile

Iodoform slowly releases iodine (p.2169) when applied to the tissues and is used for its mild antiseptic action. Bismuth Subnitrate and Iodoform Paste (BPC 1954) (BIPP) has been applied to wounds and abscesses. Sterile gauze impregnated with the paste has also been used for packing cavities after oral and otorhinological surgery.

Adverse effects on the nervous system. Encephalopathy has been associated with the use of bismuth subnitrate and iodoform paste (BIPP) for the packing of wound cavities after ear, nose, and throat, oral, and maxillofacial surgery,[1,2] although there is some debate as to whether the bismuth or the iodoform component is responsible.[1-3] However, encephalopathy has been reported after application of iodoform gauze without bismuth.[4,5] CNS toxicity due to both iodine and bismuth has been reported[6] in an 86-year-old woman from an intra-oral plug of BIPP following partial maxillectomy. Five days after surgery the patient started to experience loss of appetite and lightheadedness, and by day 11 was suffering from fainting episodes, confusion, and paranoid ideation and was becoming increasingly aggressive. On day 14 the BIPP pack was removed; 7 days later the patient's condition improved and when discharged 5 days later she was alert and cooperative.

1. Wilson APR. The dangers of BIPP. *Lancet* 1994; **344:** 1313–14.
2. Youngman L, Harris S. BIPP madness; an iatrogenic cause of acute confusion. *Age Ageing* 2004; **33:** 406–7.
3. Farrell RWR. Dangers of bismuth iodoform paraffin paste. *Lancet* 1994; **344:** 1637–8.
4. Roy P-M, *et al.* Dangers of bismuth iodoform paraffin paste. *Lancet* 1994; **344:** 1708.
5. Yamasaki K, *et al.* Delirium and a subclavian abscess. *Lancet* 1997; **350:** 1294.
6. Harris RA, Poole A. Beware of bismuth: post maxillectomy delirium. *Aust N Z J Surg* 2002; **72:** 846–7.

Hypersensitivity. A retrospective analysis of 185 patients[1] who were treated with a bismuth-iodoform-paraffin paste (BIPP) impregnated ribbon gauze pack after ear surgery found the incidence of allergic reactions to be 5.9%. A fivefold increase risk of developing allergic reactions was also found in those with previous exposure to BIPP. Three cases of allergic contact otitis externa have been reported following the use of bismuth subnitrate and iodoform paste to pack the ear after surgery.[2]

1. Lim PVH, *et al.* Hypersensitive allergic reactions to bismuth-iodoform-paraffin paste following ear surgery. *J Laryngol Otol* 1998; **112:** 335–7.
2. Roest MAB, *et al.* Allergic contact otitis externa due to iodoform in BIPP cavity dressings. *Contact Dermatitis* 2002; **46:** 360.

Preparations

BPC 1954: Bismuth Subnitrate and Iodoform Paste; Compound Iodoform Paint.

Proprietary Preparations (details are given in Part 3)
Ger.: Jodoform†; Opraclean.

Multi-ingredient: ***Arg.:*** Aseptobron; ***Ital.:*** Pasta Iodoformica Radiopaca; ***Spain:*** Alvogil; ***Switz.:*** Alvogyl; ***UK:*** OxBipp.

Isopropyl Alcohol

Alcohol isopropílico; Alcohol isopropylicus; Alkohol izopropylowy; Dimethyl Carbinol; Isopropanol; Isopropylalkohol; Isopropylique, alcool; Isopropyylialkoholi; Izopropil Alkol; Izopropil-alkohol; Izopropilo alkoholis; 2-Propanol; Secondary Propyl Alcohol. Propan-2-ol.

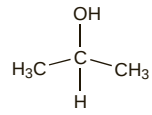
Изопропиловый Спирт

$(CH_3)_2CHOH$ = 60.10.

CAS — 67-63-0.

ATC — D08AX05.

ATC Vet — QD08AX05.



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

Ph. Eur. 6.2 (Isopropyl Alcohol). A clear colourless liquid. Miscible with water and with alcohol. Protect from light.

USP 31 (Isopropyl Alcohol). A transparent, colourless, mobile, volatile, flammable liquid with a characteristic odour. Miscible with water, with alcohol, with chloroform, and with ether. Store in airtight containers remote from heat.

Adverse Effects, Treatment, and Precautions

Isopropyl alcohol is considered to be more toxic than ethyl alcohol (p.1625), and the symptoms of intoxication appear to be similar, except that isopropyl alcohol has no initial euphoric action and gastritis, haemorrhage, pain, nausea, and vomiting are more prominent.