

Martindale

Thirty-sixth edition

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Fr.: Strepsik: Strepsik Lidocaine: Strepsik Miel-Citron: Strepsik Vitamine C. Strepsikpray Lidocaine: Gert: Doberdan Synergie: Neo-Angin; Gert: Strepsik: Meng Kong: Strepsik: Strepsik Dual Action: Mung; Neo-Angin; Gret: Strepsik: Strepsik Menthol and Eucalyptus; Strepsik Plus: Strepsik Vitamin C. India: Col Q. Cofsikt; IAt: Strepsik: Strepsik: Strepsik: Strepsik: Plus: Strepsik: Strepsik: Plus: Strepsik: Strepsik: Plus: Strepsik: Strepsik: Strepsik: Strepsik: Dual Action: Strepsik: Vitamin C. India: Benagol: Mentolo-Eucaliptolo; Benagol: Vitamina: C. India: Benagol: Benagol: Mentolo-Eucaliptolo; Benagol: Vitamina: C. India: Strepsik: Andard: Acopnuch; Planza Lonsqu: (Plessa: Angeren): Strepsik: (Chapacuc: Thochagi: Strepsik: S

Ascorbyl Palmitate

Ascorbilo, palmitato de; Ascorbyle, palmitate d'; Ascorbylis palmitas: Askorbylio palmitatas; Askorbyloalmitat; Askorbylioalmitati; Askorbylioalmitati; Askorbylioalmitati; Askorbylioalmitati; Askorbylioalmitati; Vitamin C Palmitate. L-Ascorbic acid 6-hexadecanoate; L-Ascorbic acid 6-palmitate; 3-Oxo-L-gulofuranolactone 6-palmita tate.

 $C_{22}H_{38}O_7 = 414.5.$ CAS — 137-66-6. - 137-66-6.

NOTE. The code E304 is used for fatty acid esters of ascorbic acid, which include ascorbyl palmitate.

Pharmacopoeias. In Eur. (see p.vii). Also in USNF.
Ph. Eur. 6.2 (Ascorbyl Palmitate). A white or yellowish-white powder. Practically insoluble in water, freely soluble in alcohol and in methyl alcohol, practically insoluble in dichloromethane and in fatty oils. Store in airtight containers. Protect from light.
USNF 26 (Ascorbyl Palmitate). A white to yellowish-white powder with a characteristic odour. Very slightly soluble in water, in chloroform, in ether, and in vegetable oils; soluble 1 in 125 of alcohol. Store at 8° to 15° in airtight containers.

Ascorbyl palmitate is an antoxidant used as a preservative in Ascorbyl palmitate is an antoxidant used as a preservative in pharmaceutical products and foods. It is often used with alpha tocopherol (p. 1992), and this combination shows marked synergy. As it is a fat-soluble derivative of vitamin C (ascorbic acid, p. 1983), ascorbyl palmitate is sometimes used as a source of vitamin C in nutritional supplements.

Preparations

Proprietary Preparations (details are given in Part 3) Chile: Neolucid-C.

Multi-ingredient: Hong Kong: Proflavanol†; Melaysia; Proflavanol Port.: Thiospot; Singapore: Proflavanol.

Benzalkonium Chloride (BAN, HNN)

Bensalkoniumklorid; Bentsalkoniumkloridi; Benzalconio Cloruro; Benzalkonii chloridum; Benzalkonio chloridas; Benzalkoniowy chlorek; Benzalkonium Chloratum; Benzalkonium, chlorure de; Benzalkonium-chlorid; Benzalkónium-klorid; Benzalkonyum Klorür; Cloreto de Benzalconio; Cloruro de benzalconio.

Бензалкония Хлорид

CAS - 8001-54-5.

ATC - D08AJ01; D09AA11; R02AA16.

ATC Vet - QD08AJ01; QD09AA11; QR02AA16.

R = C8H17 to C18H37

Pharmacopoeias. In Chin., Eur. (see p.vii), Int., and Jpn. Also in USNF. Some pharmacopoeias also have a monograph for a solution.

des benzalkoniu m bromide.

Chin. also includes benzalkonium bromide.

Ph. Eur. 6.2 (Benzakonium Chloride). A mixture of alkylbenzyldimethylammonium chlorides, the alkyl groups having chain
lengths of C₈ to C₁₈. It contains not less than 95% and not more
than 104% of alkylbenzyldimethylammonium chlorides, calculated as C₂₂H₄₀CIN with reference to the anhydrous substance.
A white or yellowish-white powder, or gelatinous yellowishwhite pieces, hygroscopic and soapy to the touch. It forms a clear
molten mass on heating. It contains not more than 10% of water.
Very soluble in water and in alcohol. An aqueous solution froths
coniously when shaken. usly when shaken.

USNF 26 (Benzalkonium Chloride). A mixture of alkylb USNP 26 (Senzaikonium Chiorice). A mixture of aikytienzy-idimethylammonium chlorides of the general formula $[C_6H_5.CH_2.N(CH_3)_2.R]CI$, in which R represents a mixture of the alkyls having chain lengths from C_8 to C_{16} . It contains not less than 40% of the $C_{12}H_{25}$ compound, calculated on the anhydrous substance, not less than 20% of the $C_{12}H_{25}$ compound, and not less than 70% of the 2 compounds together. A white or yellowish-white, thick gel, or gelatinous pieces with a mild aromatic adour. It contains not more than 15% of water.

A write or yellowish-white, thick gel, or gelatinous pieces with a mild aromatic odour. It contains not more than 15% of water. Very soluble in water and in alcohol; the anhydrous form is soluble 1 in 100 of ether and 1 in 6 of benzene. A solution in water is usually slightly alkaline and foams strongly when shaken. Store in airtight containers.

Incompatibility. Benzalkonium chloride is incompatible with soaps and other anionic surfactants, citrates, iodides, nitrates, permanganates, salicylates, silver salts, tartrates, and zinc oxide and sulfate. Incompatibilities have been demonstrated with ingredients of some commercial rubber mixes or plastics. Incompatibilities have also been reported with other substances inclung aluminium, cotton dressings, fluorescein sodium, hydrogen peroxide, hypromellose, kaolin, hydrous wool fat, and some sulfonamides.

Adverse Effects, Treatment, and Precautions

As for Cetrimide, p.1634. Because some rubbers are incompatible with benzalkonium chloride silicone rubber teats should be used on eye drop containers unless the suitability has been established.

Catheters and cannulas. For reference to benzalkonium chloride used in the manufacturing process of heparin-bonded catheters interfering with determination of serum concentrations of sodium and potassium, see under Precautions for Heparin,

Effects on the eyes. Benzalkonium chloride is one of the most disruptive ophthalmic additives to the stability of the lipid film and to corneal epithelial membranes; toxicity studies have tended to be carried out using relatively high concentrations of benzalkonium chloride but damage to the tear film and cornecountarium and the concentrations of the tear film and cornecountarium chloride. junctival surface have been noted in patients receiving regular long-term treatment for glaucoma with eye drops preserved with benzalkonium chloride in usual concentrations. 3.4

Corneal toxicity has also been reported in patients inadvertently exposed to benzalkonium chloride as a preservative in viscoelastic material during cataract surgery. The use of preservatives in eye drops should generally be avoided and the formulation of such preparations in single-dose containers is desirable. Benzalkonium chloride is not suitable for use in solutions for storing and washing bydophilic soft contact lenses, as it can hind to the and washing hydrophilic soft contact lenses, as it can bind to the lenses and may later produce ocular toxicity when the lenses are worn.⁶ Similarly, benzalkonium chloride use in anaesthetic eye drops is discouraged, as the anaesthetic component reduces the blink reflex and increases the contact time with the eye drops ounk retiex and increases the contact time with the eye crops which may consequently result in increased toxicity due to the preservative. Patients with dry eye syndrome are also at increased risk of toxicity as the comeal epithelium is exposed to the full strength of the eye drops, in addition to which these patients do not produce enough tears to dilute the preservative in the eye

- Burstein NL. The effects of topical drugs and preservatives of the tears and corneal epithelium in dry eye. Trans Ophthalmo Soc U K 1985; 104: 402-9.
- Burstein NL. Corneal cytotoxicity of topically applied drugs, ve hicles and preservatives. Surv Ophthalmol 1980; 25: 15-30.
- Herreras JM, et al. Ocular surface alteration after long-term treatment with an antiglaucomatous drug. Ophthalmology 1992;
- 4. Kuppens EVMJ, et al. Effect of timolol with and without preservative on the basal tear turnover in glaucoma. Br J Ophthalmol 1995; 79: 339–42.
- moi 1995; 93: 339-42.
 Selftheriadis H. et al. Corneal toxicity secondary to inadvertent use of benzalkonium chloride preserved viscoelastic material in cataract surgery. Br J Ophthalmol 2002; 86: 299-305.
 Gasset AR. Benzalkonium chloride toxicity to the human cornea. Am J Ophthalmol 1977; 84: 169-71.

Effects on the respiratory tract. Hypersensitivity to benzal-konium chloride, used as a preservative in nasal drops, was con-firmed in a patient by a challenge that produced nasal congestion

and irritation of the eyes and throat lasting 48 hours. A review of 18 studies (14 in vivo, 4 in vitro) where benzalkonium chloride was used as the preservative in multidose nasal products found that 8 studies (all in vivo) found no toxic effects, while 10 reported degenerative changes to the nasal epithelia or exacerbation of rhinitis medicamentosa. However, in only 2 of these 10 studies with the difference heaven becambeauting the price and course. were the differences between benzalkonium chloride and control groups found to be significant, and both of these included the use of oxymetazoline, which is known to cause rhinitis medicamen-

Benzalkonium chloride used as a preservative in nebulised solu-tions of anti-asthma drugs has been reported to cause dose-relat-ed bronchoconstriction especially in asthmatic patients, 3 and has been associated with the precipitation of respiratory arrest.4

- Hillerdal G. Adverse reaction to locally applied preservatives in nose drops. ORL J Otorhinolaryngol Relat Spec 1985; 47: 278-9.
- Marple B, et al. Safety review of benzalkonium chloride used as a preservative in intranasal solutions: an overview of conflicting data and opinions. Otolarymgol Head Neck Surg 2004; 130: 121.41.
- Committee on Drugs, American Academy of Pediatrics. "Inactive" ingredients in pharmaceutical products: update. Pediatrics 1997; 99: 268-78.
- Boucher M, et al. Possible association of benzalkonium chloride in nebulizer solutions with respiratory arrest. Ann Pharmacother 1992; 26: 772-4.

Interactions

Benzalkonium chloride is not suitable for use in eye drops containing local anaesthetics (see Effects on the Eves, above).

Uses and Administration

Benzalkonium chloride is a quaternary ammonium antiseptic and disinfectant with actions and uses similar to those of the other cationic surfactants (see Cetrimide, p. 1634). It is also used as an antimicrobial preservative for pharmaceutical products. Benzalkonium bromide and benzalkonium saccharinate have also been

Solutions of benzalkonium chloride 0.01 to 0.1% are used for cleansing skin, mucous membranes, and wounds. More dilute solutions of 0.005% are suitable for irrigation of deep wounds. A 0.02 to 0.05% solution has been used as a vaginal douche. An aqueous solution containing 0.005 to 0.02% has been used for irrigation of the bladder and urethra and a 0.0025 to 0.005% solution for retention lavage of the bladder.

Creams containing benzalkonium chloride are used in the treatment of napkin rash and other dermatoses

A 0.2 to 0.5% solution has been used as a shampoo in seborrhoeic dermatitis.

Lozenges containing benzalkonium chloride are used for the treatment of superficial infections of the mouth and throat

Benzalkonium chloride is used as a preservative in ophthalmic solutions at a concentration of 0.01 to 0.02%, and in nasal and otic solutions at a concentration of 0.002 to 0.02%. Benzalkonium chloride is used for disinfecting rigid contact lenses (p.1622) but is unsuitable as a preservative in solutions for washing and storing hydrophilic soft contact lenses (see also Effects on the Eyes, above).

Benzalkonium chloride is also used as a spermicide.

Solutions of 0.13% are used for disinfection and storage of surgical instruments, sometimes with the addition of sodium nitrite to inhibit rust.

Action. The antibacterial effect of benzalkonium chloride 0.003% was enhanced by 0.175% of benzyl alcohol, phenylpro-panol, or phenethyl alcohol. For the use of phenethyl alcohol with benzalkonium chloride as a preservative for ophthalmic so-lutions, see Antimicrobial Action, under Phenethyl Alcohol, p.1655.

Richards RME, McBride RJ. Enhancement of benzalkonium chloride and chlorhexidine acetate activity against Pseudomonas aeruginosa by aromatic alcohols. J Pharm Sci 1973; 62: 2035-7.

Catheter-related sepsis. Benzalkonium chloride has been investigated1,2 for in orporation into catheters to reduce catheterrelated sepsis (p.1624).

- Tebbs SE, Elliott TSJ. A novel, antimicrobial central venous catheter impregnated with benzalkonium chloride. J Antimicrob Chemother 1993; 31: 261-71.
- 2. Moss HA, et al. A central venous catheter coated with benzalkonium chloride for the prevention of catheter-related microbial colonization. Eur J Anaesthesiol 2000; 17: 680-7.

Preparations

USNF 26: Benzalkonium Chloride Solution.

Proprietary Preparations (details are given in Part 3)

Proprietary Preparations (details are given in Part 3)

Arg.: Benzalcream; Hidratant Pharmatex: Usnicon; Austral.: Bepanther;
Detto Fresh: Belg.: Cedium; Berz.: Bacterian; Flumurici Solucao Nasak

Canad.: Antiseptic Skin Cream; Chillet Germosepti: Cat.: Pharmatex: Fr.:
Humex: Pharmatex; Sparapiaie; Gerz.: Baktonium; Kilakon: Laudamonium;
Lysolorm Kilavoni; Hong Kong: Pharmatex; Humg.: Pharmatex; Hr.: Dettol Fresh: kreef: Pharmatex; Ital.: Affa C.: Amuclean: Benakoro: Bergagyn;
Bluestenh: Cerrost Cirosterial Ambiente: Cirosterial Deterferri: Detergit Dimann Rt; DiMitt Diseptit; Disiger: Disinyt: Display; Distask Distenh: Eso
Deterferri: Eso Ferri: Esosan Cass: Esosan Soap; Germicidin; Germozo:
Clean: Heis: Hygienist Pavimenti e Plastrellet; Indina Light; Lacribase; Loziner Vittora: Massterit Neo-Desogen; Noricat; Polisan; Sanaform; Sanaform; Sanaform; Sanaform; Sanaform; Sanaform; Sanaform; Alexie: Unbrizalt; Merthiolatet; MZ: Dettok Dettol Fresh: Virasohe; Port.:
Pharmatex: Rus.: Pharmatex: (Dapwarexc): Spermatex (Cnepwarexc);
Spain: Armit; Crema Contracepti Lanzas Mini Ovulo Lanzas: Switz: Benzaltex; Thai: Pose-Bac; Turkiz Zelan; Zefara; Zefok Zefort: Zefsolin; Zenfeloto, Zernar. UKB Bradosot Dermax Herapeutic Shampoo; Dettol Antiseptic Wash: Dettol Fresh: USA: Bacti-Cleanse, Benza: Mycocide NS: OnyClean; Zephiran; Vanez: Decomed.

Multi-Ingredient: Arg.: Antisepthic Plus: Crema de Ordene; Eurocoal;

ielatot Zentari UK Bradosol Dermax Therapeutic Shampoo: Dettol Antiseptic Wash: Dettol Fresh USA: Bacti-Cleanse: Benza: Mycocide NS: OnyClean; Zephirax Venez: Decomed.

Multi-ingredients Arg.: Antisepthic Plus: Crema de Ordene; Eurocoal;
Heal Antiseptico: Merthiolate Nis; Muelita: Neo Colbirot: Oilalfo; Polviderm
NF: Soquette: Australs: Annimice Clean Sion Face Wash: Gum-Eset; Mycil
Healthy Feet; Oilatum Plus: Pasyk Solyptolt; TAGG†; Virasolve: Australa:
Aleot: Dequonal: Dermaspray; Belagin: Cetrilan: Colpatin; Colpista;
Colpistar: Colpistatin: Dermaspray; Belagin: Cetrilan: Colpatin; Colpista;
Colpistar: Colpistatin: Dermolt; Dinitle Donnaget: Drapolene: Ginestatin:
Higider: Nasolin; Ookzinco: Pomada Minancora: Rinotilt; Tricomax: Vagi Biotic; Visolon: Canad.; Bactine: Family Medic First Ald Treatment: MediDarn Protectaid; Tanas; Chiller Dermobarrins: Desagin; Medisept; Orajel
Compuesto; Ca.: Coldrex: Laryplus: Dr. Rentschler: Halstabletten; Oila
mp Plus: Septolete: Fix: Acarcid; Biseptifile; Dermaspraid: Antiseptique:
Dermobacter: Humex; Kenakol: Mercry; Mercrylsoins; Pharmatex;
Rhinofiumoti; Ger: Baccalint; Bacilloid rasant; Cutasept; Dequonal:
Dorithricin Original: Dynexan Mundget Freia-Derm; Freka-Sept 80; Gingcain D: Hexaquart 15; Hexaquart 5: Indidn: Incidine rest and: Incidin Dertar;
Incidin perfekt: Incidur: Sprayt; Inovat; Kohrsolin FF; Korsolex Extra: Korslex FF; Lyselot Medi; Mikrobac; Quatohex Sekusept Extra N: Sekusept
forte; Septolit; Skrman Soft: Ultrasol-F; Grz: Beta Opthiole: Cutasept:
Olamy; Hong Konig: Dermobacter: Dermojela: Drapolene; Myck; Oilatum Plus: Froetcatad; Virasolve; Hung; Ecolorex: Laryplast; Dorithricin, India:
Rashifice: Indon: Mesochrome: Oilatum Plus: Protectad; Oironedies Promote: Citrosii Alcolico Pargue; Tortoredies
Aphitagone; Aptha-X: Emulsiderm Garonsept; India: Agiput; AZ IS;
Barrycidal; Bemonalcoot Cerosteni: Cerost; Citrored 80 and 85; Citrored
Chrungico; Citroredies Pronto: Citrosii Alcolico Resoreri Ilhorior; Septolete
(Cerro-Are): S.Afr.: Oilatum Plus

Benzethonium Chloride (BAN, INN)

Bensetoniumklorid; Bentsetoniumkloridi; Benzethonii chloridum; Benzéthonium, chlorure de; Benzethonium-chlorid; Benzetonio chloridas; Benzetoniowy chlorek; Benzetónium-klorid; Cloruro de bencetonio; Diisobutylphenoxyethoxyethyldimethylbenzylammonium chloride. Benzyldimethyl(2-{2-{4-(1,1,3,3-tetramethylbutyl)phenoxy]ethoxy}ethyl)ammonium chloride.

Бензетония Хлорид $C_{27}H_{42}CINO_2 = 448.1.$ CAS — 121-54-0. ATC — ROZAAO9. ATC Vet - QROZAA09.

Pharmacopoeias. In Eur. (see p.vii), Jpn, and US. Ph. Eur. 6.2 (Benzethonium Chloride). A white or yellowish-white powder. Very soluble in water and in alcohol; freely soluble in dichloromethane. An aqueous solution froths copiously when shaken. Protect from light.

USP 31 (Benzethonium Chloride). White crystals with a mild odour. Soluble 1 in less than 1 of water, of alcohol, and of chlo-roform, and 1 in 6000 of ether. A 1% solution in water is slightly alkaline to litmus. Store in airtight containers. Protect from light.

Incompatibility. Benzethonium chloride is incompatible with soaps and other anionic surfactants.

Profile

Benzethonium chloride is a quaternary ammonium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p.1634). It is used as a preservative in etic products. It has also been used as a nharmaceutical and cosm vaginal spermicide.

Denzethonium chloride, which produced mild skin irritation at a concentration of 5% but not lower, was not considered to be a sensitiser, and was considered to be safe at a concentration of 0.5% in cosmetics applied to the skin and at a maximum concentration of 0.02% in cosmetics used in the eye area.1

The Expert Panel of the American College of Toxicology, Final report on the safety assessment of benzethonium chloride and methylbenzethonium chloride. J Am Coll Toxicol 1985; 4: 65-106.

Preparations

USP 31: Benzethonium Chloride Concentrate; Benzethonium Chloride Tincture; Benzethonium Chloride Topical Solution.

Proprietary Preparations (details are given in Part 3)
Coned.: Clearskin Antibacterial; Neutrogena Antiseptic Cleanser†; Skin
Cleanser & Deodonizer†; S.Afizi Johnson's Antiseptic Powder; USA: Antiseptic Wound & Skin Cleanser:

septic Wound & Skin Cleanser.

Multi-ingredients Arg.: Butimerin: Solumerin: Austral.: Summers Eve Feminine: Belg.: Neo-Golaseptine, Braz.: Andolba: Hipodex: Solemil†; Spray Anti-Septico: Genedi: Antiseptic Skin Cream†; Lipscrex Plus: Lipscrex Pl

Benzoates

Renzoatos.

Benzoic Acid

Acide benzoïque; Acidum benzoicum; Bensoesyra; Bentsoehappo: Benzoesäure; Benzoesav; Benzoico, ácido; Benzoine rūgštis; Dracylic Acid; E210; Kwas benzoesowy; Kyselina benzoová. C6H5.CO2H = 122.1. CAS - 65-85-0.

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

Ph. Eur. 6.2 (Benzoic Acid). A white or almost white, crystalline powder or colourless crystals, odourless or with a very slight characteristic odour. Slightly soluble in water, soluble in boiling water, freely soluble in alcohol and in fatty oils. M.p. 121° to

USP 31 (Benzoic Acid). White crystals, scales, or needl a slight characteristic odour. Soluble 1 in 300 of water, 1 in 3 of alcohol, 1 in 5 of chloroform, and 1 in 3 of ether; freely volatile in steam. Congealing range 121° to 123°.

Incompatibility. The incompatibilities of benzoic acid are described under Sodium Benzoate, below.

Sodium Benzoate

Benzoan sodný; Benzoato sódico; E211; Natrii benzoas; Natrio benzoatas; Natrium Benzoicum; Natriumbensoat; Natriumbentsoaatti; Nátrium-benzoát; Sodii Benzoas; Sodium, benzoate de; Sodu benzoesan; Sodyum Benzoat.

C6H5.CO2Na = 144.1. CAS -- 532-32-1.

Pharmacopoeias. In Chin., Eur. (see p.vii), Jpn, and Viet. Also

Ph. Eur. 6.2 (Sodium Benzoate). A white or almost white, slightly hygroscopic, crystalline or granular powder or flakes. Freely soluble in water, sparingly soluble in alcohol (90% v/v). USNF 26 (Sodium Benzoate). A white, odourless or practically odourless, granular or crystalline powder. Soluble 1 in 2 of water, 1 in 75 of alcohol, and 1 in 50 of alcohol 90%. Incompatibility. Benzoic acid and its salts are incompatible with quaternary compounds, calcium salts, ferric salts, and salts of heavy metals. Their activity is also diminished by nonionic surfactants or due to absorption by kaolin. They are relatively inactive above a pH of about 5.

Adverse Effects and Precautions

The benzoates can cause hypersensitivity reactions, but there have also been reports of non-immunological contact urticaria. The acid can be irritant to skin, eyes, and mucous membranes.

Infants given large doses of sodium benzoate have suffered vomiting. Symptoms of overdosage reported in this group have included vomiting, irritability and, in more severe cases, renal tubular dysfunction, hypokalaemia, hypocalcaemia, and metabolic acidosis.

Premature infants have been reported to be at risk of metabolic acidosis and kernicterus.

Hypersensitivity. Respiratory reactions to benzoates may oc-cur, especially in patients susceptible to aspirin-induced asth-ma. ^{1,2} Urticarial reactions have also been associated with these compounds, ^{3,4} though at a lower incidence ³ and they can be non-immunological. ⁶ However, these reports have to be balanced against a controlled study ⁵ that showed no difference in the inci-dence of urticaria or atopic symptoms between patients given benzoic acid and those given lactose placebo. A retrospective study ⁸ of 47 patients who had previously shown a hypersensitiv-ity reaction after ingesting food or products containing benzoate sodium found that the incidence of a repeat episode of acute ur-ticaria or angioedema on re-challenge was very low (2%). Anaphylactoid reactions have been reported in 2 natients ^{3,10}

Anaphylactoid reactions have been reported in 2 patients. 9,10 Erythema multiforme has been observed in several patients.11

- ymema multiforme has been observed in several patients."
 Rosenhall L. Evaluation of intolerance to analgesics, preservatives and food colorants with challenge tests. Eur J Rexpir Dis
 1982; 63: 410–19.
 Settipane GA. Aspirin and allergic diseases: a review. Am J Med
 1983; 74 (suppl): 102–9.
 Michaelsson G, Juhlin L. Urticaria induced by preservatives and
 dye additives in food and drugs. Br J Dermatol 1973; 88:
 525–32.

- 323-32. Warin RP, Smith RJ. Challenge test battery in chronic urticaria. Br J Dermatol 1976; 94: 401-6. Wüthrich B, Fabro L. Acetysalicylaäure-und lebensmitteladditi-va-intoleranz bei urtikaria, asthma bronchiale und chronischer rhinopathie. Schweiz Med Wochenschr 1981; III: 1445-50.
- roott JR, et al. Airborne contact urticaria due to sodium ate in a pharmaceutical manufacturing plant. J Occup Med
- Nethercott JR, et al. Airborne contact urticaria due to sodium benzoate in a pharmaceutical manufacturing plant. JOccup Med 1984; 26: 734-6.
 Lahit A, Hannuksela M. Is Benzoic acid really harmful in cases of atopy and urticaria? Lancet 1981; ili: 1055.
 Nettis E, et al. Sodium benzoate-induced repeated episodes of acute urticaria/angio-oedema: randomized controlled trial. Br J Dermatol 2004; 151: 998-902.
 Montret A, Wuttin DA. et al. Anaphylatoid rescious to separal
- Dermatol 2004; 1\$1: 898-902.

 9. Moneret-Vautrin DA, et al. Anaphylactoid reaction to general anaesthesia: a case of intolerance to sodium benzoate. Anaesth Intenserve Care 1982; 19: 156-7.

 10. Michils A, et al. Anaphylaxis with sodium benzoate. Lancet 1991; 337: 1424-5.

 11. Lewis MAO, et al. Recurrent erythema multiforme; a possible role of foodstuffs. Br Dent J 1989; 166: 371-3.

Neonates. Serious metabolic disturbances in premature neonates given intravenous fluids with benzyl alcohol as a preserva-tive have been attributed to the accumulation of benzoic acid, a metabolite of benzyl alcohol (see p.1632). This risk led to the recommendation that Caffeine and Sodium Benzoate Injection (USP), which has been given as a respiratory stimulant, should not be used in neonates.

Sodium benzoate has been tried in the treatment of some neonatal metabolic disorders (see Uses and Administration, below). However, benzoates can also displace bound bilirubin from albu-However, benzoates can also displace bound bilirubin from albumin putting neonates at risk of kerniciterus. Three cases of toxicity have been reported after accidental high doses of intravenous sodium benzoate and sodium phenylacetate were given to children with hyperammonaemia. All the children initially became agitated and confused, had Kussmaul respiration (rapid, deep breathing) and developed a partial metabolic acidosis with an increased anion gap. Two patients subsequently developed cerebral oedema and hypotension and died while the third survived after haemodialysis. vived after haemodialysis.

- Edwards RC, Voegeli CJ. Inadvisability of using caffeine and so-dium benzoate in neonates. Am J Hosp Pharm 1984; 41: 658.
 Schiff D, et al. Fixed drug combinations and the displacement of bilirubin from albumin. Pediatrics 1971: 48: 139-41.
- Praphaphoj V, et al. Three cases of intravenous sodium benzoate and sodium phenylacetate toxicity occurring in the treatment of acute hyperammonaemia. J Inherit Metab Dis 2000; 23: ment of acute hypera 129-36.

Pharmacokinetics

The benzoates are absorbed from the gastrointestinal tract and conjugated with glycine in the liver to form hippuric acid, which is rapidly excreted in the urine.

Neonates, References

Green TP, et al. Disposition of sodium benzoate in newborn in-fants with hyperammonemia. J Pediatr 1983; 102: 785-90.