freely soluble in 0.1N hydrochloric acid. pH of a 10% solution in water is between 3.0 and 5.0. Store in airtight containers.

Profile

Tiletamine has similar properties to ketamine (p.1787). It is used as the hydrochloride with zolazepam (p.1037) for general anaesthesia in veterinary medicine.

Trichloroethylene *(rINN)*

Trichlorethylene; Trichlorethylenum; Trichloroethene; Trichloroéthylène; Trichloroethylenum; Trichloroetylen; Tricloroetileno.

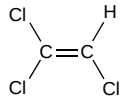
Трихлороэтилен

$CHCl:CCl_2$ = 131.4.

CAS — 79-01-6.

ATC — N01AB05.

ATC Vet — QN01AB05.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of trichloroethylene: Trichlo.

Stability. NOTE. Trichloroethylene used for anaesthetic purposes contains thymol 0.01% w/v as a stabiliser and is coloured blue for identification. It is non-flammable.

Adverse Effects and Precautions

Trichloroethylene increases the rate and decreases the depth of respiration and may be followed by apnoea. The sensitivity of the heart to beta-adrenergic activity may increase, possibly with ventricular arrhythmias.

Acute exposure to trichloroethylene may be followed by dizziness, lightheadedness, lethargy, nausea, and vomiting; hepatic and renal dysfunction may follow. Fatalities have occurred, although temporary unconsciousness is a more common manifestation.

Chronic poisoning may result in visual disturbances, intolerance to alcohol as manifested by transient redness of the face and neck (degreasers' or trichloroethylene flush), impairment of performance, hearing defects, neuralgia, and mild liver dysfunction. Prolonged contact with trichloroethylene can cause dermatitis, eczema, burns, and conjunctivitis.

Dependence has been reported in medical personnel and factory workers who regularly inhale trichloroethylene vapour.

If trichloroethylene is used as an anaesthetic it should not be used in closed-circuit apparatus since there is a reaction with soda lime to produce a toxic end product that may cause cranial nerve paralysis and possibly death.

See also Adverse Effects and Precautions for General Anaesthetics, p.1779.

◊ Reviews of the toxicity of trichloroethylene.

1. Health and Safety Executive. Trichloroethylene. *Toxicity Review* 6. London: HMSO, 1982.
2. WHO. Trichloroethylene. *Environmental Health Criteria 50.* Geneva: WHO, 1985. Available at: http://www.inchem.org/documents/ehc/ehc/ehc50.htm (accessed 26/05/04)
3. Davidson IWF, Beliles RP. Consideration of the target organ toxicity of trichloroethylene in terms of metabolite toxicity and pharmacokinetics. *Drug Metab Rev* 1991; **23:** 493–599.

Abuse. Toxicity associated with inhalation of volatile substances including trichloroethylene has been reviewed.[1,2] Trichloroethylene can damage the kidney, liver, heart, and lung. However, in young healthy subjects, organ toxicity becomes apparent only with intensive and protracted abuse of volatile substances.

1. Marjot R, McLeod AA. Chronic non-neurological toxicity from volatile substance abuse. *Hum Toxicol* 1989; **8:** 301–6.
2. Anonymous. Solvent abuse: little progress after 20 years. *BMJ* 1990; **300:** 135–6.

Carcinogenicity. The use of trichloroethylene in foods, drugs, and cosmetics was banned by the FDA after studies demonstrating that hepatocellular carcinomas could be induced in *mice* by chronic exposure to very high doses. However, similar effects have not been found in *rats* and larger species and several epidemiologic studies have failed to demonstrate an increased incidence of liver tumours, total mortality or mortality due to cancer in workers exposed to trichloroethylene. Suggestions that the carcinogenicity of trichloroethylene is due to one of its intermediate metabolites, cloral hydrate, have raised concern over the continuing use of cloral hydrate as a medicine. For further details, see p.979.

Effects on the liver. References[1,2] to hepatotoxicity after occupational exposure to trichloroethylene. See also Carcinogenicity, above.

1. McCunney RJ. Diverse manifestations of trichloroethylene. *Br J Ind Med* 1988; **45:** 122–6.
2. Schattner A, Malnick SDH. Anicteric hepatitis and uveitis in a worker exposed to trichloroethylene. *Postgrad Med J* 1990; **66:** 730–1.

Effects on the skin. A report[1] of scleroderma in 3 patients occupationally exposed to trichloroethylene and, in 2 cases, also to trichloroethane.

1. Flindt-Hansen H, Isager H. Scleroderma after occupational exposure to trichlorethylene and trichlorethane. *Acta Derm Venereol (Stockh)* 1987; **67:** 263–4.

Interactions

The arrhythmogenic effects of trichloroethylene may be potentiated by sympathomimetics such as adrenaline. Alcohol consumption after chronic exposure to trichloroethylene may result in a reddening of the skin (see Adverse Effects and Precautions, above).

See also Interactions of General Anaesthetics, p.1779.

Pharmacokinetics

Trichloroethylene is rapidly absorbed by inhalation and ingestion. Percutaneous absorption can occur. Some of the inhaled trichloroethylene is slowly eliminated through the lungs; trichloroethylene is metabolised primarily in the liver, cloral hydrate (see p.979) being the first stable major metabolite formed; most is then metabolised to trichloroethanol and trichloroacetic acid which are excreted in the urine. The latter may be used as an indicator of industrial exposure. Trichloroethylene diffuses across the placenta.

Uses and Administration

Trichloroethylene is a volatile halogenated anaesthetic given by inhalation. It has been used in some countries for the maintenance of light anaesthesia (p.1780) but it has weak anaesthetic properties compared to other halogenated anaesthetics and poor muscle relaxant activity, and safer anaesthetics are generally preferred. It has also been used to supplement anaesthesia with nitrous oxide-oxygen or halothane. Trichloroethylene is a potent analgesic and has been used in subanaesthetic concentrations to provide analgesia for obstetrics, emergency management of trauma, and other acutely painful procedures.

Trichloroethylene is used in industry as a solvent for oils and fats, for degreasing metals, and for dry cleaning. It has also been used in type correction fluids but is no longer included in most brands.

Xenon

Ksenon; Xénon; Xenón; Xenonum.

Xe = 131.293.

ATC — N01AX15.

ATC Vet — QN01AX15.

Profile

Xenon is a non-explosive gas. Mixtures of 60 or 70% v/v xenon with oxygen have been tried as a general anaesthetic.

◊ References.

1. Lachmann B, *et al.* Safety and efficacy of xenon in routine use as an inhalational anaesthetic. *Lancet* 1990; **335:** 1413–15.
2. Yagi M, *et al.* Analgesic and hypnotic effects of subanaesthetic concentrations of xenon in human volunteers: comparison with nitrous oxide. *Br J Anaesth* 1995; **74:** 670–3.
3. Goto T, *et al.* Emergence times from xenon anaesthesia are independent of the duration of anaesthesia. *Br J Anaesth* 1997; **79:** 595–9.
4. Rossaint R, *et al.* Multicenter randomized comparison of the efficacy and safety of xenon and isoflurane in patients undergoing elective surgery. *Anesthesiology* 2003; **98:** 6–13.
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7. Preckel B, Schlack W. Xenon—cardiovascularly inert? *Br J Anaesth* 2004; **92:** 786–9.
8. Sanders RD, *et al.* Xenon: elemental anaesthesia in clinical practice. *Br Med Bull* 2005; **71:** 115–35.
9. Baskar N, Hunter JD. Xenon as an anaesthetic gas. *Br J Hosp Med* 2006; **67:** 658–61.

Preparations

Proprietary Preparations (details are given in Part 3)

Port.: Lenoxe.

the extent of the benefit is unclear. A cohort study of French children registered to receive growth hormone between 1973 and 1993 suggested that the eventual outcome was not as good as expected, and treated individuals remained short.[8] However, a large American cohort that included more than 11 000 growth-hormone deficient patients found that although treated patients remained below target heights, many did achieve heights within the normal range for chronological age.[9] Maximum growth rates occurred in the first year of treatment and fell progressively thereafter, with no significant difference between growth rates after 4 years compared with pretreatment rates. A further cohort study[10] from the same French register for 1987 to 1996 found that adult heights were similar whether patients completed treatment or stopped before reaching adult height, and that patients with severe growth hormone deficiency may respond better than those with less severe deficiency. Growth hormone treatment regimens have changed over the years, and it appears that with optimal treatment it may be possible for some growth-hormone deficient children to achieve their genetic height potential.[7] An important prognostic factor is age, and for optimum results treatment should be started as early as possible in an attempt to maximise height before the onset of puberty.[2,7]

In patients with multiple pituitary hormone deficiencies, genetic defects in growth hormone synthesis, or severe organic growth hormone deficiency, growth hormone therapy should be continued into adulthood. In other patients, growth hormone deficiency may or may not persist into adult life, and retesting should be done after the patient reaches adult height and after 1 to 3 months without therapy.[2,11] In those patients who need continued treatment, the dose of growth hormone should be gradually reduced in order to maintain IGF-I concentrations within the normal range.[11]

Somatorelin (growth hormone-releasing hormone) or its analogue sermorelin have also been tried to boost growth hormone secretion in patients with growth hormone deficiency. Although there have been reports of improved growth rates, there are limited data directly comparing these with growth hormone. One large study[12] of sermorelin found that, compared with results generally reported for growth hormone therapy, fewer patients responded over a 12-month period and growth responses were poorer. Pralmorelin is a small synthetic growth hormone-releasing peptide that is also under investigation.[13,14]

In patients with Laron dwarfism (growth hormone resistance or insensitivity), conventional growth hormone therapy is ineffective because of defects in the growth hormone receptors. However, replacement therapy with mecasermin, the recombinant form of insulin-like growth factor-I, may be of substantial benefit in the treatment of this disorder.[15]

The use of growth hormone in short stature other than that due to indisputable growth hormone deficiency is controversial. Benefit has been reported from growth hormone therapy in children with chronic renal failure,[16,17] in girls with Turner's syndrome (but see p.2081), in young children (6 months to 3 years of age) with Down's syndrome,[18,19] and in Prader-Willi syndrome[20] (p.2149), all of which are associated with marked growth retardation. However, many commentators see such interventions as essentially cosmetic. The treatment of idiopathic short stature in particular, for which no underlying disorder can be identified, in particular, poses problems as the risks and also the benefits in terms of final height are uncertain.[21] Children who are born small for gestational age usually experience catch-up growth by 2 years of age. In those who do not achieve this, growth hormone therapy can induce catch-up growth and improve childhood height scores; data on adult height are limited, however.[22] Guidelines suggest that therapy is justifiable in chronic renal insufficiency,[3,6,23] Turner's syndrome,[3,6,23] Prader-Willi syndrome,[3,23] and for children born small for gestational age.[3] However, sufficient evidence of benefit is lacking for other disorders including non-growth hormone deficient short stature and growth retardation associated with Down's syndrome, and some[6] consider that growth hormone should not be given to children with constitutional delay of growth. More recently, growth hormone therapy has improved growth rate and height in children with SHOX (short stature homeobox-containing gene) deficiency.[24] Mutations and deletions of the SHOX gene, a gene involved in bone and cartilage formation, are associated with various short stature conditions such as Léri-Weill dyschondrosteosis, and are now understood to play a role in the short stature of Turner's syndrome and in some cases of idiopathic short stature.

Although sex hormones have effects on growth they may also cause premature closure of the epiphyses when given to prepubertal or pubertal children, and this has limited their use. Nonetheless, anabolic drugs such as testosterone and oxandrolone have been used in boys, and oestrogen in girls, who have constitutional delay of growth associated with delayed puberty (see p.2079). Oestrogens are not generally used for growth promotion in girls with Turner's syndrome, but as replacement therapy to promote puberty when a satisfactory height has been reached (see p.2081).

A number of other drugs have been investigated in growth retardation. Clonidine, which can promote growth hormone-releasing hormone release, has been given to children with growth hormone deficiency as well as to short children without proven deficiency, but results have been contradictory and largely unsatisfactory.[25-27] Gonadorelin analogues have also been given with growth hormone to short girls without growth hormone deficiency, in an attempt to slow bone maturation and delay puberty, thereby improving adult height.[28] However, a decrease in bone mineral density may outweigh any modest increase in height.[29] Where growth retardation is associated with zinc deficiency, zinc supplementation may be useful (see p.2000).

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8. Coste J, *et al.* Long term results of growth hormone treatment in France in children of short stature: population, register based study. *BMJ* 1997; **315:** 708–13.
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15. Laron Z. Laron syndrome (primary growth hormone resistance or insensitivity): the personal experience 1958–2003. *J Clin Endocrinol Metab* 2004; **89:** 1031–44.
16. Haffner D, *et al.* Effect of growth hormone treatment on the adult height of children with chronic renal failure. *N Engl J Med* 2000; **343:** 923–30.
17. Vimalachandra D, *et al.* Growth hormone for children with chronic renal failure. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 23/07/08).
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Growth Hormone *(BAN)* ⊗

GH; Phyone; Somatotrophin; Somatotropin; Somatotropina; STH.

Гормон Роста; Соматотропин

CAS — 9002-72-6.

Somatrem *(BAN, USAN, pINN)* ⊗

Met-HGH; Methionyl Human Growth Hormone; Somatremum.

Соматрем

$C_{995}H_{1537}N_{263}O_{301}S_8$ = 22 256.

CAS — 82030-87-3.

ATC — H01AC02.

ATC Vet — QH01AC02.

Description. Somatrem is an analogue of somatropin containing an additional (methionyl) amino-acid residue. It may be produced in bacteria from recombinant DNA.

Sometribove (*BAN*) is methionyl bovine growth hormone.

Sometripor (*BAN*) is methionyl porcine growth hormone.

Somatropin *(BAN, USAN, rINN)* ⊗

CB-311; HGH; Human Growth Hormone; LY-137998; Somatropiini; Somatropina; Somatropinas; Somatropine; Somatropinum; Szomatropin.

Соматропин

$C_{990}H_{1528}N_{262}O_{300}S_7$ = 22 125.

CAS — 12629-01-5.

ATC — H01AC01.

ATC Vet — QH01AC01.

Description. Somatropin is synthetic human growth hormone having the normal structure of the major (22K) component of natural human pituitary growth hormone. It consists of a single polypeptide chain of 191 amino acids with disulfide linkages between positions 53 and 165 and between 182 and 189. For labelling purposes, the name may carry in parentheses an approved code in lower case letters indicative of the method of production: (epr) indicates production by enzymatic conversion of a precursor produced by a bacterium genetically modified by recombinant DNA technology; (rbe) indicates production from bacteria genetically modified by recombinant DNA technology; (rmc) indicates production from genetically engineered and transformed mammalian (mouse) cells.

Somidobove (*BAN*) is synthetic bovine growth hormone.

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

Ph. Eur. 6.2 (Somatropin). A protein having the structure (191 amino acid residues) of the major component of growth hormone produced by the human pituitary. A white or almost white powder, containing not less than 2.5 units/mg. Store at 2° to 8° in airtight containers.

Ph. Eur. 6.2 (Somatropin Concentrated Solution). A clear or slightly turbid, colourless solution. It may contain buffer salts and other auxiliary substances. Store at –20° in airtight containers. Avoid repeated freezing and thawing.

USP 31 (Somatropin). A protein hormone consisting of 191 amino acid residues, and its structure corresponds to the major component of the growth hormone extracted from human pituitary glands. It is produced as a lyophilised powder or bulk solution by methods based on recombinant DNA technology. The lyophilised powder contains not less than 910 micrograms of somatropin per mg, calculated on the anhydrous basis. The bulk solution contains not less than 910 micrograms of somatropin per mg of total protein.

Store at –25° to –10° in airtight containers.

Units

4.4 units of human growth hormone (somatropin) are contained in 1.75 mg of freeze-dried purified human growth hormone, with 20 mg of glycine, 2 mg of mannitol, 2 mg of lactose, and 2 mg of sodium bicarbonate, in one ampoule of the first International Standard (1987).