Doses used have varied according to the degree of muscle relaxation required. Doses of neuromuscular blockers need to be carefully titrated for individual patients according to response, and may vary with the procedure, the other drugs given, and the state of the patient; monitoring of the degree of block is recommended in order to reduce the risk of overdosage. An initial dose of 6 to 9 mg intravenously has been suggested followed by 3 to 4.5 mg after 3 to 5 minutes if necessary; additional doses of 3 mg may be given as required for prolonged procedures. Higher doses have been given in some countries. It has also been given intramuscularly but absorption is slow and erratic. Tubocurarine should be given with caution in reduced doses to patients with renal impairment; if large or repeated doses are given neuromuscular block may be prolonged.

Tubocurarine chloride has also been used to control the muscle spasms of tetanus (p.1901).

Preparations

USP 31: Tubocurarine Chloride Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Decurin; ***Israel:*** Curarine†; Tubarine†.

Vecuronium Bromide *(BAN, USAN, rINN)*

Bromuro de vecuronio; Org-NC-45; Vecuronii bromidum; Vécuronium, bromure de; Vekuroniumbromid; Vekuronium-bromid; Vekuroniumbromidi; Vekuronyum Bromür; Wekuroniowy bromek. 1-(3α,17β-Diacetoxy-2β-piperidino-5α-androstan-16β-yl)-1-methylpiperidinium bromide.

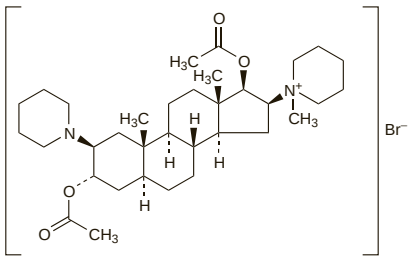
Векурония Бромид

$C_{34}H_{57}BrN_2O_4$ = 637.7.

CAS — 50700-72-6.

ATC — M03AC03.

ATC Vet — QM03AC03.



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

Ph. Eur. 6.2 (Vecuronium Bromide). White or almost white crystals or crystalline powder. Slightly soluble in water; sparingly soluble in dehydrated alcohol and in acetonitrile; freely soluble in dichloromethane. Store in airtight containers. Protect from light and moisture.

USP 31 (Vecuronium Bromide). White or creamy white crystals, or a crystalline powder. Slightly soluble in water and in acetone; sparingly soluble in alcohol. Store in airtight containers.

Incompatibility. A solution containing vecuronium bromide 1 mg/mL was found to be visually incompatible with furosemide.[1] For incompatibilities of competitive neuromuscular blockers in general, see under Atracurium on p.1902.

1. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; **54:** 64–5.

Adverse Effects, Treatment, and Precautions

As for competitive neuromuscular blockers in general (see Atracurium, p.1902).

Vecuronium bromide has little histamine-releasing activity although a local reaction at the site of injection has been reported; bronchospasm and anaphylactoid reactions have been rarely reported. It also has little vagolytic or ganglion-blocking activity and produces no significant adverse cardiovascular effects at usual doses.

Caution may be needed in patients with hepatic or renal impairment (see under Uses and Administration, below); dosage adjustments may be required in renal failure.

The elderly. It has been recommended that neuromuscular function should be monitored in elderly patients receiving vecuronium since there may be a risk of prolonged block.[1]

1. Slavov V, *et al.* Comparison of duration of neuromuscular blocking effect of atracurium and vecuronium in young and elderly patients. *Br J Anaesth* 1995; **74:** 709–11.

Pregnancy. The proportion of vecuronium crossing the placenta after doses of 60 to 80 micrograms/kg was considered clinically insignificant and its use during obstetric anaesthesia was considered safe for the newborn.[1]

1. Demetriou M, *et al.* Placental transfer of Org NC 45 in women undergoing caesarean section. *Br J Anaesth* 1982; **54:** 643–5.

Interactions

For interactions associated with competitive neuromuscular blockers, see Atracurium, p.1903.

Pharmacokinetics

On intravenous injection vecuronium is rapidly distributed. It is taken up by the liver and partly metabolised; the metabolites have some neuromuscular blocking activity. It is excreted mainly in bile as unchanged drug and metabolites; some is also excreted in urine. The plasma elimination half-life is reported to range from about 30 to 80 minutes.

Uses and Administration

Vecuronium bromide is an aminosteroidal competitive neuromuscular blocker (see Atracurium, p.1905).

After intravenous injection muscle relaxation occurs within about 1.5 to 2 minutes and lasts for about 20 to 30 minutes.

Vecuronium bromide is used for endotracheal intubation and to provide muscle relaxation in general anaesthesia for surgical procedures (see Anaesthesia, p.1900) and to aid controlled ventilation (see Intensive Care, p.1901).

Doses of neuromuscular blockers need to be carefully titrated for individual patients according to response, and may vary with the procedure, the other drugs given, and the state of the patient; monitoring of the degree of block is recommended in order to reduce the risk of overdosage. The usual initial dose for intubation is 80 to 100 micrograms/kg by intravenous injection, although reduced initial doses of 30 to 50 micrograms/kg are suggested following the use of suxamethonium. Higher initial doses ranging from 150 to 300 micrograms/kg have sometimes been used for other procedures. However, it is recommended that the dose should not exceed 100 micrograms/kg in caesarean section or neonatal surgery. Maintenance doses of 20 to 30 micrograms/kg may be given as required during prolonged procedures; in the USA a lower maintenance dose of 10 to 15 micrograms/kg is recommended. Neuromuscular blockade may also be maintained with an intravenous infusion given at a rate of 0.8 to 1.4 micrograms/kg per minute but should be preceded by an initial bolus injection of 40 to 100 micrograms/kg. UK licensed product information recommends that in obese patients the dosage of vecuronium should be reduced taking into account lean body-mass.

Children older than 5 months can be given adult doses but children up to 1 year may have a more rapid response and the high initial dose for intubation may not be necessary. Neonates and infants below 5 months of age may be more sensitive to vecuronium and it is recommended that they should be given an initial test dose of 10 to 20 micrograms/kg, followed by increments according to response. The duration of action and recovery is longer in neonates and infants than in children and adults and they may require smaller maintenance doses given less frequently.

Administration in hepatic impairment. Although the manufacturers make no specific recommendations for dosage reduction in hepatic impairment, the duration of action of vecuronium was reported to be significantly prolonged in patients with cholestasis[1] or cirrhosis with oesophageal varices[2] given a dose of 200 micrograms/kg intravenously. Plasma clearance was significantly reduced and the elimination half-life significantly increased from a mean of 58 to 98 minutes.[1] A dose of 150 micrograms/kg was found to have a similar onset and duration of action in patients with hepatic impairment and healthy controls,[2] but a dose of 100 micrograms/kg had a slower onset and slightly shorter duration of action in those with liver disturbance.[3] After a dose of vecuronium, rapid and extensive hepatic uptake occurs, which largely determines its short duration of action. However, as the dose increases this mechanism becomes saturated, and hepatic elimination becomes more important in terminating activity. This would help to explain the variation in results seen with the different doses. Caution is needed if large single doses or repeated doses are given to patients with hepatic impairment.

1. Lebrault C, *et al.* Pharmacokinetics and pharmacodynamics of vecuronium in patients with cholestasis. *Br J Anaesth* 1986; **58:** 983–7.
2. Hunter JM, *et al.* The use of different doses of vecuronium in patients with liver dysfunction. *Br J Anaesth* 1985; **57:** 758–64.
3. Bell CF, *et al.* Use of atracurium and vecuronium in patients with oesophageal varices. *Br J Anaesth* 1985; **57:** 160–8.

Administration in renal impairment. A small proportion of vecuronium bromide is excreted in urine and it may be given in usual doses to patients with renal failure.[1,2] No clinically significant difference in elimination half-life, clearance, or duration of action were reported[1] between patients with renal failure and those with normal renal function. The onset of neuromuscular block may be slightly slower in renal failure[2] and these patients may require an increase of around 20% in the initial dose of vecuronium.[3] However, the dosage requirement for maintenance of neuromuscular block may be reduced by about 20%[3] and slight prolongation of block may occur if dosage is not adjusted, but reversal of residual block with neostigmine is prompt and effective.[2]

Resistance to vecuronium has been reported[2] in 2 anephric patients. Total doses of 620 and 660 micrograms/kg produced maximum neuromuscular block of 77% and 36%, respectively but, despite the high doses used, there were no adverse effects or residual curarisation.

1. Fahey MR, *et al.* Pharmacokinetics of Org NC 45 (Norcuron) in patients with and without renal failure. *Br J Anaesth* 1981; **53:** 1049–53.
2. Hunter JM, *et al.* Comparison of vecuronium, atracurium and tubocurarine in normal patients and in patients with no renal function. *Br J Anaesth* 1984; **56:** 941–51.
3. Gramstad L. Atracurium, vecuronium and pancuronium in end-stage renal failure: dose-response properties and interactions with azathioprine. *Br J Anaesth* 1987; **59:** 995–1003.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Galaren; Gobbicuronio; Norcuron†; Rivecrum; Vecural; Vecuron; ***Austral.:*** Norcuron; ***Austria:*** Norcuron; ***Belg.:*** Norcuron; ***Braz.:*** Norcuron; Vecuron; ***Canad.:*** Norcuron†; ***Chile:*** Norcuron; ***Cz.:*** Norcuron; ***Fin.:*** Norcuron; ***Fr.:*** Norcuron; ***Ger.:*** Norcuron; ***Gr.:*** Norcuron; ***Hong Kong:*** Norcuron; ***Hung.:*** Norcuron; ***India:*** Norcuron; ***Indon.:*** Norcuron; ***Irl.:*** Norcuron†; ***Israel:*** Norcuron; ***Ital.:*** Norcuron; ***Jpn:*** Musculax; ***Malaysia:*** Norcuron; ***Mex.:*** Bromivec; Curlem; Norcuron; ***Neth.:*** Norcuron; ***Norw.:*** Norcuron; ***NZ:*** Norcuron; ***Philipp.:*** Norcuron; ***Pol.:*** Norcuron; ***Port.:*** Norcuron; ***Rus.:*** Norcuron (Норкурон); ***S.Afr.:*** Norcuron; ***Singapore:*** Norcuron; ***Spain:*** Norcuron; ***Swed.:*** Norcuron; ***Switz.:*** Norcuron; ***Thai.:*** Norcuron; ***Turk.:*** Norcuron; ***UK:*** Norcuron; ***USA:*** Norcuron; ***Venez.:*** Norcuron†; Prorelax; Vecuron.

Nonionic Surfactants

A surfactant is a compound that can reduce the interfacial tension between 2 immiscible phases. This is because the molecule contains 2 localised regions, one hydrophilic in nature and the other hydrophobic. Nonionic surfactants differ from anionic surfactants (p.2138) by the absence of charge on, or ionisation of, the molecule; they are generally less irritant than anionic or cationic surfactants.

Hydrophilic groups include the oxyethylene group ($–O.CH_2.CH_2–$) and the hydroxyl group (–OH). By varying the number of these groups in a hydrophobic molecule, such as a fatty acid, substances are obtained that range from strongly hydrophobic and water-insoluble compounds, such as glyceryl monostearate, to strongly hydrophilic and water-soluble compounds, such as the macrogols. These 2 extreme types are not satisfactory as emulsifying agents, though they are useful stabilisers in the presence of efficient emulsifying agents. Between these extremes are the nonionic emulsifying agents in which the proportions of hydrophilic and hydrophobic groups are more evenly balanced; these include some of the macrogol esters and ethers, and sorbitan derivatives. Nonionic surfactants may be classified according to their *hydrophilic-lipophilic balance* (HLB). This is an arbitrary scale of values denoting the relative affinity of the surfactant for oil and water. Lipophilic surfactants have low HLB values (less than 10) and are generally used as antifoaming agents, water-in-oil emulsifying agents, and as wetting agents; hydrophilic surfactants have higher HLB values (greater than 10) and are generally used as oil-in-water emulsifying agents and solubilising agents.

Nonionic surfactants also have applications in the food, cosmetic, paint, pesticide, and textile industries as well as being used as oil slick dispersants. Some macrogol ethers such as nonoxinol 9 are used as spermicides.

By virtue of the processes used in their manufacture, nonionic surfactants are usually mixtures of related compounds; the properties of a particular material may vary from one manufacturer to another and there may be variation in batches from an individual source. Since nonionic surfactants do not ionise to any great extent in solution, they are generally compatible with both anionic and cationic substances, but they reduce the antimicrobial action of many preservatives.

The range of nonionic surfactants used in pharmaceutical practice is large and their classification can be varied and complex. The principal groups of nonionic surfactants are outlined below.

Glycol and glycerol esters are a group of nonionic surfactants consisting of fatty acid esters of glycols and glycerol. Hydrophobic properties predominate and these compounds are poor emulsifying agents if used alone, though they are useful stabilisers for both oil-in-water and water-in-oil emulsions. If a small amount of soap, sulfated fatty alcohol, or other surfactant is added to the esters, a 'self-emulsifying' product is formed, which is capable of producing satisfactory oil-in-water emulsions. **Acetoglycerides** are mixed glyceryl esters in which the glycerol is esterified partly with a fatty acid and partly with acetic acid.

Macrogol esters are polyoxyethylene esters of fatty acids, mainly stearates. The hydrophilic properties of the oxyethylene group are weaker than those of the hydroxyl group but by introducing a sufficient number into a fatty acid molecule, substances are produced in which the hydrophilic and hydrophobic properties are sufficiently well balanced for the esters to act as efficient oil-in-water emulsifying agents. They may also be used as wetting and solubilising agents. Since the ester linkage is prone to hydrolysis, these compounds are less resistant to acids and alkalis than the macrogol ethers.

Macrogol ethers are condensation products prepared by reaction between fatty alcohols or alkylphenols and ethylene oxide. The ether linkage confers good stability to acids and alkalis. Macrogol ethers are widely used in the preparation of oil-in-water emulsions and as wetting and solubilising agents.

Sorbitan derivatives are derivatives of the cyclic mono- or di-anhydrides of sorbitol. They consist of *sorbitan esters*, which are prepared by esterification of one or more of the hydroxyl groups in the anhydrides with a fatty acid such as stearic, palmitic, oleic, or lauric acid, and *polysorbates*, which are polyoxyethylene derivatives of the sorbitan esters. Sorbitan esters are oil-soluble, water-dispersible, nonionic surfactants and are effective water-in-oil emulsifiers. Polysorbates are more hydrophilic, water-soluble compounds and are used as oil-in-water emulsifying agents. By varying the number of oxyethylene groups in the molecule, and the type of fatty acid in the sorbitan ester, surfactants with a wide range of properties may be obtained.

Poloxamers are copolymers of polyoxyethylene and polyoxypropylene. They are used as oil-in-water emulsifiers and as solubilising and wetting agents in pharmaceutical preparations intended for internal use.

Other nonionic compounds with surface activity such as the higher fatty alcohols are covered in the chapter on Paraffins and Similar Bases (p.2028).

Diacetylated Monoglycerides

Monoglicéridos diacetilados.

Моноглицериды Диацетилированные

Pharmacopoeias. In *USNF*.

USNF 26 (Diacetylated Monoglycerides). Consists of glycerol esterified with edible fat-forming fatty acids and acetic acid. A clear liquid. Very soluble in alcohol 80%, in vegetable oils, and in mineral oils; sparingly soluble in alcohol 70%. Store in airtight containers. Protect from light.

Profile

Diacetylated monoglycerides have been used as plasticisers, pharmaceutical excipients, and food additives.

Diethylene Glycol Monopalmitostearate

Diethylene Glycol Monostearate; Diéthylène Glycol (Stéarate de); Diéthylèneglycol, palmitostéarate de; Diethylenglycoli Monopalmitostearas; Diethylenglycoli palmitostearas; Diethylenglykol monopalmitostearát; Diethylenglykol palmito stearát; Diethyleni Glycoli Stearas; Dietilenglicol, monopalmitoestearato de; Dietilenglikolio palmitostearatas; Dietiléneglikol-monopalmitát és monosztearát; Dietyleeniglykolipalmitostearaatti; Dietylenglykolpalmitostearat; Diglycol Stearate.

Диэтиленгликоля Монопальмитостеарат

CAS — 106-11-6 (diethylene glycol monostearate); 36381-62-1 (diethylene glycol monopalmitate).

Pharmacopoeias. In *Eur.* (see p.vii). *USNF* includes Diethylene Glycol Stearates.

Ph. Eur. 6.2 (Diethylene Glycol Palmitostearate). A mixture of diethylene glycol mono- and di-esters of stearic and palmitic acids produced by esterification of diethylene glycol and stearic acid of vegetable or animal origin. It contains 45.0 to 60.0% of monoesters and 35.0 to 55.0% of diesters, and a maximum of 2.5% of free diethylene glycol. A white or almost white, waxy solid. Practically insoluble in water; soluble in hot alcohol and in acetone. M.p. 43° to 50°. Protect from light.

USNF 26 (Diethylene Glycol Stearates). A mixture of diethylene glycol mono- and di-esters of stearic and palmitic acids. It contains not less than 45.0% of monoesters produced from the condensation of ethylene glycol and stearic acid of vegetable or animal origin. A white or almost white, waxy solid. Practically insoluble in water; soluble in hot alcohol and in acetone. M.p. 43° to 50°. Store in airtight containers.

Profile

Diethylene glycol monopalmitostearate has similar properties and uses to glyceryl monostearate or self-emulsifying glyceryl monostearate (p.1915). Diethylene glycol monolaurate and mono-oleate have also been used.

Ethylene Glycol Monopalmitostearate

Ethylene Glycol Monostearate; Ethylene Glycol Stearate; Éthylène Glycol (Stéarate d'); Éthylèneglycol, monopalmitostéarate d'; Ethyleneglycoli Monopalmitostearas; Ethylenglycoli monopalmitostearas; Ethylenglycoli Monostearas; Ethylenglykol-monopalmitostearát; Ethyleni Glycoli Stearas; Etilenglicol, monopalmitoestearato de; Etilenglikolio monopalmitostearatas; Etiléneglikol-monopalmitát és monosztearát; Etyleeniglykolimonopalmitostearaatti; Etylenglykolmonopalmitostearat.

Этиленгликоля Монопальмитостеарат

CAS — 111-60-4 (ethylene glycol monostearate); 4219-49-2 (ethylene glycol monopalmitate).

Pharmacopoeias. In *Eur.* (see p.vii). *USNF* includes Ethylene Glycol Stearates.

Ph. Eur. 6.2 (Ethylene Glycol Monopalmitostearate). A mixture of ethylene glycol mono- and di-esters of stearic and palmitic acids. It contains not less than 50% of monoesters produced from the condensation of ethylene glycol and stearic acid and not more than 5% of free ethylene glycol. A white or almost white, waxy solid. Practically insoluble in water; soluble in hot alcohol and in acetone. M.p. 54° to 60°. Protect from light.

USNF 26 (Ethylene Glycol Stearates). A mixture of ethylene glycol mono- and di-esters of stearic and palmitic acids. It contains not less than 50% of monoesters produced from the condensation of ethylene glycol and stearic acid of vegetable or animal origin. A white or almost white, waxy solid. Practically insoluble in water; soluble in hot alcohol and in acetone. M.p. 54° to 60°. Store in airtight containers.

Profile

Ethylene glycol monopalmitostearate has similar properties and uses to glyceryl monostearate or self-emulsifying glyceryl monostearate (p.1915). Ethylene glycol monolaurate and mono-oleate have also been used.

Glyceryl Behenate

Glicerol, behenato de.

Глицерил Бегенат

Pharmacopoeias. In *USNF*. *Eur.* (see p.vii) includes Glycerol Dibehenate.

Ph. Eur. 6.2 (Glycerol Dibehenate; Glyceroli Dibehenas). A mixture of diacylglycerols, mainly dibehenoylglycerol, together with variable quantities of mono- and triacylglycerols. It contains 15 to 23% of monoacylglycerols, 40 to 60% of diacylglycerols, and 21 to 35% of triacylglycerols, obtained by esterification of glycerol and behenic acid. A hard, waxy mass or powder or white or almost white, unctuous flakes. Practically insoluble in water; partly soluble in hot alcohol; soluble in dichloromethane. M.p. 65° to 77°.

USNF 26 (Glyceryl Behenate). A mixture of glycerides of fatty acids, mainly behenic acid. A fine powder with a faint odour. M.p. about 70°. Practically insoluble in water and in alcohol; soluble in chloroform. Store in airtight containers at a temperature not exceeding 35°.

Profile

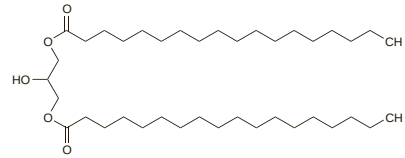
Glyceryl behenate is used as a lubricant and binder in tablet-making.

Glyceryl Distearate

Glicerin-disztearát; Glicerol, diestearato de; Glicerolio distearatas; Glycerol Distearate; Glycérol, distéarate de; Glyceroldistearat; Glycerol-distearát; Glyceroli distearas; Glyserolidistearaatti.

Глицерилдистеарат

CAS — 1323-83-7.



Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF*.

Ph. Eur. 6.2 (Glycerol Distearate). A mixture of diacylglycerols, mainly distearoylglycerol, together with variable quantities of mono- and triacylglycerols. It contains 8 to 22% of monoacylglycerols, 40 to 60% of diacylglycerols, and 25 to 35% of triacylglycerols, obtained by partial glycerolysis of vegetable oils containing triacylglycerols of palmitic or stearic acid or by esterification of glycerol with stearic acid. The fatty acids may be of vegetable or animal origin.