the base; vardenafil hydrochloride trihydrate 11.85 mg is equivalent to about 10 mg of vardenafil.

The usual dose is 10 mg taken about 25 minutes to one hour before sexual intercourse. The dose may be increased or decreased depending on response. The maximum recommended dose is 20 mg, and vardenafil should not be taken more than once in 24 hours. The dose may be taken with or without food, but onset of activity may be delayed if taken with a high-fat meal.

- An initial dose of 5 mg is recommended in elderly patients, which may be increased to 10 mg and then to 20 mg if necessary.
- In patients stabilised on alpha blocker therapy, the dose of vardenafil should be no more than 5 mg daily and it should not be taken within 6 hours of the alpha blocker, although this interval may not be necessary with tamsulosin.
- A maximum daily dose of vardenafil 5 mg is advised in patients taking erythromycin (dose not specified in licensed product information), itraconazole (200 mg daily), or ketoconazole (200 mg daily). A daily dose of 2.5 mg is recommended for those taking clarithromycin (dose not specified in licensed product information), itraconazole (400 mg daily), or ketoconazole (400 mg daily).
- A maximum dose of vardenafil 2.5 mg every 24 hours is recommended in patients taking HIV-protease inhibitors. This dose should be reduced to 2.5 mg every 72 hours in those taking ritonavir-boosted regimens, although this combination may be best avoided (see also Interactions, above).

For doses in hepatic or renal impairment, see below.

◊ Reviews.

1. Keating GM, Scott LJ. Vardenafil: a review of its use in erectile dysfunction. *Drugs* 2003; **63:** 2673–2703.
2. Crowe SM, Streetman DS. Vardenafil treatment for erectile dysfunction. *Ann Pharmacother* 2004; **38:** 77–85.
3. Kendirci M, *et al.* Vardenafil: a novel type 5 phosphodiesterase inhibitor for the treatment of erectile dysfunction. *Expert Opin Pharmacother* 2004; **5:** 923–32.
4. Markou S, *et al.* Vardenafil (Levitra) for erectile dysfunction: a systematic review and meta-analysis of clinical trial reports. *Int J Impot Res* 2004; **16:** 470–8.
5. van Ahlen H, *et al.* The real-life safety and efficacy of vardenafil: an international post-marketing surveillance study—results from 29 358 German patients. *J Int Med Res* 2005; **33:** 337–48.
6. Montorsi F, *et al.* Vardenafil for the treatment of erectile dysfunction: a critical review of the literature based on personal clinical experience. *Eur Urol* 2005; **47:** 612–21.

Administration in hepatic impairment. An initial dose of 5 mg of vardenafil is recommended by UK licensed product information in patients with mild to moderate hepatic impairment (Child-Pugh category A to B), which may be increased if necessary, according to response and tolerability. The maximum dose recommended in patients with moderate hepatic impairment is 10 mg. Vardenafil has not been evaluated in severe hepatic impairment (Child-Pugh category C).

Administration in renal impairment. In the UK, an initial dose of 5 mg of vardenafil is recommended by licensed product information in patients with a creatinine clearance of less than 30 mL/minute, which may be increased to 10 mg and then to 20 mg if necessary, according to response and tolerability. US licensing information does not consider adjustment to be necessary. The pharmacokinetics of vardenafil have not been studied in patients requiring dialysis.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Levitra; ***Austral.:*** Levitra; ***Austria:*** Levitra; ***Belg.:*** Levitra; ***Braz.:*** Levitra; Vivanza; ***Canad.:*** Levitra; ***Chile:*** Levitra; ***Cz.:*** Levitra; Vivanza; ***Denm.:*** Levitra; ***Fin.:*** Levitra; ***Fr.:*** Levitra; ***Ger.:*** Levitra; ***Gr.:*** Levitra; ***Hong Kong:*** Levitra; ***Hung.:*** Levitra; ***Indon.:*** Levitra; ***Irl.:*** Levitra; ***Israel:*** Levitra; ***Ital.:*** Levitra; Vivanza†; ***Malaysia:*** Levitra; ***Mex.:*** Levitra; ***Neth.:*** Levitra; Vivanza; ***Norw.:*** Levitra; ***NZ:*** Levitra; ***Philipp.:*** Levitra; ***Pol.:*** Levitra; ***Port.:*** Levitra; Vivanza; ***Rus.:*** Levitra (Левитра); ***S.Afr.:*** Levitra; ***Singapore:*** Levitra; ***Spain:*** Levitra; ***Swed.:*** Levitra; ***Switz.:*** Levitra; ***Thai.:*** Levitra; ***Turk.:*** Levitra; ***UK:*** Levitra; ***USA:*** Levitra; ***Venez.:*** Levitra.

Yohimbine Hydrochloride *(BAN)*

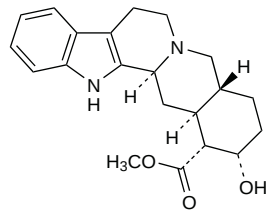
Aphrodine Hydrochloride; Chlorhydrate de Québrachine; Corynine Hydrochloride; Yohimbina, hidrocloruro de; Yohimbine, chlorhydrate de; Yohimbini hydrochloridum. Methyl 17α-hydroxy-yohimban-16α-carboxylate hydrochloride.

$C_{21}H_{26}N_2O_3$,HCl = 390.9.

CAS — 146-48-5 (yohimbine); 65-19-0 (yohimbine hydrochloride).

ATC — G04BE04.

ATC Vet — QG04BE04.



(yohimbine)

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

Ph. Eur. 6.2 (Yohimbine Hydrochloride). A white or slightly yellowish, crystalline powder. Sparingly soluble in water; practically insoluble in alcohol and in dichloromethane. A 1% solution in water has a pH of 3.5 to 5.5. Store in airtight containers. Protect from light.

USP 31 (Yohimbine Hydrochloride). A white to yellow powder. Slightly soluble in water and in alcohol; soluble in boiling water. Store in airtight containers.

Profile

Yohimbine is the principal alkaloid of the bark of the yohimbe tree, *Pausinystalia yohimbe* (*Corynanthe yohimbi*) (Rubiaceae); it is also found in *Rauwolfia serpentina*. It is an alpha$_2$-adrenoceptor blocker with a short duration of action. It has an antidiuretic effect and produces increases in heart rate and blood pressure. It has been reported to cause CNS effects including anxiety and manic reactions. It has been given orally in the treatment of erectile dysfunction (p.2179) and for its alleged aphrodisiac properties but convincing evidence of such an effect is lacking. It is contra-indicated in renal or hepatic disease.

Adverse effects. A warning about the potential adverse effects, including anxiety, manic reactions, bronchospasm, and a lupus-like syndrome, associated with yohimbine taken in health food products.[1] Interactions with tricyclic antidepressants and with phenothiazines might also occur.

1. De Smet PAGM, Smeets OSNM. Potential risks of health food products containing yohimbe extracts. *BMJ* 1994; **309:** 958.

Uses. References to the use of yohimbine in erectile dysfunction.

1. Ernst E, Pittler MH. Yohimbine for erectile dysfunction: a systematic review and meta-analysis of randomised clinical trials. *J Urol (Baltimore)* 1998; **159:** 433–6.
2. Tam SW, *et al.* Yohimbine: a clinical review. *Pharmacol Ther* 2001; **91:** 215–43.
3. Lebret T, *et al.* Efficacy and safety of a novel combination of L-arginine glutamate and yohimbine hydrochloride: a new oral therapy for erectile dysfunction. *Eur Urol* 2002; **41:** 608–13.
4. Guay AT, *et al.* Yohimbine treatment of organic erectile dysfunction in a dose-escalation trial. *Int J Impot Res* 2002; **14:** 25–31.

Preparations

USP 31: Yohimbine Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Yohimex†; ***Austria:*** Yocon; ***Belg.:*** Yocoral; ***Braz.:*** Yomax; ***Canad.:*** Yocon; ***Chile:*** Yocon; ***Denm.:*** Virigen; ***Fr.:*** Yocoral; ***Ger.:*** Pluriviron mono†; Yocon; ***Port.:*** Zumba; ***Singapore:*** Urobine†; ***UK:*** Prowess Plain; ***USA:*** Aphrodyne; Yocon.

Multi-ingredient: ***Arg.:*** Ferona; Optimina Plus; ***Austria:*** Pasuma-Dragees; ***Braz.:*** Geravitine†; Libiplus; Testofran†; Tonaton; ***Fin.:*** Potentol†; ***Hong Kong:*** Wari-Procomil; ***Indon.:*** Sirec; ***Israel:*** Tesopalmed Forte cum Yohimbine; ***Thai.:*** Wari-Procomil†; ***UK:*** Prowess.

Vaccines Immunoglobulins and Antisera

The agents described in this section are immunological agents used for both active and passive immunisation.

Active immunisation is the exposure of the immune system to antigens in the form of micro-organisms or products of their activity in order to stimulate production of antibodies and acquired cell-mediated responses with a specific protective capacity. It may be a natural process after infection, or an artificial process induced by giving *vaccines*. It is inevitably a slow process dependent upon the rate at which the antibodies can be produced. Although the terms vaccination and immunisation are often used synonymously and interchangeably, *vaccination* simply refers to giving a vaccine whereas *immunisation* implies the development of protective levels of antibodies.

Passive immunisation, which results in immediate short-term protection, may be achieved by giving exogenous antibodies in the form of *antisera* (of animal origin) or *immunoglobulins*.

Antisera

Antisérums; Antisueros; Immunsera.

Антисыворотки

Description

Antisera (immunosera) are sterile preparations containing immunoglobulins obtained from the serum of immunised animals by purification. The term antisera includes antitoxins, which are antibodies that combine with and neutralise specific toxins, and antivenins (antivenoms), which are antitoxins directed against the toxic principle of the venoms of poisonous animals such as certain snakes and arthropods.

Antisera are obtained from healthy animals immunised by injections of the appropriate toxins or toxoids, venins, or suspensions of micro-organisms or other antigens. The specific immunoglobulins may be obtained from the serum by fractional precipitation and enzyme treatment or by other chemical or physical means. A suitable antimicrobial preservative may be added, and is invariably added if the product is issued in multidose containers. The Ph. Eur. 6.2 directs that when antisera contain phenol, the concentration is not more than 0.25%. The antiserum is distributed aseptically into sterile containers, which are sealed so as to exclude micro-organisms. Alternatively they may be supplied as freeze-dried preparations for reconstitution immediately before use.

Adverse Effects and Precautions

Reactions are liable to occur after the injection of any serum of animal origin. Anaphylaxis (type I hypersensitivity reaction, p.561) may occur, with hypotension, dyspnoea, urticaria, and shock, which requires management as a medical emergency (see p.1205).

Serum sickness (type III hypersensitivity reaction, p.561) may also occur, frequently 7 to 10 days after the injection of serum of animal origin.

Before injecting serum, information should be obtained whenever possible as to whether the patient is subject to hypersensitivity disorders or has received serum injections before. Sensitivity testing should be performed before giving antisera. The patient must be kept under observation after giving a full dose of antisera. Adrenaline injection and resuscitation facilities should be available.

Uses and Administration

Antisera have the specific power of neutralising venoms or bacterial toxins, or combining with the bacterium, virus, or other antigen used for their preparation. Most antisera in current use are antitoxins or antivenins. The use of antisera to induce passive immunity has declined; immunoglobulins are preferred. Although antisera are defined as being of animal origin (see above), the term antisera has been used in some countries to describe antitoxins of human origin (immunoglobulins).

Immunoglobulins

Immunglobuline; Inmunoglobulinas.

Иммуноглобулины

Description

Immunoglobulins are produced by B lymphocytes as part of the humoral response to foreign antigens. Immunoglobulins used in clinical practice are preparations containing antibodies, usually prepared from human plasma or serum, and mainly comprise IgG. Normal immunoglobulin, prepared from material from blood donors, contains several antibodies against infectious diseases prevalent in the general population, whereas specific immunoglobulins contain minimum specified levels of one antibody. Antibodies may also be prepared by genetic engineering techniques.

Adverse Effects

Local reactions with pain and tenderness at the site of intramuscular injection may follow the use of immunoglobulins. Hypersensitivity reactions, including, rarely, anaphylactic reactions, have also been reported; such reactions, though, are far less frequent than after the use of antisera of animal origin.

Some immunoglobulins are available as intravenous preparations. Systemic reactions with fever, chills, facial flushing, headache, and nausea may occur, particularly at high rates of infusion.

Precautions

Strenuous efforts are made to screen human donor material used in the preparation of immunoglobulins; the transmission of infections, including hepatitis B and HIV, which has been associated with the use of certain blood products (see p.1056), does not appear to be a problem with the immunoglobulins currently in use.

IgA, present in some immunoglobulin preparations, may give rise to the production of anti-IgA antibodies in patients with IgA deficiencies, with the consequent risk of anaphylactic reactions. For precautions in such patients, see Hypersensitivity under Adverse Effects and Precautions in Normal Immunoglobulins, p.2226.

Interactions

Immunoglobulins may interfere with the ability of live vaccines to induce an immune response and a suitable interval should separate their use (see Vaccines, Interactions, p.2202).

Uses and Administration

Immunoglobulins are used for passive immunisation, thus conferring immediate protection against some infectious diseases. They are preferred to antisera of animal origin as the incidence of adverse reactions is lower.

It is generally important to follow the conferment of passive immunity, which is largely an emergency procedure, by the injection of suitable antigens to produce active immunity.

Vaccines

Vacunas.

Вакцины

Description

Vaccines are traditionally preparations of antigenic materials that are given with the objective of inducing in the recipient active immunity to specific infecting agents or toxins or antigens produced by them. They may contain living or killed micro-organisms, bacterial toxoids, or antigenic material from particular parts of the infecting organism, which may be derived from the organism or produced by recombinant DNA technology. Vaccines may be single-component vaccines or mixed combined vaccines. Vaccines against some non-infectious diseases are being developed.

Storage. All vaccines are sensitive to heat to differing extents, with oral poliomyelitis vaccines and measles vaccines the most heat-sensitive of the commonly used vaccines. Freeze-dried vaccines become much more heat-sensitive once reconstituted. The effect of heat on vaccines is generally irreversible loss of potency, but in some cases heat exposure may also cause the vaccine to become more reactogenic. The system used for storing and distributing vaccines at sufficiently low temperature is called the cold chain, and consists of a series of storage and transport links all designed to keep the vaccine at the correct temperature until it reaches the user. WHO recommends[1] that oral poliomyelitis vaccines be stored at −25 to −15° and that, in general, freeze-dried vaccines should be stored at 2 to 8°.

Some vaccines are also sensitive to excessive cold, notably hepatitis B vaccines and Haemophilus influenzae vaccines, and care should be taken not to store them at too low a temperature.[1]

In addition to temperature sensitivity, some vaccines are also sensitive to strong light, such as BCG vaccines, measles-containing vaccines, and rubella-containing vaccines. These are usually supplied in dark brown glass vials for protection, but further care should be taken to keep them covered.[1]

Further advice concerning vaccine storage is given in the references below.[2-6]

1. WHO. What are the correct conditions for storing EPI vaccines? Available at: http://www.who.int/vaccines-access/vacman/temperature/temperature.htm (accessed 26/09/05)
2. Galazka A, *et al.*: Global Programme for Vaccines and Immunization. *Thermostability of vaccines.* Geneva: WHO, 1998. Also available at: http://whqlibdoc.who.int/hq/1998/WHO_GPV_98.07.pdf (accessed 14/07/08)
3. Department of Vaccines and Other Biologicals. *Temperature monitors for vaccines and the cold chain.* Geneva: WHO, 1999. Also available at: http://www.who.int/vaccines-documents/DocsPDF/www9804.pdf (accessed 15/09/05)
4. CDC. Notice to readers: guidelines for maintaining and managing the vaccine cold chain. *MMWR* 2003; **52:** 1023–5. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5242.pdf (accessed 24/05/06)
5. Australian Government Department of Health and Ageing. National vaccine storage guidelines: strive for 5 (2005). Available at: http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/5B7381C34C511E54CA25719D00183397/06.00File/strive-4-five.pdf (accessed 14/07/08)
6. Public Health Agency of Canada. National vaccine storage and handling guidelines for immunization providers (2007). Available at: http://www.phac-aspc.gc.ca/publicat/2007/nvshglp-ldemv/index-eng.php (accessed 05/06/08)

Adverse Effects

Injection of a vaccine may be followed by a local reaction, possibly with inflammation and lymphangitis. An induration or sterile abscess may develop at the injection site. Fever, headache, and malaise may start a few hours after injection and last for 1 or 2 days. Hypersensitivity reactions may occur and anaphylaxis has been reported rarely.

Further details, if appropriate, of adverse effects of vaccines may be found in the respective individual monographs.

Anaphylaxis. In a retrospective study[1] in the USA conducted to quantify the risk of anaphylaxis after vaccination of children and adolescents, only 5 cases potentially associated with vaccines were identified from more than 7.5 million doses given. Vaccines implicated were generally given in combination and included the following components: diphtheria and tetanus; diphtheria, tetanus, and pertussis; hepatitis B; Haemophilus influenzae; measles, mumps, and rubella; and oral poliomyelitis. One case followed measles, mumps, and rubella vaccine given alone. It was concluded that vaccine-associated anaphylaxis is a rare event.

1. Bohlke K, *et al.* Risk of anaphylaxis after vaccination of children and adolescents. *Pediatrics* 2003; **112:** 815–20.

Long-term effects. The introduction of routine childhood vaccination has been accompanied by concerns over the safety and possible long term sequelae of some commonly used vaccines. Difficulties have arisen in distinguishing temporal and causal associations and in some cases the perceived dangers of vaccination have impeded uptake. Among the disorders that have been temporally (but generally not causally) associated with childhood vaccination are neurological disorders, sudden infant death syndrome, type 1 diabetes mellitus, and demyelinating disorders. Information on adverse effects associated with specific vaccines can be found under diphtheria, tetanus, and pertussis vaccines (p.2210), hepatitis B vaccines (p.2215), influenza vaccines (p.2218), measles, mumps, and rubella vaccines (p.2223), and pertussis vaccines (p.2230).

Additives or excipients have sometimes been alleged to be the cause of adverse reactions—see below for further details.

References.

1. Jefferson T. Vaccination and its adverse effects: real or perceived. *BMJ* 1998; **317:** 159–60.
2. Ball LK, *et al.* Risky business: challenges in vaccine risk communication. *Pediatrics* 1998; **101:** 453–8.
3. Hiltunen M, *et al.* Immunisation and type 1 diabetes mellitus: is there a link? *Drug Safety* 1999; **20:** 207–12.