due to hypersensitivity. In addition high parenteral doses can result in cardiac arrhythmias; intravenous or intramuscular doses should be given slowly. Thrombosis has been reported at the injection site.

Intracavernosal injection can cause dose-related priapism and local fibrosis has been reported after long-term therapy.

Papaverine should be given with caution to patients with reduced gastrointestinal motility. Caution is also advised in the presence of cardiac conduction disorders or unstable cardiovascular disease, especially when papaverine is given parenterally. Intravenous dosage is contra-indicated in patients with complete AV block.

Glaucoma. There appeared to be no basis for the manufacturers' recommendation that papaverine should be used with caution in patients with glaucoma.[1] There was no obvious mechanism to support such a warning and only 1 report of an adverse reaction had been received by the FDA. The author had given papaverine intracavernosally to patients with glaucoma and had observed no deterioration.

1. Swartz DA, Todd MW. Intracavernous papaverine and glaucoma. *JAMA* 1990; **264:** 570.

Intracavernosal administration. Systemic adverse effects occurring after intracavernosal injection of papaverine are infrequent but include dizziness and syncope,[1,2] probably related to the hypotensive effects of papaverine; abnormal liver function test results have also occurred.[1-3]

The most serious acute adverse effect is priapism[1,2,4] and patients should be instructed to seek medical help if an erection lasts for more than 4 hours. Detumescence can be effected by aspiration of blood from the corpus or by local injection of an alpha-adrenergic agonist such as adrenaline, metaraminol, or phenylephrine (see Priapism under Alprostadil, p.2184). Other local effects include haematoma, infection, and, on long-term therapy, fibrosis and penile distortion.[1,2]

Dispensing errors have resulted in inadvertent injection of *papaveretum* with potentially fatal consequences.[2,5,6]

1. Krane RJ, *et al.* Impotence. *N Engl J Med* 1989; **321:** 1648–59.
2. Bénard F, Lue TF. Self-administration in the pharmacological treatment of impotence. *Drugs* 1990; **39:** 394–8.
3. Levine SB, *et al.* Side effects of self-administration of intracavernous papaverine and phentolamine for the treatment of impotence. *J Urol (Baltimore)* 1989; **141:** 54–7.
4. Virag R. About pharmacologically induced prolonged erection. *Lancet* 1985; **i:** 519–20.
5. Robinson LQ, Stephenson TP. Self injection treatment for impotence. *BMJ* 1989; **299:** 1568.
6. Gregoire A. Self injection treatment for impotence. *BMJ* 1990; **300:** 537.

Interactions

Levodopa. For the effects of papaverine on levodopa, see p.808.

Pharmacokinetics

The biological half-life of papaverine given orally is reported to be between 1 and 2 hours, but there is wide interindividual variation. It is about 90% bound to plasma proteins.

Papaverine is mainly metabolised in the liver and excreted in the urine, almost entirely as glucuronide-conjugated phenolic metabolites.

The reports of infrequent systemic effects after intracavernosal injection of papaverine indicate that there is some distribution to the systemic circulation from the corpus cavernosus.

Uses and Administration

Papaverine is an alkaloid present in opium, although it is not related chemically or pharmacologically to the other opium alkaloids. Papaverine has a direct relaxant effect on smooth muscle which is attributed in part to its ability to inhibit phosphodiesterase. It has been given in the management of cerebral, peripheral, and coronary vascular disorders; it is also given as an antispasmodic for gastrointestinal disorders and coughs. However, there is little evidence to justify its clinical use in these conditions.

Papaverine hydrochloride has been given orally in doses of up to 600 mg daily. Sustained-release preparations have been used. The codecarboxylase derivative, cromesilate, hydrobromide, monophosadenine, nicotinate, sulfate, and teprosilate have also been used. Papaverine hydrochloride has also been given in doses of 30 to 120 mg by intramuscular or slow intravenous injection, repeated every 3 hours as needed (but see Adverse Effects and Precautions, above).

Papaverine hydrochloride has been given by injection into the corpus cavernosum of the penis for the treatment of erectile dysfunction (p.2179). Doses have ranged from 2.5 to 60 mg, but must be initially titrated by the prescriber. Doses up to about 30 mg have been combined with phentolamine.

Preparations

BP 2008: Papaverine Injection;
USP 31: Papaverine Hydrochloride Injection; Papaverine Hydrochloride Tablets.

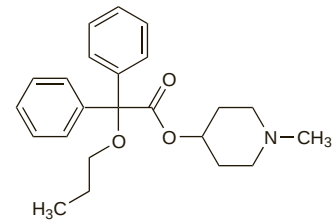
Proprietary Preparations (details are given in Part 3)
Arg.: Mesotina; Ova†; ***Braz.:*** Dipaverina†; ***USA:*** Pavabid†; ***Venez.:*** Atrophena†; Atroveran; Papaveryl; Tropaverin†.

Multi-ingredient: ***Arg.:*** Antipasmol; Antispasmina; Gastranil†; Hepatodirectol; Saltos†; Trixol†; ***Austria:*** Androskat; Asthma 23 D; Myocardon; Ora-Gallin compositum; ***Braz.:*** Analgosedan†; Calmazin†; Codeverin†; Dipirol†; Ductoveran; Espasmalgon†; Espasmocron; Gaba†; Melpaz†; Monotrean; Monotrean B6; Nicopaverina B6†; Nicopaverina†; Pasmalgin†; Plenocedan†; Revulsan†; Sedalene; Sedalin; Spasmotropin; Vagostesyl; ***Chile:*** Belupan†; Buton; Dipatropin; Dolospam; Papatropin†; ***Cz.:*** Contraspan†; Spasmoveralgin Neo†; ***Fr.:*** Acticarbine; ***Hong Kong:*** Bromhexine Compound; Codolax; Codomex Orange†; Codomex Purple†; Codoplex; Enterocin Compound; Methor-Co; Metoplex; ***Hung.:*** Bilagit†; Meristin; Neo-Bilagit; Troparinum; ***India:*** Brovon; ***Indon.:*** Sanmag; Spaslic; Spasmal; Spasminal; ***Israel:*** Patropin; Spasmalgin; ***Ital.:*** Antispasmina Colica; Monotrean†; ***Mex.:*** Acilin; Ayoral†; Taliviform†; ***Neth.:*** Androskat; ***Pol.:*** Biospasmil; Fortestomachicae; Spasticol; Tolargin; ***Port.:*** Antispasmina Colica; Cosmaxil†; ***Spain:*** Sulmetin Papaver; Sulmetin Papaverina†; ***Swed.:*** Spasmofen; ***Switz.:*** Dolopyrine†; Spasmosol; ***UK:*** Brovon; ***USA:*** Tri-Mix; ***Venez.:*** Atrobel; Cloverin†; Neo-Atropan†; Tropifen†.

Propiverine Hydrochloride *(BANM, rINNM)*

BUP-4 (propiverine); Hidrocloruro de propiverina; Propiverin Hidroklorür; Propivérine, Chlorhydrate de; Propiverini Hydrochloridum. 1-Methyl-4-piperidyl diphenylpropoxyacetate hydrochloride.

Пропиверина Гидрохлорид
$C_{23}H_{29}NO_3,HCl$ = 403.9.
CAS — 60569-19-9 (propiverine); 54556-98-8 (propiverine hydrochloride).
ATC — G04BD06.
ATC Vet — QG04BD06.



(propiverine)

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219. Hypotension and drowsiness may also occur with propiverine. Propiverine is contra-indicated in patients with moderate or severe hepatic impairment (but see below). Liver enzyme values should be monitored in patients receiving long-term therapy. Skeletal retardation has occurred in the offspring of *animals* given high doses of propiverine during pregnancy and therefore its use is not recommended during pregnancy.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220). Hypotension may occur in patients treated with propiverine and isoniazid. Drowsiness may be enhanced by drugs with CNS-depressant properties.

Pharmacokinetics

Propiverine is absorbed from the gastrointestinal tract and peak plasma concentrations are achieved about 2.3 hours after oral doses. It undergoes extensive first-pass metabolism and the average absolute bioavailability is reported to be about 41%. Plasma concentrations of the principal metabolite, the *N*-oxide, greatly exceed those of the parent compound. Protein binding is about 90% for propiverine and 60% for the *N*-oxide metabolite. Propiverine and its metabolites are excreted in the urine, bile, and faeces. The elimination half-life is about 20 hours.

◊ References.

1. Haustein K-O, Hüller G. On the pharmacokinetics and metabolism of propiverine in man. *Eur J Drug Metab Pharmacokinet* 1988; **13:** 81–90.

Uses and Administration

Propiverine hydrochloride is a tertiary antimuscarinic with actions similar to those of atropine (p.1220). It is used for the management of urinary frequency, urgency, and incontinence (p.2180) in neurogenic bladder disorders and in idiopathic detrusor instability. Usual oral doses of propiverine hydrochloride are 15 mg two or three times daily, increased to 4 times daily if required. Some patients may respond to 15 mg once daily. A daily dose of 60 mg should not be exceeded. Propiverine hydrochloride can also be given as a modified-release preparation in a dose of 30 mg once daily.

Administration in hepatic impairment. Although UK licensed product information for propiverine does not recommend its use in patients with moderate or severe hepatic impairment some[1] suggest that on pharmacokinetic grounds it may be given to those with mild to moderate degrees of impairment at recommended doses without increasing the risk of adverse effects.

1. Siepmann M, *et al.* Pharmacokinetics and safety of propiverine in patients with fatty liver disease. *Eur J Clin Pharmacol* 1998; **54:** 767–71.

Urinary incontinence. Although propiverine is licensed in the UK for use in urinary frequency, urgency, and incontinence (see above), guidelines subsequently issued by NICE consider that although it should be an option for urinary frequency in women with overactive bladder syndrome, use in women with overt incontinence is not recommended.[1]

1. NICE. Urinary incontinence: the management of urinary incontinence in women (issued October 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/CG40NICEguideline.pdf (accessed 02/09/08)

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Mictonetten; Mictonorm; ***Ger.:*** Mictonetten; Mictonorm; ***Jpn:*** BUP-4; ***Port.:*** Detrunorm†; Mictonorm; ***S.Afr.:*** Detrunorm; ***Thai.:*** Mictonorm; ***UK:*** Detrunorm.

Pygeum Africanum

African Prune; Afrikankirsikkapuunkuori (pygeum africanum bark); Afrikinių slyvų žievė (pygeum africanum bark); Kůra slivoně africké (pygeum africanum bark); Pruni Africanae; Pruni africanae cortex (pygeum africanum bark); Prunier d'Afrique; Prunier d'Afrique, écorce de (pygeum africanum bark).
ATC — G04CX01.
ATC Vet — QG04CX01.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Pygeum Africanum Bark; Pygeum Bark BP 2008). The whole or cut, dried bark of the stems and branches of *Prunus africana* (*Pygeum africanum*).
USP 31 (Pygeum). The bark of *Prunus africana* (*Pygeum africanum*) (Rosaceae). It contains not less than 9.0% of extractable matter.

Profile

An extract from the bark of the tree *Prunus africana* (*Pygeum africanum*) is used in the treatment of benign prostatic hyperplasia (p.2178). Like some other phytotherapies for this disorder, it appears to contain various sitosterols. A usual oral dosage is 100 mg daily.

Benign prostatic hyperplasia. Pygeum africanum appears to produce a modest benefit on urological symptoms and measures of urinary flow.

References.

1. Andro M-C, Riffaud J-P. Pygeum africanum extract for the treatment of patients with benign prostatic hyperplasia: a review of 25 years of published experience. *Curr Ther Res* 1995; **56:** 796–817.
2. Buck AC. Phytotherapy for the prostate. *Br J Urol* 1996; **78:** 325–36.
3. Ishani A, *et al.* Pygeum africanum for the treatment of patients with benign prostatic hyperplasia: a systematic review and quantitative meta-analysis. *Am J Med* 2000; **109:** 654–64.

Preparations

USP 31: Pygeum Capsules.

Proprietary Preparations (details are given in Part 3)
Austria: Tadenan; ***Braz.:*** Prostem; ***Cz.:*** Tadenan; ***Fr.:*** Tadenan; ***Gr.:*** Foudanil; Rotamat; Tadenan; ***Hung.:*** Tadenan†; ***Ital.:*** Pigenil; Tadenan; ***Mex.:*** Tadenom; ***Philipp.:*** Tadenan; ***Pol.:*** Poldanen; Tadenan; ***Port.:*** Tadenan†; ***Rus.:*** Tadenan (Таденан); Trianol (Трианол); ***Spain:*** Acubiron; Bidrolar; Pronitol; Tuzanil; ***Switz.:*** Tadenan; ***Thai.:*** Tadenan.

Multi-ingredient: ***Arg.:*** Catiz Plus; Normoprost Compuesto; Normoprost Plus; Ultracal; ***Austria:*** Prostatonin; ***Braz.:*** Prostem Plus; ***Canad.:*** Prostate Ease; Prostease; ***Cz.:*** Prostatonin†; ***Hong Kong:*** Prostease; ***Pol.:*** Neopoldanen; ***Port.:*** Neo Urgenin; ***Spain:*** Neo Urgenin; Prosturol; Tebetane Compuesto; ***Switz.:*** Prostatonin.

Saw Palmetto

American Dwarf Palm; *Brahea serrulata*; PA-109; Palmera de Florida; Sabal; Sabal, fruit de (saw palmetto fruit); *Sabal serrulata*; Sabalis Serrulatae; Sabalis serrulatae fructus (saw palmetto fruit); Sågpalmettofrukt (saw palmetto fruit); Sahapalmunhedelmä (saw palmetto fruit); *Serenoa repens*; *Serenoa serrulatum*; Serenový plod (saw palmetto fruit); Šliaužiančiųjų serenojų vaisiai (saw palmetto fruit).
ATC — G04CX02.
ATC Vet — QG04CX02.

Pharmacopoeias. In *Eur.* (see p.vii) and *US*. *US* also includes the extract and the powdered form.
Ph. Eur. 6.2 (Saw Palmetto Fruit). The dried, ripe fruit of *Ser-*