Effects on mental function. Oxybutynin was associated with the development of acute confusional states in 4 patients with Parkinson's disease and some cognitive impairment.[1] A study[2] of healthy subjects, aged 65 years or older, also found oxybutynin to cause cognitive impairment.

1. Donnellan CA, *et al.* Oxybutynin and cognitive dysfunction. *BMJ* 1997; **315:** 1363–4.
2. Katz IR, *et al.* Identification of medications that cause cognitive impairment in older people: the case of oxybutynin chloride. *J Am Geriatr Soc* 1998; **46:** 8–13.

Night terrors. Night terrors have been reported in 5 patients taking oxybutynin.[1] Four of the patients were young children and the fifth was an elderly woman. Rechallenge was positive in 2 cases.

1. Valsecia ME, *et al.* New adverse effect of oxybutynin: "night terror". *Ann Pharmacother* 1998; **32:** 506.

Overdosage. A report[1] of a 34-year-old woman who ingested 100 mg of oxybutynin. The main symptoms were antimuscarinic effects and included drowsiness, hallucinations, dilatation of pupils, and urinary retention. Tachycardia resolved shortly after admission to hospital but ventricular ectopic beats and bigeminy persisted for over 24 hours. The patient recovered with symptomatic treatment.

1. Banerjee S, *et al.* Poisoning with oxybutynin. *Hum Exp Toxicol* 1991; **10:** 225–6.

Porphyria. Oxybutynin hydrochloride is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220).

Itraconazole. Use of itraconazole with oxybutynin resulted in moderate increases of serum concentrations of the latter.[1] However, concentrations of the active metabolite of oxybutynin, *N*-desethyloxybutynin, were virtually unchanged and the interaction was considered to be of minor clinical significance.

1. Lukkari E, *et al.* Itraconazole moderately increases serum concentrations of oxybutynin but does not affect those of the active metabolite. *Eur J Clin Pharmacol* 1997; **52:** 403–6.

Pharmacokinetics

After oral doses of oxybutynin, peak plasma concentrations are reached within one hour. Oxybutynin is also absorbed after application to the skin. It is highly bound to plasma proteins. Oxybutynin undergoes extensive first-pass metabolism, particularly by the cytochrome P450 isoenzyme CYP3A4, and systemic oral bioavailability has been reported to be only 6%. *N*-desethyloxybutynin is an active metabolite. Oxybutynin and its metabolites are excreted in the urine and faeces, and an elimination half-life of 2 to 3 hours has been reported. Oxybutynin has been detected in breast milk. Evidence suggests that it may cross the blood-brain barrier.

◊ References.

1. Gupta SK, Sathyan G. Pharmacokinetics of an oral once-a-day controlled-release oxybutynin formulation compared with immediate-release oxybutynin. *J Clin Pharmacol* 1999; **39:** 289–96.
2. Appell RA, *et al.* Pharmacokinetics, metabolism, and saliva output during transdermal and extended-release oral oxybutynin administration in healthy subjects. *Mayo Clin Proc* 2003; **78:** 696–702.
3. Reiz JL, *et al.* Pharmacokinetics and pharmacodynamics of once-daily controlled-release oxybutynin and immediate-release oxybutynin. *J Clin Pharmacol* 2007; **47:** 351–7.

Uses and Administration

Oxybutynin hydrochloride is a tertiary amine antimuscarinic with actions similar to those of atropine (p.1220); it also has direct effects on smooth muscle. It is used for the management of urinary frequency, urgency, and incontinence in neurogenic bladder disorders and in idiopathic detrusor instability, and as an adjunct to nonpharmacological therapy for nocturnal enuresis.

Usual oral doses of oxybutynin hydrochloride are 5 mg two or three times daily, increased to 5 mg four times daily if required. In elderly patients lower doses of 2.5 or 3 mg twice daily initially, increased to 5 mg twice daily if necessary, may be adequate. Modified-release preparations of oxybutynin hydrochloride are also available. The initial dose is 5 mg once daily, increased by 5 mg at weekly intervals if necessary, up to a maximum of 20 or 30 mg daily, depending on the preparation. Oxybutynin is also given via a transdermal patch that supplies 3.9 mg of oxybutynin daily. The patch should be applied to intact skin on the abdomen, hip, or buttocks and replaced every 3 to 4 days; re-application to the same site should be avoided for 7 days.

In the UK, oxybutynin hydrochloride is licensed for neurogenic bladder disorders in children from the age of 5 years; in both the UK and the USA it is licensed from the age of 6 years as a modified-release formulation. The initial oral dose of conventional formulations is 2.5 or 3 mg twice daily, increased to 5 mg two or three times daily according to response; as a modified-release tablet the initial dose is 5 mg once daily, increased by 5-mg increments to a maximum daily dose of 15 or 20 mg, depending on the preparation, and according to response. Modified-release preparations are not recommended for children who are unable to swallow the tablet whole. The *BNFC* suggests that children aged 2 to 5 years may be given a dose of 1.25 to 2.5 mg as a conventional oral formulation 2 or 3 times daily. Children from the age of 2 years may also be given oxybutynin by intravesical instillation, in a dose of 5 mg (as the hydrochloride) in 30 mL of solution, 2 or 3 times daily.

Oxybutynin is also licensed in the treatment of nocturnal enuresis in children over 5 years, as the conventional formulations, in similar doses to those used for neurogenic bladder disorders; the last dose should usually be given before bedtime. However, the *BNFC* considers that drug therapy for nocturnal enuresis is usually not needed in children under 7 years of age.

Nocturnal enuresis. Antimuscarinics such as oxybutynin reduce uninhibited bladder contractions but, although they may be of use in diurnal enuresis, they are rarely of benefit in nocturnal enuresis (p.2180) alone. Oxybutynin did not appear to be effective in treating primary nocturnal enuresis in children with normal bladders.[1] However, children with low bladder capacity and detrusor instability may derive some benefit from oxybutynin.[2,3]

1. Lovering JS, *et al.* Oxybutynin efficacy in the treatment of primary enuresis. *Pediatrics* 1988; **82:** 104–6.
2. Koşar A, *et al.* Effectiveness of oxybutynin hydrochloride in the treatment of enuresis nocturna: a clinical and urodynamic study. *Scand J Urol Nephrol* 1999; **33:** 115–18.
3. Nevéus T. Oxybutynin, desmopressin and enuresis. *J Urol (Baltimore)* 2001; **166:** 2459–62.

Urinary incontinence. In addition to its antimuscarinic effect, oxybutynin has a direct antispasmodic effect which also contributes to reducing the number of uninhibited bladder contractions in urge incontinence (see p.2180). It is effective when given orally[1-4] or via a transdermal patch.[5-7] NICE considers conventional oral oxybutynin formulations to be the drug of first choice in women with overactive bladder syndrome or mixed incontinence if bladder training has been ineffective.[8] However, adverse effects may limit its use; if immediate-release oxybutynin is not well tolerated, a controlled-release or transdermal formulation may be considered as an alternative.[8]

Oxybutynin given orally can be useful in the management of neurogenic detrusor hyperreflexia in adults[9,10] and children.[11] Direct instillation of oxybutynin into the bladder has also been tried. In one study[12] that included patients aged 1 to 34 years, 21 out of 32 patients became totally continent using an intravesical dose of 300 micrograms/kg daily, given in 3 divided doses. A further 7 patients became continent with doses titrated up to a maximum of 900 micrograms/kg daily, but another 4 remained incontinent. Other reports[13,14] have used single or multiple doses of 5 mg, often prepared by dispersing a crushed 5-mg tablet in 30 mL of distilled water or sodium chloride 0.9%.

1. Riva D, Casolati E. Oxybutynin chloride in the treatment of female idiopathic bladder instability: results from double blind treatment. *Clin Exp Obstet Gynecol* 1984; **11:** 37–42.
2. Moore KH, *et al.* Oxybutynin hydrochloride (3 mg) in the treatment of women with idiopathic detrusor instability. *Br J Urol* 1990; **66:** 479–85.
3. Tapp AJS, *et al.* The treatment of detrusor instability in postmenopausal women with oxybutynin chloride: a double blind placebo controlled study. *Br J Obstet Gynaecol* 1990; **97:** 521–6.
4. Siddiqui MA, *et al.* Oxybutynin extended-release: a review of its use in the management of overactive bladder. *Drugs* 2004; **64:** 885–912.
5. Davila GW, *et al.* A short-term, multicenter, randomized double-blind dose titration study of the efficacy and anticholinergic side effects of transdermal compared to immediate release oral oxybutynin treatment of patients with urge urinary incontinence. *J Urol (Baltimore)* 2001; **166:** 140–5.
6. Dmochowski RR, *et al.* Efficacy and safety of transdermal oxybutynin in patients with urge and mixed urinary incontinence. *J Urol (Baltimore)* 2002; **168:** 580–6.
7. Dmochowski RR, *et al.* Comparative efficacy and safety of transdermal oxybutynin and oral tolterodine versus placebo in previously treated patients with urge and mixed urinary incontinence. *Urology* 2003; **62:** 237–42.
8. 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)
9. O'Leary M, *et al.* Effect of controlled-release oxybutynin on neurogenic bladder function in spinal cord injury. *J Spinal Cord Med* 2003; **26:** 159–62.
10. Bennett N, *et al.* Can higher doses of oxybutynin improve efficacy in neurogenic bladder? *J Urol (Baltimore)* 2004; **171:** 749–51.
11. Franco I, *et al.* Efficacy and safety of oxybutynin in children with detrusor hyperreflexia secondary to neurogenic bladder dysfunction. *J Urol (Baltimore)* 2005; **173:** 221–5.
12. Haferkamp A, *et al.* Dosage escalation of intravesical oxybutynin in the treatment of neurogenic bladder patients. *Spinal Cord* 2000; **38:** 250–4.
13. Szollar SM, Lee SM. Intravesical oxybutynin for spinal cord injury patients. *Spinal Cord* 1996; **34:** 284–7.
14. Lose G, Nørgaard JP. Intravesical oxybutynin for treating incontinence resulting from an overactive detrusor. *BJU Int* 2001; **87:** 767–73.

Preparations

BP 2008: Oxybutynin Tablets;
USP 31: Oxybutynin Chloride Extended-Release Tablets; Oxybutynin Chloride Syrup; Oxybutynin Chloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Continex†; Delak; Ditropan; Oxi-Q; Oxitina; Oxyurin; Retebem; Retemicon; Soxsup; Urequin; ***Austral.:*** Ditropan; Oxytrol; ***Austria:*** Cystrin; Detrusan; Ditropan; Lyrinel; ***Belg.:*** Ditropan; Driptane†; ***Braz.:*** Frenurin†; Incontinol; Retemic; ***Canad.:*** Ditropan; Nu-Oxybutyn; Oxybutyn†; Oxytrol; ***Chile:*** Odranal; Oxiburin†; Urazol; Uricont; ***Cz.:*** Cystrin†; Ditropan; Driptane†; Kentera; Uroxal; ***Denm.:*** Kentera; ***Fin.:*** Cystrin; Ditropan; Kentera; Oksibutin†; Spasmoxyl†; ***Fr.:*** Ditropan; Driptane; Zatur†; ***Ger.:*** Cystonorm†; Dridase; Lyrinel; Oxyb; Oxybase†; Oxybugamma; Oxybutin; Oxybuton; Oxymedin; Ryol; Spasyt; ***Gr.:*** Ditropan; Kentera; Lyrinel; Oxybase; ***Hong Kong:*** Ditropan†; ***Hung.:*** Ditropan; Uroxal; ***India:*** Oxyspas; ***Irl.:*** Cystrin; Ditropan; Kentera; Lyrinel XL; Renamel†; ***Israel:*** Novitropan; ***Ital.:*** Ditropan; ***Malaysia:*** Ditropan†; ***Mex.:*** Inprax; Lyrinel; Nefryl; Tavor; ***Neth.:*** Cystrin†; Dridase; Kentera; ***Norw.:*** Kentera; ***Philipp.:*** Driptane; ***Pol.:*** Cystrin; Ditropan; Driptane; Uroton; ***Port.:*** Ditropan; Kentera; Lyrinel; ***Rus.:*** Driptane (Дриптан); Novitropan (Новитропан)†; ***S.Afr.:*** Ditropan; Lenditro; Oxyspas†; Urihexal; ***Singapore:*** Ditropan†; Obutin; ***Spain:*** Ditropan; Dresplan; ***Swed.:*** Ditropan; Kentera; Oxybase†; ***Switz.:*** Ditropan; ***Thai.:*** Diutropan; ***Turk.:*** Uropan; ***UK:*** Cystrin; Ditropan; Kentera; Lyrinel XL; ***USA:*** Ditropan; Oxytrol; ***Venez.:*** Reteven.

Papaverine *(BAN)*

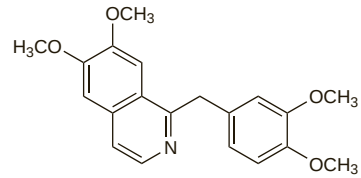
Papaveriini; Papaverin; Papaverina; Papaverinum. 6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)isoquinoline.

$C_{20}H_{21}NO_4$ = 339.4.

CAS — 58-74-2.

ATC — A03AD01; G04BE02.

ATC Vet — QA03AD01; QG04BE02.



NOTE. Papaverine should not be confused with papaveretum (p.105).

Papaverine Hydrochloride *(BANM)*

Papaveriinihydrokloridi; Papaverina, hidrocloruro de; Papavérine, chlorhydrate de; Papaverin-hidroklorid; Papaverin-hydrochlorid; Papaverinhydrokloríd; Papaverini hydrochloridum; Papaverinii Chloridum; Papaverinium Chloride; Papaverino hidrochloridas; Papaweryny chlorowodorek. 6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)isoquinoline hydrochloride.

$C_{20}H_{21}NO_4$,HCl = 375.8.

CAS — 63817-84-5 (papaverine cromesilate); 61-25-6 (papaverine hydrochloride); 39024-96-9 (papaverine monophosadenine); 2053-26-1 (anhydrous papaverine sulfate).

ATC — A03AD01; G04BE02.

ATC Vet — QA03AD01; QG04BE02.

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

Ph. Eur. 6.2 (Papaverine Hydrochloride). White or almost white crystals or crystalline powder. Sparingly soluble in water; slightly soluble in alcohol. A 2% solution in water has a pH of 3.0 to 4.0.

USP 31 (Papaverine Hydrochloride). Odourless white crystals or white, crystalline powder. Soluble 1 in 30 of water and 1 in 120 of alcohol; soluble in chloroform; practically insoluble in ether. pH of a 2% solution in water is between 3.0 and 4.5. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects and Precautions

Adverse effects of oral papaverine include gastrointestinal disturbance, flushing of the face, headache, malaise, drowsiness, skin rash, sweating, orthostatic hypotension, and dizziness. Jaundice, eosinophilia, and signs of altered liver function may occur, sometimes