

**Genetic polymorphism.** Two patients who developed elevated liver enzyme values while receiving tolcapone, one of whom also had hepatic dysfunction while receiving entacapone, were found to be poor metabolisers with regard to UDP-glucuronosyltransferase activity.<sup>1</sup> Such patients may be predisposed to COMT-inhibitor induced hepatotoxicity.

- Martignoni E, et al. Two patients with COMT inhibitor-induced hepatic dysfunction and UGT1A9 genetic polymorphism. *Neurology* 2005; **65**: 1820–2.

### Interactions

Tolcapone may influence the pharmacokinetics of drugs metabolised by catechol-*O*-methyltransferase; a dose reduction of such drugs should be considered when given with tolcapone. Increased concentrations of benserazide and its active metabolite have been reported when given with tolcapone. Licensed product information advises that non-selective MAOIs should not be used with tolcapone.

### Pharmacokinetics

Tolcapone is rapidly absorbed from the gastrointestinal tract and maximum plasma concentrations have been obtained within 2 hours of an oral dose; food delays and decreases the absorption. Absolute bioavailability is reported to be about 65%. Tolcapone is more than 99% bound to plasma proteins (mainly albumin) and is not widely distributed into body tissues. It is extensively metabolised, mainly by conjugation to the inactive glucuronide, but methylation by catechol-*O*-methyltransferase to 3-*O*-methyltolcapone and metabolism by cytochrome P450 isoenzymes CYP3A4 and CYP2A6 also occurs. About 60% of a dose is excreted in the urine with the remainder appearing in the faeces. The elimination half-life has been reported to be about 2 to 3 hours. The clearance of unbound tolcapone may be reduced by 50% in patients with moderate cirrhotic liver disorders.

### References

- Dingemans J, et al. Integrated pharmacokinetics and pharmacodynamics of the novel catechol-*O*-methyltransferase inhibitor tolcapone during first administration to humans. *Clin Pharmacol Ther* 1995; **57**: 508–17.
- Jorga KM, et al. Effect of liver impairment on the pharmacokinetics of tolcapone and its metabolites. *Clin Pharmacol Ther* 1998; **63**: 646–54.
- Jorga K, et al. Metabolism and excretion of tolcapone, a novel inhibitor of catechol-*O*-methyltransferase. *Br J Clin Pharmacol* 1999; **48**: 513–20.
- Jorga K, et al. Population pharmacokinetics of tolcapone in parkinsonian patients in dose finding studies. *Br J Clin Pharmacol* 2000; **49**: 39–48.

### Uses and Administration

Tolcapone is a peripheral inhibitor of catechol-*O*-methyltransferase (COMT), an enzyme involved in the metabolism of dopamine and levodopa. It is used as an adjunct to levodopa and dopa-decarboxylase inhibitor combinations in the management of Parkinson's disease for patients who cannot be stabilised on these levodopa combinations or for those who experience 'end-of-dose' deterioration. Because of the risk of serious hepatotoxicity (see Effects on the Liver, above) the FDA in the USA restricted its use to when other adjunctive therapy was ineffective or contra-indicated. In the EU, tolcapone was withdrawn from the market in November 1998 and subsequently returned in 2004, its use being similarly restricted to patients who fail to respond to, or are intolerant of, other COMT inhibitors.

The usual recommended dosage of tolcapone is 100 mg given orally three times daily; up to a maximum of 200 mg three times daily may be considered if the clinical benefit justifies the increased risk of hepatotoxicity. The first dose of the day should be taken at the same time as the combined levodopa preparation. Most patients already taking more than 600 mg of levodopa daily will require a reduction in their dosage of levodopa; patients on lower levodopa doses may also require a dose reduction.

Tolcapone should be withdrawn if a substantial clinical benefit is not obtained within the first 3 weeks of treatment. An adjustment in the levodopa dose may be necessary following tolcapone withdrawal.

**Parkinsonism.** Tolcapone is a reversible peripheral inhibitor of catechol-*O*-methyltransferase (COMT), an enzyme involved in the metabolism of levodopa and dopamine.<sup>1</sup> It appears to differ from entacapone (p.804) by being a more potent COMT inhibitor in the periphery and by penetrating into the brain (although the significance of any central effects of COMT inhibition are not known).<sup>1</sup> When given to patients with Parkinson's disease (p.791) and levodopa-related fluctuations in disability or 'end-of-dose' effects, it has prolonged the clinical benefit obtained with levodopa and allowed the total daily dosage of levodopa to be reduced.<sup>2,3</sup> Benefit has also been reported<sup>4</sup> when added to levodopa therapy in patients with stable Parkinson's disease. However, a systematic review<sup>5</sup> concluded that there were insufficient data to demonstrate any significant difference in efficacy between tolcapone and bromocriptine or pergolide in the adjunctive treatment of levodopa-induced motor complications.

The use of tolcapone is restricted in some countries because of the risk of serious hepatotoxicity (see Effects on the Liver, above).

- Nutt JG. Catechol-*O*-methyltransferase inhibitors for treatment of Parkinson's disease. *Lancet* 1998; **351**: 1221–2.

- Kurth MC, et al. Tolcapone improves motor function and reduces levodopa requirement in patients with Parkinson's disease experiencing motor fluctuations: a multicenter, double-blind, randomised, placebo-controlled trial. *Neurology* 1997; **48**: 81–7.
- Rajput AH, et al. Tolcapone improves motor function in parkinsonian patients with the "wearing-off" phenomenon: a double-blind placebo-controlled, multicenter trial. *Neurology* 1997; **49**: 1066–71.
- Waters CH, et al. Tolcapone Stable Study Group. Tolcapone in stable Parkinson's disease: efficacy and safety of long-term treatment. *Neurology* 1997; **49**: 665–71.
- Deane KHO, et al. Catechol-*O*-methyltransferase inhibitors versus active comparators for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 16/02/06).

### Preparations

**USP 31:** Tolcapone Tablets.

**Proprietary Preparations** (details are given in Part 3)

**Arg:** Tasmar; **Austria:** Tasmar; **Belg:** Tasmar; **Braz:** Tasmar; **Chile:** Tasmar; **Cz:** Tasmar; **Denn:** Tasmar; **Fin:** Tasmar; **Fr:** Tasmar; **Ger:** Tasmar; **Gr:** Tasmar; **Hong Kong:** Tasmar; **Hung:** Tasmar; **Irl:** Tasmar; **Ital:** Tasmar; **Mex:** Tasmar; **Neth:** Tasmar; **NZ:** Tasmar; **Philipp:** Tasmar; **Pol:** Tasmar; **Port:** Tasmar; **Rus:** Tasmar (Тасмап); **S.Afr:** Tasmar; **Spain:** Tasmar; **Swed:** Tasmar; **Switz:** Tasmar; **UK:** Tasmar; **USA:** Tasmar.

## Trihexyphenidyl Hydrochloride

(BANM, rINN)

Benzhexol Hydrochloride; Cloridrato de Trihexifenidila; Cycloclolum; Hidrocloruro de trihexifenidilo; Trihexisfenidilio hidrocloreid; Trihexisfenidilyl chlorowoderek; Trihexisfenidilylhydrochlorid; Trihexifenidilhydrochlorid; Trihexifenidylhydrochlorid; Trihexyphenidylhydrochlorid; Trihexyphenidyle, chlorhydrate de; Trihexyphenidyle, Chlorhydrate de; Trihexyphenidyl hydrochloridum; Trihexyphenidylum Chloratum. 1-Cyclohexyl-1-phenyl-3-piperidinopropan-1-ol hydrochloride.

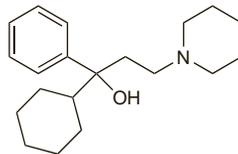
Тригексифенидила Гидрохлорид

C<sub>20</sub>H<sub>31</sub>NO.HCl = 337.9.

CAS — 144-11-6 (trihexyphenidyl); 52-49-3 (trihexyphenidyl hydrochloride).

ATC — N04AA01.

ATC Vet — QN04AA01.



(trihexyphenidyl)

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

**Pharmacopoeias.** In *Chin., Eur.* (see p.vii), *Int., Jpn.* and *US Ph. Eur.* **6.2** (Trihexyphenidyl Hydrochloride). A white or almost white, crystalline powder. Slightly soluble in water; sparingly soluble in alcohol and in dichloromethane. A 1% solution in water has a pH of 5.2 to 6.2.

**USP 31** (Trihexyphenidyl Hydrochloride). A white or slightly off-white, crystalline powder, having not more than a very faint odour. Slightly soluble in water; soluble in alcohol and in chloroform. Store in airtight containers.

### Adverse Effects, Treatment and Precautions

As for Atropine Sulfate, p.1219. In some patients, such as those with arteriosclerosis or a history of drug idiosyncrasy, trihexyphenidyl may produce mental disturbances, excitement, or nausea and vomiting; such patients should be allowed to develop a tolerance by starting with a small initial dose and gradually increasing it until an effective level is reached. If a severe reaction occurs, trihexyphenidyl should be stopped for a few days and resumed at a lower dose. Trihexyphenidyl may provoke or exacerbate tardive dyskinesia.

**Abuse.** Trihexyphenidyl hydrochloride has been abused for its euphoric effect<sup>1</sup> especially by psychiatric patients.<sup>2</sup> Its abuse potential in schizophrenic patients has been questioned<sup>3</sup> and its unpleasant antimuscarinic effects tend to limit its repeated use,<sup>4</sup> but a small survey among psychiatric patients found that trihexyphenidyl was reported to be the antimuscarinic most frequently abused;<sup>5</sup> procyclidine, benztropine, and orphenadrine (in decreasing order of frequency) were also misused. A later analysis of health insurance data from one region of France<sup>6</sup> examined prescriptions for trihexyphenidyl in 3028 subjects, most of whom were also receiving antipsychotics, and concluded that there was evidence of an abnormal pattern of use in about 2%.

Patients in this subgroup were mostly young, male, and also receiving benzodiazepines or high doses of buprenorphine.

- Crawshaw JA, Mullen PE. A study of benzhexol abuse. *Br J Psychiatry* 1984; **145**: 300–3.
- Pullen GP, et al. Anticholinergic drug abuse: a common problem? *BMJ* 1984; **289**: 612–13.
- Goff DC, et al. A placebo-controlled trial of trihexyphenidyl in unmedicated patients with schizophrenia. *Am J Psychiatry* 1994; **151**: 429–31.
- WHO. WHO expert committee on drug dependence: twenty-ninth report. *WHO Tech Rep Ser* 856 1995.
- Buhrich N, et al. Misuse of anticholinergic drugs by people with serious mental illness. *Psychiatr Serv* 2000; **51**: 928–9.
- Frauger E, et al. Détournement d'usage du trihexyphenidyle (Artane, Parkinane): tendances récentes. *Thérapie* 2003; **58**: 541–7.

**Effects on the heart.** Paradoxical sinus bradycardia developed in a schizophrenic patient after receiving trihexyphenidyl for extrapyramidal effects due to antipsychotic medication.<sup>1</sup> Normal sinus rhythm was restored after trihexyphenidyl was stopped. The patient had previously received trihexyphenidyl and suffered bradycardia which at the time was attributed to haloperidol.

- Blumensohn R, et al. Bradycardia due to trihexyphenidyl hydrochloride. *Drug Intell Clin Pharm* 1986; **20**: 786–7.

**Effects on mental function.** Trihexyphenidyl 2 mg by mouth significantly impaired memory function compared with placebo in a study in 13 elderly patients.<sup>1</sup> Impairment of memory has also been observed in patients with Parkinson's disease given antimuscarinics such as trihexyphenidyl.<sup>2</sup> However, impairment may be reversible on stopping the antimuscarinic (see Atropine, p.1220).

- Potamianos G, Kellett JM. Anti-cholinergic drugs and memory: the effects of benzhexol on memory in a group of geriatric patients. *Br J Psychiatry* 1982; **140**: 470–2.
- Sadeh M, et al. Effects of anticholinergic drugs on memory in Parkinson's disease. *Arch Neurol* 1982; **39**: 666–7.

**Overdosage.** A 34-year-old woman developed a toxic reaction with widely dilated pupils, dry skin, and visual hallucinations within 24 hours of taking about 300 mg of trihexyphenidyl hydrochloride with suicidal intent.<sup>1</sup> After 3 to 4 days the hallucinations were replaced by illusions; complete recovery occurred after a week, with no special treatment. Death associated with moderate blood concentrations of trihexyphenidyl (0.12 micrograms/mL) has been reported<sup>2</sup> in a schizophrenic patient recovering from a respiratory infection. It was thought possible that he had increased his dose to counteract developing tardive dyskinesia, and that the toxic effects had been exacerbated by respiratory inflammation; there was no evidence of suicidal intent.

- Ananth JV, et al. Toxic psychosis induced by benzhexol hydrochloride. *Can Med Assoc J* 1970; **103**: 771.
- Gall JAM, et al. Death due to benzhexol toxicity. *Forensic Sci Int* 1995; **71**: 9–14.

**Withdrawal.** A 61-year-old woman who had taken trihexyphenidyl 6 mg daily for a year for Parkinson's disease developed encephalopathy and miosis on two occasions when treatment was abruptly withdrawn.<sup>1</sup> Slowly tapered withdrawal avoided these effects.

- Johkura K, et al. Trihexyphenidyl withdrawal encephalopathy. *Ann Neurol* 1997; **41**: 133–4.

### Interactions

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

**Chlorpromazine.** For the effect of trihexyphenidyl on plasma concentrations of chlorpromazine, see Antiparkinsonian Drugs, p.974.

### Pharmacokinetics

Trihexyphenidyl hydrochloride is well absorbed from the gastrointestinal tract and has been stated to exert an effect within 1 hour of an oral dose.

**Half-life.** The reported half-life of trihexyphenidyl has varied according to the assay method used. Values reported when using radioreceptor and chromatographic techniques have ranged from about 1 to more than 24 hours<sup>1</sup> and from 10 to 29 hours,<sup>2</sup> respectively, but the sensitivity and specificity of these methods have been criticised.<sup>3</sup> With a more recently developed radioimmunoassay it was found that after oral doses there was an initial elimination phase with an estimated half-life of 5.33 hours followed by a terminal elimination phase with an estimated half-life of 32.7 hours.

- Burke RE, Fahn S. Pharmacokinetics of trihexyphenidyl after short-term and long-term administration to dystonic patients. *Ann Neurol* 1985; **18**: 35–40.
- Garbarg S, et al. Comparaison pharmacoclinique de deux formes galéniques de trihexyphenidyle. *Encephale* 1983; **IX**: 167–74.
- He H, et al. Development and application of a specific and sensitive radioimmunoassay for trihexyphenidyl to a pharmacokinetic study in humans. *J Pharm Sci* 1995; **84**: 561–7.

### Uses and Administration

Trihexyphenidyl hydrochloride is a tertiary amine antimuscarinic with actions similar to those of atropine

(p.1220). It also has a direct antispasmodic action on smooth muscle.

Trihexyphenidyl hydrochloride is given orally in the symptomatic treatment of parkinsonism (p.791), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value against tardive dyskinesias. It has been used in the treatment of dystonias, but see Extrapyramidal Disorders, below. Trihexyphenidyl hydrochloride is given in 3 or 4 divided doses daily before or with food.

In **Parkinson's disease** the usual initial dose of 1 mg daily is gradually increased at intervals of 3 to 5 days by increments of 2 mg to 6 to 10 mg daily according to response; for advanced cases, 12 to 15 mg daily or even more (up to 20 mg daily) may be needed. As a rule, postencephalitic patients tolerate and require the larger doses.

Usual doses for **drug-induced extrapyramidal symptoms** lie within the range of 5 to 15 mg daily, although as little as 1 mg daily may be sufficient in some cases.

Since the elderly and arteriosclerotic patients are more susceptible to the adverse effects of antimuscarinics a dose at the lower end of the range is usually recommended.

Antimuscarinic treatment of parkinsonism should never be terminated suddenly and it is usual when changing from one drug to another to withdraw one in small amounts while gradually increasing the dose of the other.

Trihexyphenidyl hydrochloride may be given with other drugs used for the relief of parkinsonism, such as

levodopa, but the dose of each drug may need to be reduced. Trihexyphenidyl hydrochloride 3 to 6 mg daily is usually adequate.

**Extrapyramidal disorders.** Antimuscarinics such as trihexyphenidyl are used in the management of dystonias (p.809) although only about half of all children and adolescents, and fewer adults (who tolerate antimuscarinics less well) show any response. Adverse effects may be limited by starting with a low dose: one suggested regimen<sup>1</sup> starts with trihexyphenidyl 1 mg daily and rises up to 12 mg daily over the next 4 to 6 weeks; some patients may require up to 60 to 100 mg daily. The *BNFC* suggests that children aged 1 month to 18 years may be given oral doses of 1 to 2 mg daily in 1 or 2 divided doses, adjusted according to response.

1. Jankovic J. Dystonia: medical therapy and botulinum toxin. *Adv Neurol* 2004; **94**: 275–86.

### Preparations

**BP 2008:** Trihexyphenidyl Tablets;

**USP 31:** Trihexyphenidyl Hydrochloride Elixir; Trihexyphenidyl Hydrochloride Extended-release Capsules; Trihexyphenidyl Hydrochloride Tablets.

**Proprietary Preparations** (details are given in Part 3)

**Arg.:** Artane; **Austral.:** Artane; **Austria:** Artane; **Belg.:** Artane; **Braz.:** Artane; Trihexidyl; **Canad.:** Apo-Trihex; **Chile:** Artane†; Tenvatil; Tonaril; **Denm.:** Peragit; **Fr.:** Artane; Parkinane; **Ger.:** Artane; Parkopan; **Gr.:** Artane; **Hong Kong:** Apo-Trihex; Artandy; Artane; **India:** Pacitane; Farnon; **Indon.:** Arkin; Artane; Hexymer; **Irl.:** Artane†; **Israel:** Artane†; Partane; Rodenal; **Ital.:** Artane; **Malaysia:** Aca; Apo-Trihex; Uphazhexol†; **Mex.:** Artane†; Hipokinon; Kexidil; **Neth.:** Artane; **Pol.:** Parkopan; **Port.:** Artane; **S.Afr.:** Artane; **Singapore:** Apo-Trihex; Beahexol; **Spain:** Artane; **Swed.:** Pargitan; **Thai.:** Aca; Acamed; Artane†; Pozhexol; Tridy; **UK:** Broflox; **USA:** Trihexy.

**Multi-ingredient:** **Ger.:** Spasman†; **India:** Sycot; Trinicalm Forte; Trinicalm Plus; **Spain:** Largatrex†.

### Tropatepine Hydrochloride (rINN)

Hidrocloruro de tropatepina; SD-1248-17; Tropatépine, Chlorhydrate de; Tropatepini Hydrochloridum. 3-(Dibenzo[*b,e*]thiepin-11(6*H*)-ylidene)tropane hydrochloride.

Тропатепина Гидрохлорид

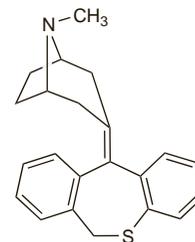
C<sub>23</sub>H<sub>23</sub>NS.HCl = 370.0.

CAS — 27574-24-9 (tropatepine); 27574-25-0

(tropatepine hydrochloride).

ATC — N04AA12.

ATC Vet — QN04AA12.



(tropatepine)

### Profile

Tropatepine hydrochloride is an antimuscarinic with actions and uses similar to those of trihexyphenidyl (p.820). It is used in the management of parkinsonism (p.791), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value in tardive dyskinesias. Tropatepine hydrochloride is given orally in usual doses of 10 to 30 mg daily; it is also given intramuscularly or by slow intravenous injection in doses of 10 to 20 mg daily.

### Preparations

**Proprietary Preparations** (details are given in Part 3)

**Fr.:** Lepticur.