5. Ward CD. Does selegiline delay progression of Parkinson's disease? A critical re-evaluation of the DATATOP study. *J Neurol Neurosurg Psychiatry* 1994; **57:** 217–20.
6. Brannan T, Yahr MD. Comparative study of selegiline plus -dopa–carbidopa versus -dopa–carbidopa alone in the treatment of Parkinson's disease. *Ann Neurol* 1995; **37:** 95–8.
7. The Parkinson Study Group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med* 1993; **328:** 176–83.
8. Parkinson Study Group. Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP subjects not requiring levodopa. *Ann Neurol* 1996; **39:** 29–36.
9. Parkinson Study Group. Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP patients requiring levodopa. *Ann Neurol* 1996; **39:** 37–45.
10. Olanow CW, *et al.* The effect of deprenyl and levodopa on the progression of Parkinson's disease. *Ann Neurol* 1996; **38:** 771–7.
11. Parkinson's Disease Research Group of the United Kingdom. Comparison of therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease. *BMJ* 1995; **311:** 1602–7.
12. Myllylä VV, *et al.* Early selegiline therapy reduces levodopa dose requirement in Parkinson's disease. *Acta Neurol Scand* 1995; **91:** 177–82.
13. Larsen JP, Boas J. Norwegian-Danish Study Group. The effects of early selegiline therapy on long-term treatment and parkinsonian disability: an interim analysis of a Norwegian-Danish 5-year study. *Mov Disord* 1997; **12:** 175–82.
14. Pålhagen S, *et al.* Selegiline slows the progression of the symptoms of Parkinson disease. *Neurology* 2006; **66:** 1200–6.
15. Parkinson's Disease Research Group in the United Kingdom. Comparisons of the therapeutic effects of levodopa, levodopa and selegiline, and bromocriptine in patients with early, mild Parkinson's disease: three year interim report. *BMJ* 1993; **307:** 467–72.
16. Olanow CW, *et al.* Patients taking selegiline may have received more levodopa than necessary. *BMJ* 1996; **312:** 702–3.
17. Ahlskog JE. Treatment of early Parkinson's disease: are complicated strategies justified? *Mayo Clin Proc* 1996; **71:** 659–70.
18. Mizuno Y, Kondo T. Mortality associated with selegiline in Parkinson's disease: what do the available data mean? *Drug Safety* 1997; **16:** 289–94.
19. Ben-Shlomo Y, *et al.* Investigation by Parkinson's Disease Research Group of United Kingdom into excess mortality seen with combined levodopa and selegiline treatment in patients with early, mild Parkinson's disease: further results of randomised trial and confidential inquiry. *BMJ* 1998; **316:** 1191–6.
20. Abrams KR. Monitoring randomised controlled trials. *BMJ* 1998; **316:** 1183–4.
21. Breteler MMB. Selegiline, or the problem of early termination of clinical trials. *BMJ* 1998; **316:** 1182–3.
22. Thorogood M, *et al.* Mortality in people taking selegiline: observational study. *BMJ* 1998; **317:** 252–4.
23. Macleod AD, *et al.* Monoamine oxidase B inhibitors for early Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 16/02/06).
24. Olanow CW, *et al.* Effect of selegiline on mortality in patients with Parkinson's disease: a meta-analysis. *Neurology* 1998; **51:** 825–30.
25. Ives NJ, *et al.* Monoamine oxidase type B inhibitors in early Parkinson's disease: meta-analysis of 17 randomised trials involving 3525 patients. *BMJ* 2004; **329:** 593–6.
26. The Parkinson Study Group. Mortality in DATATOP: A multicenter trial in early Parkinson's disease. *Ann Neurol* 1998; **43:** 318–25.

Smoking cessation. Selegiline has been investigated as an aid to smoking cessation (p.2354).

References.

1. George TP, *et al.* A preliminary placebo-controlled trial of selegiline hydrochloride for smoking cessation. *Biol Psychiatry* 2003; **53:** 136–43.
2. Biberman R, *et al.* A randomized controlled trial of oral selegiline plus nicotine skin patch compared with placebo plus nicotine skin patch for smoking cessation. *Addiction* 2003; **98:** 1403–7.

Preparations

BP 2008: Selegiline Oral Solution; Selegiline Tablets;
USP 31: Selegiline Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

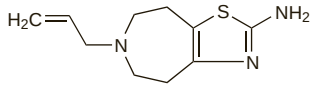
Arg.: Brintenal; Jumex; Kinabide†; Zelapar; ***Austral.:*** Eldepryl; Selgene; ***Austria:*** Amboneural; Cognitiv; Jumex; Regepar; Xilopar; ***Belg.:*** Eldepryl; ***Braz.:*** Deprilan; Elepril; Jumexil; Niar; Parkexin; ***Canad.:*** Eldepryl†; ***Chile:*** Selgina; ***Cz.:*** Apo-Seleg; Cognitiv; Jumex; Niar; Segalin†; Sepatrem†; ***Denm.:*** Eldepryl; ***Fin.:*** Eldepryl; ***Fr.:*** Deprenyl; Otrasel; ***Ger.:*** Amindan†; Antiparkin; Jutagilin; MAOtil†; Movergan; Selegam†; Selemerck; Selepark; Selgimed; Xilopar; ***Gr.:*** Cosmopril; Ermolax; Feliselin; Krautin; Legil; Procythol; Resostyl; ***Hong Kong:*** Julab; Jumex; Sefmex; Selegos; ***Hung.:*** Cognitiv; Jumex; Primulex†; ***India:*** Selerin; Selgin; ***Indon.:*** Jumex; ***Irl.:*** Eldepryl; ***Israel:*** Jumex; ***Ital.:*** Egibren; Jumex; Selecom; Seledat; Xilopar; ***Jpn:*** FP Tab; ***Malaysia:*** Ginex†; Jumex; Sefmex; Selegos†; ***Mex.:*** Niar; ***Neth.:*** Eldepryl; ***Norw.:*** Eldepryl; ***NZ:*** Eldepryl; Selgene†; ***Philipp.:*** Jumex; ***Pol.:*** Apo-Selin; Jumex; Parkinil†; Segan; Selerin; Selgin; Selgres; ***Port.:*** Jumex; Niponeurin; Xilopar; ***Rus.:*** Cognitiv (Когнитив); Segan (Сеган); Selegos (Селегос); ***S.Afr.:*** Eldepryl; Parkilyne; ***Singapore:*** Jumex; Selegos; ***Spain:*** Plurimen; ***Swed.:*** Eldepryl; ***Switz.:*** Jumexal; Selecim†; ***Thai.:*** Elegelin†; Julab; Jumex; Kinline†; Sefmex; Seline†; ***Turk.:*** Moverdin; Seldepar; ***UK:*** Eldepryl; Zelapar; ***USA:*** Atapryl; Carbex; Eldepryl; Emsam; Zelapar; ***Venez.:*** Jumex.

Talipexole Hydrochloride *(rINNM)*

Alefexole Hydrochloride; B-HT-920; Hidrocloruro de talipexol; Talipexole, Chlorhydrate de; Talipexoli Hydrochloridum. 6-Allyl-2-amino-5,6,7,8-tetrahydro-4*H*-thiazolo[4,5-*d*]azepine dihydrochloride.

Талипексола Гидрохлорид

$C_{10}H_{15}N_3S,2HCl$ = 282.2.
CAS — 101626-70-4 (talipexole); 36085-73-1 (talipexole hydrochloride).



(talipexole)

Profile

Talipexole hydrochloride is a dopamine D_2-agonist that is used in the management of parkinsonism (p.791) in usual oral doses of 1.2 to 3.6 mg daily, in divided doses. It has also been investigated in the treatment of schizophrenia.

Preparations

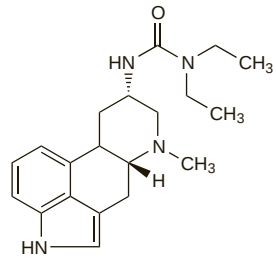
Proprietary Preparations (details are given in Part 3)
Jpn: Domin.

Terguride *(rINN)*

Tergurida; Terguridum. 1,1-Diethyl-3-(6-methylergolin-8α-yl) urea.

Тергурид

$C_{20}H_{28}N_4O$ = 340.5.
CAS — 37686-84-3.



Profile

Terguride, an ergot derivative, is a partial dopamine agonist with general properties similar to those of bromocriptine (p.798). It is used in the treatment of disorders related to hyperprolactinaemia (p.2079) in a usual oral dose of 500 micrograms twice daily. It is also being investigated in the management of parkinsonism.

◊ References.

1. Krause W, *et al.* Pharmacokinetics and endocrine effects of terguride in healthy subjects. *Eur J Clin Pharmacol* 1990; **38:** 609–15.
2. Baronti F, *et al.* Partial dopamine agonist therapy of levodopa-induced dyskinesias. *Neurology* 1992; **42:** 1241–3.

Preparations

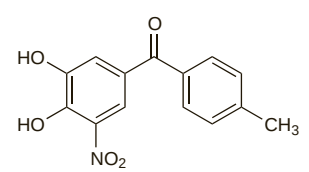
Proprietary Preparations (details are given in Part 3)
Cz.: Mysalfon†; ***Jpn:*** Teluron.

Tolcapone *(BAN, USAN, rINN)*

Ro-40-7592; Tolcapona; Tolcaponum; Tolkapon; Tolkaponi. 3,4-Dihydroxy-4′-methyl-5-nitrobenzophenone; 3,4-Dihydroxy-5-nitrophenyl(4-methylphenyl)methanone.

Толкапон

$C_{14}H_{11}NO_5$ = 273.2.
CAS — 134308-13-7.
ATC — N04BX01.
ATC Vet — QN04BX01.



Pharmacopoeias. In *US.*

USP 31 (Tolcapone). A yellow, fine powder or fine powder with lumps. Insoluble in water and in *n*-hexane; Freely soluble in acetone and in tetrahydrofuran; sparingly soluble in chloroform and in dichloromethane; soluble in methyl alcohol and in ethyl acetate. Store in airtight containers at a temperature between 20° and 25°. Protect from light.

Adverse Effects

The most common adverse effects associated with tolcapone are diarrhoea, nausea, vomiting, constipation, abdominal pain, dry mouth, anorexia, dyskinesia, dystonia, dizziness, orthostatic hypotension, hallucinations, confusion, excessive dreaming, somnolence, headache, increased sweating, and sleep disorders. Diarrhoea may be severe enough for treatment to be stopped. Increases in liver enzyme values have occurred and hepatitis and hepatic failure, sometimes fatal, have been reported. Isolated cases of neuroleptic malignant syndrome have also been reported following dose reduction or stopping tolcapone; rhabdomyolysis may develop as a complication of the syndrome. Tolcapone and its metabolites can produce a yellow intensification in the colour of urine.

Effects on the liver. The UK CSM had noted[1] that, after a report[2] in September 1998 of fatal acute hepatic failure associated with tolcapone, the European Committee for Proprietary Medicinal Products (CPMP) had reviewed all reports of hepatic injury with tolcapone. There had been 10 reports of serious hepatic adverse reactions since tolcapone was marketed in October 1997, which included 7 reports of hepatitis, 3 of which had a fatal outcome. Serious hepatic reactions occurred unpredictably and their development was not always predicted by liver function monitoring. Consequently, in the EU, the marketing authorisation for tolcapone was suspended in November 1998. This suspension was lifted in April 2004 by the CPMP after further review.

In some countries such as the USA, tolcapone has always remained available albeit with restricted indications and strict monitoring requirements (see Precautions, below). Up to 2003, there had been no further reports of fatal hepatic failure following the introduction of these measures although the number of patients eligible to receive the drug has been reduced.[3]

1. CSM/MCA. Withdrawal of tolcapone (Tasmar). *Current Problems* 1999; **25:** 2. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023233&RevisionSelectionMethod=LatestReleased (accessed 11/08/08)
2. Assal F, *et al.* Tolcapone and fulminant hepatitis. *Lancet* 1998; **352:** 958.
3. Borges N. Tolcapone-related liver dysfunction: implications for use in Parkinson's disease therapy. *Drug Safety* 2003; **26:** 743–7.

Effects on the skin. For reference to the development of vitiligo in a patient following addition of tolcapone to levodopa/carbidopa treatment, see under Levodopa, p.806.

Precautions

Tolcapone should not be given to patients with hepatic impairment or raised liver enzyme values. Liver enzymes should be monitored:

- when starting treatment with tolcapone or on increasing the dose to 200 mg three times daily
- every 2 weeks during the first year of therapy
- every 4 weeks for a further 6 months
- every 8 weeks thereafter

Tolcapone should be stopped if liver enzyme levels exceed the upper limit of normal or if signs or symptoms suggestive of the onset of hepatic failure occur. Patients who have developed evidence of hepatic injury while receiving tolcapone should not be given the drug again.

Tolcapone should be used with caution in patients with severe renal impairment.

It is contra-indicated in patients with severe dyskinesia or with a history of neuroleptic malignant syndrome (NMS). It is also contra-indicated in patients with a history of nontraumatic rhabdomyolysis or symptoms of hyperpyrexia and confusion possibly related to NMS. Patients with phaeochromocytoma should not be given tolcapone.

Use with levodopa may cause dizziness and orthostatic hypotension; if affected patients should not drive or operate machinery. Excessive daytime sleepiness and sudden onset of sleep may also occur with combination use (see Effects on Mental Function, under Adverse Effects of Levodopa, p.805) and again, caution is advised when driving or operating machinery; patients who suffer such effects should not drive or operate machinery until the effects have stopped recurring.

Abrupt withdrawal or dose reduction of tolcapone should be monitored carefully because of the risk of developing symptoms resembling NMS.

The elderly. Confusion occurred in 3 elderly patients with severe Parkinson's disease after the addition of tolcapone to their antiparkinsonian therapy.[1] It was suggested that a starting dose of tolcapone 100 mg daily might be more suitable in frail patients with severe disease. It was noted[2] that a reduction in levodopa dosage is generally recommended when tolcapone is given to patients such as these, who were receiving 500 to 600 mg of levodopa daily.

1. Henry C, Wilson JA. Catechol-O-methyltransferase inhibitors in Parkinson's disease. *Lancet* 1998; **351:** 1965–6.
2. Harper J, Vieira B. Catechol-O-methyltransferase inhibitors in Parkinson's disease. *Lancet* 1998; **352:** 578.

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.[1] Such patients may be predisposed to COMT-inhibitor induced hepatotoxicity.

1. 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.

1. Dingemanse 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.
2. Jorga KM, *et al.* Effect of liver impairment on the pharmacokinetics of tolcapone and its metabolites. *Clin Pharmacol Ther* 1998; **63:** 646–54.
3. Jorga K, *et al.* Metabolism and excretion of tolcapone, a novel inhibitor of catechol-O-methyltransferase. *Br J Clin Pharmacol* 1999; **48:** 513–20.
4. 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.[1] 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).[1] 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.[2,3] Benefit has also been reported[4] when added to levodopa therapy in patients with stable Parkinson's disease. However, a systematic review[5] 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).

1. Nutt JG. Catechol-O-methyltransferase inhibitors for treatment of Parkinson's disease. *Lancet* 1998; **351:** 1221–2.
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, randomized, placebo-controlled trial. *Neurology* 1997; **48:** 81–7.
3. 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.
4. 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.
5. 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; ***Denm.:*** 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 (Тасмар); ***S.Afr.:*** Tasmar; ***Spain:*** Tasmar; ***Swed.:*** Tasmar; ***Switz.:*** Tasmar; ***UK:*** Tasmar; ***USA:*** Tasmar.

Trihexyphenidyl Hydrochloride

(BANM, rINNM)

Benzhexol Hydrochloride; Cloridrato de Triexilfenidila; Cyclodolum; Hidrocloruro de trihexifenidilo; Triheksifenidilio hidrochloridas; Triheksyfenidylu chlorowodorek; Triheksyfenidyylihydrokloridi; Trihexifenidilhidroklorid; Trihexyfenidyl-hydrochlorid; Trihexyfenidylhydroklorid; Trihexyphénidyle, chlorhydrate de; Trihexyphénidyle, Chlorhydrate de; Trihexyphenidyli hydrochloridum; Trihexyphenidylium Chloratum. 1-Cyclohexyl-1-phenyl-3-piperidinopropan-1-ol hydrochloride.

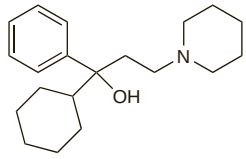
Тригексифенидила Гидрохлорид

$C_{20}H_{31}NO,HCl = 337.9$.

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[1] especially by psychiatric patients.[2] Its abuse potential in schizophrenic patients has been questioned[3] and its unpleasant antimuscarinic effects tend to limit its repeated use,[4] but a small survey among psychiatric patients found that trihexyphenidyl was reported to be the antimuscarinic most frequently abused;[5] procyclidine, benzatropine, and orphenadrine (in decreasing order of frequency) were also misused. A later analysis of health insurance data from one region of France[6] 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.

1. Crawshaw JA, Mullen PE. A study of benzhexol abuse. *Br J Psychiatry* 1984; **145:** 300–3.
2. Pullen GP, *et al.* Anticholinergic drug abuse: a common problem? *BMJ* 1984; **289:** 612–13.
3. Goff DC, *et al.* A placebo-controlled trial of trihexyphenidyl in unmedicated patients with schizophrenia. *Am J Psychiatry* 1994; **151:** 429–31.
4. WHO. WHO expert committee on drug dependence: twenty-ninth report. *WHO Tech Rep Ser 856* 1995.
5. Buhrich N, *et al.* Misuse of anticholinergic drugs by people with serious mental illness. *Psychiatr Serv* 2000; **51:** 928–9.
6. Frauger E, *et al.* Détournement d'usage du trihexyphénidyle (Artane , Parkinane): tendances récentes. *Therapie* 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.[1] 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.

1. 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.[1] Impairment of memory has also been observed in patients with Parkinson's disease given antimuscarinics such as trihexyphenidyl.[2] However, impairment may be reversible on stopping the antimuscarinic (see Atropine, p.1220).

1. 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.
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.[1] 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[2] 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.

1. Ananth JV, *et al.* Toxic psychosis induced by benzhexol hydrochloride. *Can Med Assoc J* 1970; **103:** 771.
2. 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.[1] Slowly tapered withdrawal avoided these effects.

1. 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[1] and from 10 to 29 hours,[2] respectively, but the sensitivity and specificity of these methods have been criticised.[3] With a more recently developed radio immunoassay 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.

1. Burke RE, Fahn S. Pharmacokinetics of trihexyphenidyl after short-term and long-term administration to dystonic patients. *Ann Neurol* 1985; **18:** 35–40.
2. Garbarg S, *et al.* Comparaison pharmacoclinique de deux formes galéniques de trihexyphénidyle. *Encephale* 1983; **IX:** 167–74.
3. 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