

sulfoxide appeared to be compensatorily increased in slow hydroxylators.

- Axelsson R. On the serum concentrations and antipsychotic effects of thioridazine, thioridazine side-chain sulfoxide and thioridazine side-chain sulfone, in chronic psychotic patients. *Curr Ther Res* 1977; **21**: 587-605.
- von Bahr C, et al. Plasma levels of thioridazine and metabolites are influenced by the debrisoquin hydroxylation phenotype. *Clin Pharmacol Ther* 1991; **49**: 234-40.

Uses and Administration

Thioridazine is a phenothiazine with general properties similar to those of chlorpromazine (p.975). It has a piperidine side-chain and, unlike chlorpromazine, has little antiemetic activity.

The use of thioridazine has been restricted to the treatment of schizophrenia (p.955) in patients who fail to show an adequate response to treatment with other antipsychotics. Its use in other psychiatric disorders was abandoned after it was felt that there was an unacceptable balance of risks and benefits as a result of its cardiotoxic potential; it has been withdrawn in some countries, including the UK.

For all patients starting thioridazine it is recommended that a baseline ECG and electrolyte screening are performed. An ECG should also be repeated before each dose increase, 1 week after the maximum therapeutic dose has been reached, and at 6-monthly intervals in those who continue treatment. Serum electrolyte concentrations should also be monitored periodically during treatment and any imbalance corrected.

Thioridazine is given orally as the hydrochloride or the base, and doses may be expressed in terms of either. In some countries, doses of oral liquid preparations have been given in terms of the base, whereas those of the tablets have been given as the hydrochloride. In the USA, all doses are given in terms of the hydrochloride. Thioridazine 22.8 mg is equivalent to about 25 mg of thioridazine hydrochloride.

In the treatment of schizophrenia thioridazine hydrochloride should be started at the usual dose of 50 to 100 mg three times daily and slowly titrated upwards to a maximum of 800 mg daily if necessary; doses should be reduced once effective control is achieved. The daily dosage range is 200 to 800 mg, which may be given in 2 to 4 divided doses. It has been recommended that increases in doses should be no more than 100 mg weekly.

Thioridazine should be given in lower initial doses to patients with a low body-mass or those with hepatic or renal impairment; dosage increases should also be more gradual.

In those patients who require withdrawal of thioridazine, the dose should be gradually reduced over 1 to 2 weeks to avoid symptoms such as gastrointestinal disorders, dizziness, anxiety, and insomnia that are sometimes seen after abruptly stopping high-dose or long-term treatment.

References

- Fenton M, et al. Thioridazine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 25/03/08).

Preparations

USP 31: Thioridazine Hydrochloride Oral Solution; Thioridazine Hydrochloride Tablets; Thioridazine Oral Suspension.

Proprietary Preparations (details are given in Part 3)

Arg.: Mellerit; **Austral.:** Aldazine; Mellerit; **Austria:** Mellerit; **Belg.:** Mellerit; **Braz.:** Mellerit; **Chile:** Mellerit; **Denm.:** Mellerit; **Fin.:** Mellerit; **Fr.:** Mellerit; **Ger.:** Mellerit; **Gr.:** Mellerit; **Hong Kong:** Mellerit; **Hung.:** Mellerit; **India:** Thion; **Indon.:** Mellerit; **Ir.:** Mellerit; **Malaysia:** Mellerit; **Mex.:** Dazithin; Mellerit; **Neth.:** Mellerit; **Norw.:** Mellerit; **NZ:** Aldazine; Mellerit; **Port.:** Mellerit; **Rus.:** Sonarax (Сонарак); Thiodazine (Тюдазин); Thion (Тюрион); Tison (Тисон); **S.Afr.:** Mellerit; **Spain:** Mellerit; **Swed.:** Mallorin; **Switz.:** Mellerit; **Thai.:** Calmani; Dazine; Risdazine; Thiomed; Thosia; **Turk.:** Mellerit; **UK:** Mellerit; **USA:** Mellerit; **Venez.:** Mellerit.

Tiapride Hydrochloride (BANM, rINNM)

FLO-1347; Hidrocloruro de tiaprida; Tiapride, chlorhydrate de; Tiaprid-hydrochlorid; Tiaprid-hydrochlorid; Tiapridhydrochlorid; Tiaprid hydrochloridum; Tiapridhydrochloridi; Tiaprido hydrochloridas. *N*-(2-Diethylaminoethyl)-2-methoxy-5-methylsulphonylbenzamide hydrochloride.

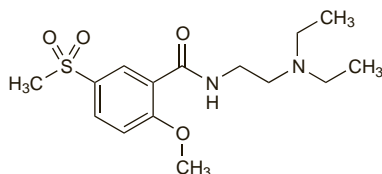
Тиаприда Гидрохлорид

$C_{15}H_{24}N_2O_4S \cdot HCl = 364.9$.

CAS — 51012-32-9 (tiapride); 51012-33-0 (tiapride hydrochloride).

ATC — N05AL03.

ATC Vet — QN05AL03.



(tiapride)

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

Ph. Eur. 6.2 (Tiapride Hydrochloride). A white or almost white crystalline powder. Very soluble in water; slightly soluble in dehydrated alcohol; soluble in methyl alcohol. A 5% solution in water has a pH of 4.0 to 6.0.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969.

Effects on the cardiovascular system. Torsade de pointes developed after a single dose of tiapride in an elderly patient with cardiac disease, a known risk factor for such arrhythmias.¹

- Iglesias E, et al. Tiapride-induced torsade de pointes. *Am J Med* 2000; **109**: 509.

Interactions

As for Chlorpromazine, p.973.

Pharmacokinetics

Tiapride is rapidly absorbed after oral doses and peak plasma concentrations occur after 1 to 2 hours. It is excreted largely unchanged in the urine. The plasma half-life is reported to range from 3 to 4 hours. It is thought to be distributed into breast milk on the basis of animal studies.

◇ The steady-state pharmacokinetics of tiapride have been studied in 5 elderly patients with tardive dyskinesia, and in 2 patients with Huntington's chorea.¹ All patients received tiapride 100 mg three times daily by mouth for 7 days. The mean peak plasma concentration of tiapride was 1.47 micrograms/mL, achieved a mean of 1.4 hours after dosing, and the mean elimination half-life was 3.8 hours. These values did not differ significantly from those previously reported in younger healthy subjects, although renal clearance was slightly lower in these patients. About half of the dose of tiapride was excreted unchanged by the kidneys; a metabolite, probably *N*-monodesethyltiapride was detected in the urine but its identity was not confirmed.

- Roos RAC, et al. Pharmacokinetics of tiapride in patients with tardive dyskinesia and Huntington's disease. *Eur J Clin Pharmacol* 1986; **31**: 191-4.

Uses and Administration

Tiapride is a substituted benzamide with general properties similar to those of sulpiride (p.1028).

It is usually given as the hydrochloride in the management of behavioural disorders and to treat dyskinesias. Doses are expressed in terms of the equivalent amount of base; tiapride hydrochloride 222.2 mg is equivalent to about 200 mg of tiapride. Oral doses of 200 to 400 mg daily are usually given, although higher daily doses have been used, particularly in the management of dyskinesias. Tiapride hydrochloride has also been given by intramuscular or intravenous injection.

Disturbed behaviour. For a discussion of the management of disturbed behaviour including limitations on the use of antipsychotics, see p.954.

References

- Gutzmann H, et al. Measuring the efficacy of psychopharmacological treatment of psychomotoric restlessness in dementia: clinical evaluation of tiapride. *Pharmacopsychiatry* 1997; **30**: 6-11.
- Allain H, et al. Double blind study of tiapride versus haloperidol and placebo in agitation and aggressiveness in elderly patients with cognitive impairment. *Psychopharmacology (Berl)* 2000; **148**: 361-6.

Extrapyramidal disorders. Tiapride has been tried in the treatment of antipsychotic-induced tardive dyskinesia (p.971), but, as with all antipsychotics, improvement may only be short-term.

Tiapride has also been tried in the treatment of Tourette's syndrome (p.954).

For reference to the use of tiapride in suppressing the adverse effects of levodopa on respiration, see p.806.

CHOREA. Antipsychotics have some action against choreiform movements as well as being of use to control the behavioural disturbances of Huntington's chorea, and tiapride has been quite widely used for this purpose. For a discussion of the management of various choreas, see p.953.

References

- Roos RAC, et al. Tiapride in the treatment of Huntington's chorea. *Acta Neurol Scand* 1982; **65**: 45-50.
- Deroover J, et al. Tiapride versus placebo: a double-blind comparative study in the management of Huntington's chorea. *Curr Med Res Opin* 1984; **9**: 329-38.

Substance dependence. An early review¹ concluded that the role of tiapride in acute alcohol withdrawal (p.1626) was likely to be limited as patients at risk of severe reactions would still require adjunctive therapy for the control of hallucinations and seizures. Following detoxification, tiapride appeared to help, to some degree, to alleviate distress, improve abstinence and drinking behaviour, and facilitate reintegration within society.² Interest in its use with carbamazepine continues.^{3,5}

- Peters DH, Faulds D. Tiapride: a review of its pharmacology and therapeutic potential in the management of alcohol dependence syndrome. *Drugs* 1994; **47**: 1010-32.
- Shaw GK, et al. Tiapride in the prevention of relapse in recently detoxified alcoholics. *Br J Psychiatry* 1994; **165**: 515-23.

- Franz M, et al. Treatment of alcohol withdrawal: tiapride and carbamazepine versus clomethiazole: a pilot study. *Eur Arch Psychiatry Clin Neurosci* 2001; **251**: 185-92.

- Lucht M, et al. Alcohol withdrawal treatment in intoxicated vs non-intoxicated patients: a controlled open-label study with tiapride/carbamazepine, clomethiazole and diazepam. *Alcohol Alcohol* 2003; **38**: 168-75.

- Soyka M, et al. Efficacy and safety of outpatient alcohol detoxification with a combination of tiapride/carbamazepine: additional evidence. *Pharmacopsychiatry* 2006; **39**: 30-4.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Etilis; **Austria:** Delpat; **Belg.:** Tiapridal; **Braz.:** Tiapridal; **Chile:** Serepid; **Cz.:** Tiapra; Tiapridal; **Fr.:** Clemental; Equilium; Tiapridal; **Ger.:** Tiapridex; **Gr.:** Tiapridal; **Hong Kong:** Tiapridal; **Hung.:** Tiapridal; **Israel:** Doparid; **Ital.:** Itaprid; Sereprile; **Jpn.:** Gramall; **Neth.:** Betaprid; Elbaprid; Tiacob; Tiajac; Tiapridal; Tiastad; Tiazet; **Pol.:** Tiapridal; **Port.:** Normagit; Tiapridal; **Rus.:** Tiapridal (Тиаприда); **Spain:** Tiaprizal; **Switz.:** Tiapridal.

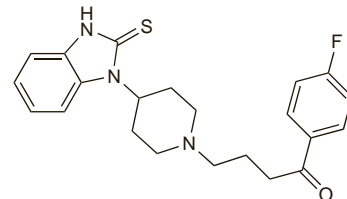
Timiperone (rINN)

DD-3480; Timiperona; Timipérone; Timiperonom. 4'-Fluoro-4-[4-(2-thioxo-1-benzimidazolyl)piperidino]butyrophenone.

Тимиперон

$C_{22}H_{24}FN_3OS = 397.5$.

CAS — 57648-21-2.



Profile

Timiperone is a butyrophenone with general properties similar to those of haloperidol (p.1000). It has been used by mouth in the treatment of schizophrenia. Timiperone has also been given by injection.

Tiotixene (BAN, rINN)

NSC-108165; P-4657B; Thiothixene (USAN); Tiotikseeni; Tiotixen; Tiotixène; Tiotixeno; Tiotixenum. (Z)-*NN*-Dimethyl-9-[3-(4-methylpiperazin-1-yl)propylidene]thioxanthene-2-sulphonamide.

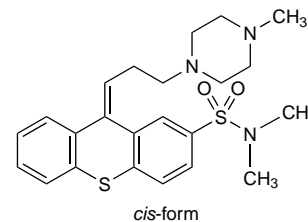
ТЮТИКСЕН

$C_{23}H_{29}N_3O_2S_2 = 443.6$.

CAS — 5591-45-7; 3313-26-6 (tiotixene Z-isomer).

ATC — N05AF04.

ATC Vet — QN05AF04.



cis-form

Pharmacopoeias. In US.

USP 31 (Thiothixene). White to tan, practically odourless, crystals. Practically insoluble in water; soluble 1 in 110 of dehydrated alcohol, 1 in 2 of chloroform, and 1 in 120 of ether; slightly soluble in acetone and in methyl alcohol. Store in airtight containers. Protect from light.

Tiotixene Hydrochloride (BANM, rINNM)

CP-12252-1; Hidrocloruro de tiotixeno; Thiothixene Hydrochloride (USAN); Tiotixène, Chlorhydrate de; Tiotixeni Hydrochloridum.

ТЮТИКСЕНА Гидрохлорид

$C_{23}H_{29}N_3O_2S_2 \cdot 2HCl \cdot 2H_2O = 552.6$.

CAS — 58513-59-0 (anhydrous tiotixene hydrochloride); 49746-04-5 (anhydrous tiotixene hydrochloride, Z-isomer); 22189-31-7 (tiotixene hydrochloride dihydrate); 49746-09-0 (tiotixene hydrochloride dihydrate, Z-isomer).

ATC — N05AF04.

ATC Vet — QN05AF04.

Pharmacopoeias. In *US*, which permits both the dihydrate and the anhydrous form.

USP 31 (Thiothixene Hydrochloride). It is anhydrous ($C_{23}H_{29}N_3O_2S_2 \cdot 2HCl = 516.5$) or contains two molecules of water of hydration. A white or practically white crystalline powder