

- Colivicchi F, et al. Ticlopidine-induced chronic cholestatic hepatitis: a case report. *Curr Ther Res* 1994; **55**: 929–31.
- Mambelli E, et al. Severe ticlopidine-induced cholestatic syndrome. *Blood Purif* 2007; **25**: 441–5.
- Ruiz-Valverde P, et al. Ticlopidine-induced granulomatous hepatitis. *Ann Pharmacother* 1995; **29**: 633–4.
- Zeolla MM, Carson JJ. Successful use of clopidogrel for cerebrovascular accident in a patient with suspected ticlopidine-induced hepatotoxicity. *Ann Pharmacother* 1999; **33**: 939–41.
- Willens HJ. Clopidogrel-induced mixed hepatocellular and cholestatic liver injury. *Am J Ther* 2000; **7**: 317–18.

Effects on the lungs. Bronchiolitis obliterans-organising pneumonia developed in a 76-year-old woman receiving ticlopidine and prednisone for temporal arteritis.¹ The condition resolved over several months when ticlopidine was withdrawn.

- Alonso-Martinez JL, et al. Bronchiolitis obliterans-organising pneumonia caused by ticlopidine. *Ann Intern Med* 1998; **129**: 71–2.

Interactions

Ticlopidine should be used with caution in patients receiving other drugs, such as anticoagulants and antiplatelets, that increase the risk of bleeding. Ticlopidine is an inhibitor of cytochrome P450, including the isoenzymes CYP2C19, CYP2D6, and CYP2B6, and may inhibit the metabolism of other drugs that are metabolised by this route. The clearance of ticlopidine may be reduced by cimetidine. Corticosteroids may antagonise the effect of ticlopidine on bleeding time.

Anticoagulants. Use of ticlopidine with anticoagulants may increase the risk of bleeding. However, ticlopidine has been reported to antagonise the effect of *acenocoumarol* (see Antiplatelets under Interactions of Warfarin, p. 1429).

Antiepileptics. For a report of acute *phenytoin* toxicity in a well-stabilised patient following addition of ticlopidine, see p.500.

Xanthines. For reference to the effect of ticlopidine on *theophylline* half-life, see p.1145.

Pharmacokinetics

Ticlopidine is rapidly and almost completely absorbed from the gastrointestinal tract. It is about 98% bound to plasma proteins. The terminal half-life during chronic dosing is reported to be about 30 to 50 hours. Ticlopidine is extensively metabolised in the liver. About 60% of a dose is excreted in the urine as metabolites and 25% in the faeces.

References

- Desager J-P. Clinical pharmacokinetics of ticlopidine. *Clin Pharmacokinet* 1994; **26**: 347–55.
- Buur T, et al. Pharmacokinetics and effect of ticlopidine on platelet aggregation in subjects with normal and impaired renal function. *J Clin Pharmacol* 1997; **37**: 108–15.

Uses and Administration

Ticlopidine hydrochloride is a thienopyridine antiplatelet drug used in thromboembolic disorders (p.1187). It appears to act by inhibiting adenosine diphosphate-mediated platelet aggregation. It may be given prophylactically as an alternative to aspirin in patients at risk of thrombotic stroke (p.1185) and in the management of intermittent claudication (see Peripheral Vascular Disease, p.1178) and ischaemic heart disease. It is also licensed as an adjunct to aspirin for the prevention of subacute stent occlusion after intracoronary stenting (but see Reperfusion and Revascularisation Procedures, below). Ticlopidine may also be used to prevent occlusion and platelet loss during extracorporeal circulatory procedures.

In the prevention of thrombotic stroke, and in intermittent claudication, ticlopidine hydrochloride is given orally in a dose of 250 mg twice daily, with meals. For the prevention of subacute stent occlusion after intracoronary stenting ticlopidine hydrochloride is given in a dose of 250 mg twice daily for 4 weeks, starting at the time of stent placement.

Regular haematological monitoring is required during ticlopidine therapy (see Adverse Effects and Precautions, above).

References

- McTavish D, et al. Ticlopidine: an updated review of its pharmacology and therapeutic use in platelet-dependent disorders. *Drugs* 1990; **40**: 238–59.

- Flores-Runk P, Raasch RH. Ticlopidine and antiplatelet therapy. *Ann Pharmacother* 1993; **27**: 1090–8.
- Sharis PJ, et al. The antiplatelet effects of ticlopidine and clopidogrel. *Ann Intern Med* 1998; **129**: 394–405.

Reperfusion and revascularisation procedures. Coronary stents are widely used as an adjunct to angioplasty to prevent acute vessel closure and to reduce restenosis (see Reperfusion and Revascularisation Procedures, p.1181). Subacute thrombosis is a major complication of their use and patients were initially treated with an aggressive combination of anticoagulants and antiplatelets. However, it is now generally recognised that antiplatelet drugs alone are adequate in most patients.

Early studies^{1–4} found that ticlopidine for 4 to 6 weeks after stenting, given with long-term aspirin, was at least as effective as an oral anticoagulant with aspirin, with some studies showing benefit in terms of thrombosis^{1,4} or bleeding complications.¹ However, the risk of neutropenia limits the use of ticlopidine, and clopidogrel is now generally preferred, although there is some evidence⁵ that shorter courses of ticlopidine (2 weeks) may be acceptable.

Ticlopidine has also been reported⁶ to improve the long-term patency of saphenous vein bypass grafts used to treat peripheral vascular disease in the legs.

- Schömig A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med* 1996; **334**: 1084–9.
- Kastrati A, et al. Restenosis after coronary stent placement and randomization to a 4-week combined antiplatelet or anticoagulant therapy: six-month angiographic follow-up of the Intracoronary Stenting and Antithrombotic Regimen (ISAR) trial. *Circulation* 1997; **96**: 462–7.
- Bertrand ME, et al. Randomized multicenter comparison of conventional anticoagulation versus antiplatelet therapy in unplanned and elective coronary stenting: the Full Anticoagulation versus Aspirin and Ticlopidine (FANTASTIC) study. *Circulation* 1998; **98**: 1597–1603.
- Leon MB, et al. A clinical trial comparing three antithrombotic drug regimens after coronary-artery stenting. *N Engl J Med* 1998; **339**: 1665–71.
- Berger PB, et al. Safety and efficacy of ticlopidine for only 2 weeks after successful intracoronary stent placement. *Circulation* 1999; **99**: 248–53.
- Beckwem J-P. Effect of ticlopidine on the long-term patency of saphenous-vein bypass grafts in the legs. *N Engl J Med* 1997; **337**: 1726–31.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Dossier; Ticlid; Trombenal; **Austral.:** Ticlid; Tilodene; **Austria:** Trombodine; Ticlodone; Tiklid; **Belg.:** Ticlid; **Braz.:** Plaketar; Ticlid; Ticlobal; **Canada.:** Ticlid; **Chile:** Ateroclar; Plaquetil; Ticlid; **Cz.:** Aplaket; Apo-Tic; Ipaton; Platigren; Tagren; Ticlid; **Fr.:** Ticlid; Ticlomed; **Ger.:** Desiticolopid; Tiklyd; **Gr.:** Anhostam-100; Anhostam-100; Etfarol; Neo Fulvigal; Neomipren; Ruxicolan; Ticlid; Ticlodone; **Hong Kong:** Aplaket; Ticlid; Tipidin; **Hung.:** Actolin; Aplatix; Ipaton; Placor; Ticlid; **India:** Ticlobest; Ticlop; Ticlopid; Tikleent; Tiklyd; **Indon.:** Agulan; Cartrilet; Goclid; Nufaclopid; Piclofin; Ticard; Tiklyd; Ticuring; **Israel:** Ticlid; **Ital.:** Anagregalf; Antigreg; Aplaket; Clox; Flulast; Flupid; Fluxidin; Klodin; Opteron; Parsilid; Ticlodone; Ticlogit; Ticloproget; Tiklid; **Jpn.:** Panaldine; **Malaysia:** Antigreg; Aplaket; Ticlid; Ticlopin; Tipidin; **Mex.:** Ticlid; **Norw.:** Ticlid; **Philipp.:** Clotidone; Ticlid; **Pol.:** Actolin; Apo-Clodin; Iclolid; Ifapidin; Ticlid; Ticlo; **Port.:** Agregaminat; Aplaket; Betifex; Isaxion; Klodopin; Movin; Opidina; Plaqueta; Previa; Ticlodox; Ticlopat; Tiklyd; Tirora; Trombopat; **Rus.:** Ticlo (Тикло); Tikleen (Тиклин); **S.Afr.:** Ticlid; **Singapore:** Antigreg; Aplaket; Tasron; Ticlid; Tipidin; **Spain:** Ticlodone; Tiklid; **Swed.:** Ticlid; **Thai:** Aplaket; Cenpidine; Sictol; Ticlidin; Ticlid; Ticlo; Ticlopin; Tikol; Ticlopin; Tipidine; Viladi; **Turk.:** Acretik; Ticlid; Ticlocard; **UAE:** Ticopar; **USA:** Ticlid; **Venez.:** Ticlid; Ticlopin.

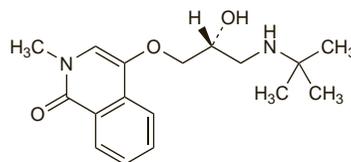
Tilisolol Hydrochloride (rINN) (X)

Hydrocloruro de tilisolol; N-696; Tilisolol, Chlorhydrate de; Tilisololi Hydrochloridum. (±)-4-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-2-methylisocarbostyryl hydrochloride.

Тилизолла Гидрохлорид

$C_{17}H_{24}N_2O_3 \cdot HCl = 340.8$

CAS — 85136-71-6 (tilisolol); 62774-96-3 (tilisolol hydrochloride).



Profile

Tilisolol hydrochloride is a non-cardioselective beta blocker (p.1225) with direct vasodilator activity. It is used in the management of angina pectoris (p.1157) and hypertension (p.1171) in oral doses of 10 to 20 mg once daily; up to a maximum of 30 mg once daily may be used if necessary.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn.: Selecal.

Timolol Maleate (BANM, USAN, rINN) (X)

Maleato de timolol; MK-950; Timolol Maleat; Timolol, maléate de; Timolol maleinát; Timololi maleas; Timololmaleaatti; Timololio maleatas; Timololmaleat; Timolol-maleát. (S)-1-*tert*-Butylamino-3-(4-morpholino-1,2,5-thiadiazol-3-yloxy)propan-2-ol maleate.

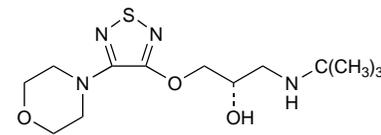
Тимолола Малеат

$C_{13}H_{24}N_4O_3 \cdot C_4H_4O_4 = 432.5$

CAS — 26839-75-8 (timolol); 91524-16-2 (timolol hemihydrate); 26921-17-5 (timolol maleate).

ATC — C07AA06; S01ED01.

ATC Vet — QC07AA06; QS01ED01.



(timolol)

NOTE. TIM is a code approved by the BP 2008 for use on single unit doses of eye drops containing timolol maleate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn.* and *US. Ph. Eur.* 6.2 (Timolol Maleate). A white or almost white, crystalline powder or colourless crystals. Soluble in water and in alcohol. A 2% solution in water has a pH of 3.8 to 4.3. Protect from light.

USP 31 (Timolol Maleate). A white to practically white, odourless or practically odourless powder. Soluble in water, in alcohol, and in methyl alcohol; sparingly soluble in chloroform and in propylene glycol; insoluble in cyclohexane and in ether. A 2% solution in water has a pH of 3.8 to 4.3.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Breast feeding. Timolol is distributed into breast milk. After installation of timolol 0.5% eye drops twice daily, concentrations of timolol in breast milk of a woman were about 6 times greater than those in serum, the values being 5.6 and 0.93 nanograms/mL respectively.¹ In a study² in patients given oral timolol 5 mg three times daily, the mean concentration in breast milk was 15.9 nanograms/mL, and the ratio of milk to plasma concentrations was 0.8; a similar ratio was found at higher doses, and the authors considered that the amount ingested by an infant would not be important. No adverse effects were seen in these studies and the American Academy of Pediatrics considers³ that timolol is therefore usually compatible with breast feeding.

- Lustgarten JS, Podos SM. Topical timolol and the nursing mother. *Arch Ophthalmol* 1983; **101**: 1381–2.
- Fidler J, et al. Excretion of oxprenolol and timolol in breast milk. *Br J Obstet Gynaecol* 1983; **90**: 961–5.
- American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. Correction. *ibid*; 1029. Also available at: <http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776> (accessed 10/01/08)

Interactions

The interactions associated with beta blockers are discussed on p.1228.

Antivirals. US licensed product information for *ritonavir* warns that ritonavir may increase concentrations of timolol and that the dose of timolol may need to be reduced if used together.

Pharmacokinetics

Timolol is almost completely absorbed from the gastrointestinal tract but is subject to moderate first-pass metabolism. Peak plasma concentrations occur about 1 to 2 hours after a dose. Low concentrations are also found in plasma after use as eye drops. Timolol has low to moderate lipid solubility. Protein binding is reported to be low. Timolol crosses the placenta and is distributed into breast milk. A plasma half-life of 4 hours has been reported. Timolol is extensively metabolised in the liver, the metabolites being excreted in the urine with some unchanged timolol. Timolol is not removed by haemodialysis.