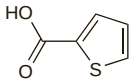
Thenoic Acid

Tenoic Acid; Tenoico, ácido; 2-Thiophenic Acid. Thiophene-2-carboxylic acid.

Тиофенкарбоновая Кислота

$C_5H_4O_2S$ = 128.1.
CAS — 527-72-0.



Profile

Thenoic acid has been given orally, rectally, or intranasally as the sodium salt, and orally as the lithium salt, in the treatment of respiratory-tract infections. The monoethanolamine salt has been used sublingually as a mucolytic.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Rhinotrophyl; Soufrane.

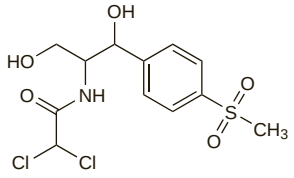
Multi-ingredient: ***Fr.:*** Glossithiase; Trophires; Trophires Compose; ***Spain:*** Trophires†.

Thiamphenicol *(BAN, USAN, rINN)*

CB-8053; Dextrosulphenidol; Thiamfenicol; Thiamfenikol; Thiamphénicol; Thiamphenicolum; Thiophenicol; Tiamfenicolo; Tiamfenikol; Tiamfenikoli; Tiamfenikolis; Tianfenicol; Win-5063-2; Win-5063 (racephenicol). (α*R*,β*R*)-2,2-Dichloro-*N*-(β-hydroxy-α-hydroxymethyl-4-methylsulphonylphenethyl)acetamide.

Тиамфеникол

$C_{12}H_{15}Cl_2NO_5S$ = 356.2.
CAS — 15318-45-3 (thiamphenicol); 847-25-6 (racephenicol).
ATC — J01BA02.
ATC Vet — QJ01BA02; QJ51BA02.



NOTE. Racephenicol, the racemic form of thiamphenicol, is *USAN*.

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).
Ph. Eur. 6.2 (Thiamphenicol). A fine, white or yellowish-white, crystalline powder or crystals. Slightly soluble in water and in ethyl acetate; sparingly soluble in dehydrated alcohol and in acetone; freely soluble in acetonitrile and in dimethylformamide; very soluble in dimethylacetamide; soluble in methyl alcohol. Protect from light and moisture.

Thiamphenicol Glycinate Hydrochloride

Thiamphenicol Aminoacetate Hydrochloride; Tiamfenicolo Glicinato Cloridrato; Tianfenicol, hidrocloruro del glicinato de.

$C_{14}H_{18}Cl_2N_2O_6S,HCl$ = 449.7.
CAS — 2393-92-2 (thiamphenicol glycinate); 2611-61-2 (thiamphenicol glycinate hydrochloride).
ATC — J01BA02.
ATC Vet — QJ01BA02.

Pharmacopoeias. In *It.*

Adverse Effects and Precautions

As for Chloramphenicol, p.240.

Thiamphenicol is probably more liable to cause dose-dependent reversible depression of the bone marrow than chloramphenicol but it is not usually associated with aplastic anaemia. Thiamphenicol also appears to be less likely to cause the 'grey syndrome' in neonates.

Doses of thiamphenicol should be reduced in patients with renal impairment. It is probably not necessary to reduce doses in patients with hepatic impairment.

Interactions

As for Chloramphenicol, p.240.

Although thiamphenicol is not metabolised in the liver and might not be expected to be affected by drugs which induce hepatic enzymes, it is reported to inhibit hepatic microsomal enzymes and may affect the metabolism of other drugs.

Antimicrobial Action

Thiamphenicol has a broad spectrum of activity resembling that of chloramphenicol (p.241). Although in general it is less active than chloramphenicol it is reported to be equally effective, and more actively bactericidal, against *Haemophilus* and *Neisseria* spp.

Cross-resistance occurs between thiamphenicol and chloramphenicol. However, some strains resistant to chloramphenicol may be susceptible to thiamphenicol.

Pharmacokinetics

Thiamphenicol is absorbed from the gastrointestinal tract after oral doses and peak serum concentrations of 3 to 6 micrograms/mL have been achieved about 2 hours after a 500-mg dose.

Thiamphenicol diffuses into the CSF, across the placenta, into breast milk, and penetrates well into the lungs. About 10% is bound to plasma proteins. The half-life of thiamphenicol is around 2 to 3 hours but unlike chloramphenicol the half-life is increased in patients with renal impairment. It is excreted in the urine, about 70% of a dose being excreted in 24 hours as unchanged drug. It undergoes little or no conjugation with glucuronic acid in the liver. A small amount is excreted in the bile and the faeces.

Uses and Administration

Thiamphenicol has been used similarly to chloramphenicol (p.241) in the treatment of susceptible infections, including sexually transmitted diseases. The usual adult oral dose is 1.5 g daily in divided doses; up to 3 g daily has been given initially in severe infections. A daily dose of 30 to 100 mg/kg may be used in children. Equivalent doses, expressed in terms of thiamphenicol base, may be given by intramuscular or intravenous injection as the more water soluble glycinate hydrochloride; 1.26 g of thiamphenicol glycinate hydrochloride is equivalent to about 1 g of thiamphenicol. Doses should be reduced in patients with renal impairment (see below).

For the treatment of gonorrhoea, oral doses of thiamphenicol have ranged from 2.5 g daily for 1 or 2 days through to 2.5 g on the first day followed by 2 g daily on each of 4 subsequent days. The single daily dose may be most appropriate for male patients with uncomplicated gonorrhoea.

Thiamphenicol glycinate hydrochloride may also be given by inhalation, or by endobronchial or intracavitary instillation.

Thiamphenicol has also been used as thiamphenicol glycinate acetylcysteinate, thiamphenicol sodium glycinate isophthalolate, and thiamphenicol palmitate.

Administration in renal impairment. Doses of thiamphenicol should be reduced in patients with renal impairment according to creatinine clearance (CC):

- CC 30 to 60 mL/minute: 500 mg twice daily
- CC 10 to 30 mL/minute: 500 mg once daily

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Fluimucil Antibiotic; Urfamycine; ***Braz.:*** Glitisol; ***Fr.:*** Thiophenicol; ***Hong Kong:*** Urfamycin; ***Indon.:*** Biothicol; Canicol; Cetathiacol; Comthycol; Conucol; Corsafen; Daiticin; Dexycol; Genicol; Ipibiofen; Kalticol; Lacophen; Lanacol; Nikolam; Nilacol; Nufathiam; Opiphen; Phenobiotic; Promixin; Renamoca; Sendicol; Thiambiotic; Thiamet; Thiamfilex; Thiamika; Thiamycin; Thislacol; Troviakol; Urfamycin; Urfekol; Venacol; Zumatab; ***Ital.:*** Fluimucil Antibiotico; Glitisol; ***Mex.:*** Tiofeniclin; ***Rus.:*** Fluimucil Antibiotic (Флуимуцил антибиотик); ***Spain:*** Fluimucil Antibiotico†; Urfamycin†; ***Switz.:*** Urfamycine; ***Thai.:*** Doqua; Thiamcin; Treomycin; Urfamycin; ***Turk.:*** Thiophenicol; Tiofen; Urfamycin.

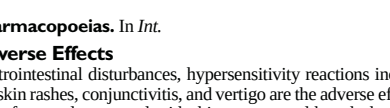
Multi-ingredient: ***Spain:*** Flumil Antibiotico; ***Thai.:*** Fluimucil Antibiotic.

Thioacetazone *(BAN, rINN)*

Amithiozone; Amitiozon; TBI/698; Tebezonum; Thiacetazone; Thioacétazone; Thioacetazonum; Tiasetazon; Tioacetazona. 4-Acetamidobenzaldehyde thiosemicarbazone.

Тиоацетазон

$C_{10}H_{12}N_4OS$ = 236.3.
CAS — 104-06-3.



Pharmacopoeias. In *Int.*

Adverse Effects

Gastrointestinal disturbances, hypersensitivity reactions including skin rashes, conjunctivitis, and vertigo are the adverse effects most frequently reported with thioacetazone although the incidence appears to vary between countries. Toxic epidermal necrolysis, exfoliative dermatitis (which has sometimes been fatal), and the Stevens-Johnson syndrome have been reported; the incidence of severe skin reactions is especially high in patients with HIV infection (see below). Thioacetazone may cause bone-marrow depression with leucopenia, agranulocytosis, and thrombocytopenia. Acute haemolytic anaemia may occur and a large percentage of patients will have some minor degree of anaemia. Hepatotoxicity with jaundice may also develop and acute hepatic failure has been reported. Cerebral oedema has been reported. Dose-related ototoxicity may occur rarely.

Incidence of adverse effects. In a 10-year series of 1212 patients with tuberculosis who were treated with a regimen of streptomycin, isoniazid, and thioacetazone, 171 (14%) had adverse reactions associated with thioacetazone. The most common adverse effects were giddiness (10%), occurring mainly when used with streptomycin, and skin rashes (3%) including exfoliation and the Stevens-Johnson syndrome.[1]

1. Pearson CA. Thiacetazone toxicity in the treatment of tuberculosis patients in Nigeria. *J Trop Med Hyg* 1978; **81:** 238–42.

Effects on the nervous system. Acute peripheral neuropathy which occurred in a 50-year-old man on 2 separate occasions within 15 minutes of a dose of thioacetazone may have been due to an allergic reaction.[1]

1. Gupta PK, *et al*. Acute severe peripheral neuropathy due to thiacetazone. *Indian J Tuberc* 1984; **31:** 126–7.

Effects on the skin. A high incidence of severe and sometimes fatal cutaneous hypersensitivity reactions to thioacetazone has been reported in patients with HIV infection being treated for tuberculosis.[1,2] WHO advised that thioacetazone should be avoided in such patients.[3] Unfortunately, thioacetazone has been one of the mainstays of tuberculosis treatment in the developing world because of its relatively low cost.[4] Some have supported a change to rifampicin-based regimens in, for example, parts of Africa with a high incidence of HIV infection.[5] Others have found a lower frequency of fatalities from adverse cutaneous reactions to thioacetazone than reported previously and have suggested that improved management might allow retention of thioacetazone in tuberculosis programmes.[6] This was rejected by other workers who considered that better and more cost-effective regimens were available than those containing thioacetazone.[7] A pragmatic approach may be to adopt a strategy depending upon the prevailing incidence of HIV infection in the population.[8] Thus, where the incidence of HIV infection is high, ethambutol should be substituted for thioacetazone; where the incidence is moderate, routine HIV testing could be used to identify patients at risk; and where the incidence is low, education of patients on the risks of skin reaction would be adequate.

1. Nunn P, *et al*. Cutaneous hypersensitivity reactions due to thiacetazone in HIV-1 seropositive patients treated for tuberculosis. *Lancet* 1991; **337:** 627–30.
2. Chintu C, *et al*. Cutaneous hypersensitivity reactions due to thiacetazone in the treatment of tuberculosis in Zambian children infected with HIV-I. *Arch Dis Child* 1993; **68:** 665–8.
3. Raviglione MC, *et al*. HIV-associated tuberculosis in developing countries: clinical features, diagnosis, and treatment, *Bull WHO* 1992; **70:** 515–26.
4. Nunn P, *et al*. Thiacetazone—avoid like poison or use with care? *Trans R Soc Trop Med Hyg* 1993; **87:** 578–82.
5. Okwera A, *et al*. Randomised trial of thiacetazone and rifampicin-containing regimens for pulmonary tuberculosis in HIV-infected Ugandans. *Lancet* 1994; **344:** 1323–8.
6. Ipuge YAI, *et al*. Adverse cutaneous reactions to thiacetazone for tuberculosis treatment in Tanzania. *Lancet* 1995; **346:** 657–60.
7. Elliott AM, *et al*. Treatment of tuberculosis in developing countries. *Lancet* 1995; **346:** 1098–9.
8. van Gorkom J, Kibuga DK. Cost-effectiveness and total costs of three alternative strategies for the prevention and management of severe skin reactions attributable to thiacetazone in the treatment of human immunodeficiency virus positive patients with tuberculosis in Kenya. *Tubercle Lung Dis* 1996; **77:** 30–6.

Hypertrichosis. Hypertrichosis occurred in 2 children receiving thioacetazone.[1]

1. Nair LV, Sugathan P. Thiacetazone induced hypertrichosis. *Indian J Dermatol Venereol* 1982; **48:** 161–3.

Precautions

The efficacy and toxicity of a regimen of treatment which includes thioacetazone should be determined in a community before it is used widely since there appear to be geographical differences.

Thioacetazone should not be given to patients with hepatic impairment. It has also been suggested that, because thioacetazone has a low therapeutic index and is excreted mainly in the urine, it should not be given to patients with renal impairment. Treatment should be stopped if rash or other signs of hypersensitivity occur. It should probably be avoided in HIV-positive patients because they are at increased risk of severe adverse effects (see Effects on the Skin, above).

Interactions

Thioacetazone may enhance the ototoxicity of streptomycin.

Antimicrobial Action

Thioacetazone is bacteriostatic. It is effective against most strains of *Mycobacterium tuberculosis*, although sensitivity varies in different parts of the world.

Thioacetazone is also bacteriostatic against *M. leprae*. Resistance to thioacetazone develops when used alone. Cross-resistance can develop between thioacetazone and ethionamide or protionamide.

Pharmacokinetics

Thioacetazone is absorbed from the gastrointestinal tract and peak plasma concentrations of 1 to 2 micrograms/mL have been obtained about 4 to 5 hours after a 150-mg dose. About 20% of a dose is excreted unchanged in the urine. A half-life of about 12 hours has been reported.

Uses and Administration

Thioacetazone has been used with other antimycobacterials as a first-line drug in the treatment of tuberculosis (p.196). Thioacetazone-containing regimens are less effective than the short-course regimens recommended by WHO but are used in long-term regimens with isoniazid in some developing countries to reduce