A usual oral regimen is a 3 to 7 day course of quinine given with 7 days of the tetracycline. The total daily dose of tetracycline should be divided, and that usually recommended is 250 mg four times daily, although 500 mg twice daily may be more practical in the field. If the patient is too ill for oral medication quinine should be given parenterally until oral therapy can be begun; tetracycline should not be used parenterally. Although tetracycline therapy is normally contra-indicated in pregnant women and children, it may have to be given if the risk of withholding the drug is judged to outweigh the risk to developing teeth and bones.

The dose of doxycycline given orally with quinine is 200 mg daily for at least 7 days.

Tetracyclines are not considered suitable for extended prophylactic use, although doxycycline 100 mg daily has been used for short-term prophylaxis in areas of high risk where other drugs are likely to be ineffective.

1. CDC. Treatment guidelines: treatment of malaria (guidelines for clinicians) (issued 28th June 2004, updated 6th March 2007). Available at: http://www.cdc.gov/malaria/pdf/clinicalguidance.pdf (accessed 28/03/07)

Mouth ulceration. Tetracyclines may be used as mouthwashes in recurrent aphthous stomatitis (p.1700) and reportedly reduce ulcer pain and duration,[1] but their potential for adverse effects if swallowed must be borne in mind, and their acidity can damage tooth enamel if poorly formulated. Topical application of a tetracycline has been tried for oral ulceration associated with Behçet's syndrome (p.1499).

1. Henricsson V, Axéll T. Treatment of recurrent aphthous ulcers with Aureomycin mouth rinse or Zendium dentifrice. *Acta Odontol Scand* 1985; **43:** 47–52.

Musculoskeletal and joint disorders. Tetracyclines, usually minocycline, are among the wide range of drugs tried in rheumatoid arthritis (p.11). Studies[1,2] indicate that minocycline can produce modest beneficial effects in patients with advanced disease, but the clinical significance of these improvements has been questioned.[3] Greater symptomatic improvements have been obtained with minocycline when it is used in patients with early rheumatoid arthritis;[4,5] continued treatment with minocycline may also reduce the need for disease-modifying antirheumatic drugs (DMARDs).[6] A systematic review,[7] which included these and some other studies, reported that the use of tetracyclines (doxycycline, minocycline, or tetracycline) for 3 months or longer was associated with a reduction in disease activity but not in joint damage when compared with placebo or a DMARD (hydroxychloroquine or methotrexate); the authors also noted that patients with early onset disease responded better to tetracyclines. There has been speculation over the role of infection as a cause of rheumatoid arthritis.[3,8] A later study[9] in patients with early seropositive disease found that initial therapy with methotrexate plus doxycycline was superior to methotrexate alone. It was also noted that therapeutic responses to doxycycline 100 mg twice daily and 20 mg twice daily were similar, suggesting that its anti-inflammatory effects were more important; however, further studies are needed.

Although there has been little convincing clinical evidence that any treatment can slow the progression of osteoarthritis (p.11), a placebo-controlled study involving 431 women with unilateral osteoarthritis of the knee found that treatment with doxycycline 100 mg twice daily over 30 months was associated with a reduction in the rate of joint space narrowing.[10] It had no effect on the contralateral knee, and did not reduce pain scores, although these were low at baseline.

The role of antibacterials is also uncertain in reactive arthritis (see Bone and Joint Infections, p.164), although long-term treatment with a tetracycline in addition to an NSAID has been reported to shorten the duration of reactive arthritis resulting from *Chlamydia trachomatis* infection.[11] However, another small study[12] found that treatment with a 4-month course of doxycycline 100 mg twice daily was not superior to a 10-day course.

1. Kloppenburg M, *et al.* Minocycline in active rheumatoid arthritis. *Arthritis Rheum* 1994; **37:** 629–36.
2. Tilley BC, *et al.* Minocycline in rheumatoid arthritis: a 48-week, double-blind, placebo-controlled trial. *Ann Intern Med* 1995; **122:** 81–9.
3. McKendry RJR. Is rheumatoid arthritis caused by an infection? *Lancet* 1995; **345:** 1319–20.
4. O'Dell JR, *et al.* Treatment of early rheumatoid arthritis with minocycline or placebo: results of a randomized double-blind, placebo-controlled trial. *Arthritis Rheum* 1997; **40:** 842–8.
5. O'Dell JR, *et al.* Treatment of early seropositive rheumatoid arthritis: a two-year, double-blind comparison of minocycline and hydroxychloroquine. *Arthritis Rheum* 2001; **44:** 2235–41.
6. O'Dell JR, *et al.* Treatment of early seropositive rheumatoid arthritis with minocycline: four-year follow-up of a double-blind, placebo-controlled trial. *Arthritis Rheum* 1999; **42:** 1691–5.
7. Stone M, *et al.* Should tetracycline treatment be used more extensively for rheumatoid arthritis? Metaanalysis demonstrates clinical benefit with reduction in disease activity. *J Rheumatol* 2003; **30:** 2112–22.
8. O'Dell JR. Is there a role for antibiotics in the treatment of patients with rheumatoid arthritis? *Drugs* 1999; **57:** 279–82.
9. O'Dell JR, *et al.* Treatment of early seropositive rheumatoid arthritis: doxycycline plus methotrexate versus methotrexate alone. *Arthritis Rheum* 2006; **54:** 621–7.
10. Brandt KD, *et al.* Effects of doxycycline on progression of osteoarthritis: results of a randomized, placebo-controlled, double-blind trial. *Arthritis Rheum* 2005; **52:** 2015–25.
11. Lauhio A. Reactive arthritis: consider combination treatment. *BMJ* 1994; **308:** 1302–3.
12. Putschky N, *et al.* Comparing 10-day and 4-month doxycycline courses for treatment of Chlamydia trachomatis-reactive arthritis: a prospective, double-blind trial. *Ann Rheum Dis* 2006; **65:** 1521–4.

Peptic ulcer disease. Tetracycline has been used as part of triple therapy to eradicate *Helicobacter pylori* in patients with peptic ulcer disease (p.1702). The usual dose of tetracycline in these regimens has been 500 mg four times daily for 2 weeks.

Periodontal disease. For the use of doxycycline in subantimicrobial doses as an adjunct in the treatment of periodontal disease, see Administration, Subantimicrobial Doses, p.268.

Skin disorders. ***ACNE.*** Tetracyclines may be used topically or orally in the treatment of acne (p.1577). In acne, antibacterials appear to act by suppressing the growth of *Propionibacterium acnes*, but also by suppressing inflammation. Topical tetracycline is used for mild inflammatory acne and as an adjunct to systemic treatment in more severe forms. Tetracyclines, given orally, are the drugs of choice for moderate acne and may be considered, in high doses, for severe acne. Licensed doses in the UK are:

- doxycycline 50 mg daily (the *BNF* advocates 100 mg daily)
- lymecycline equivalent to 300 mg of tetracycline daily
- minocycline 100 mg daily
- oxytetracycline 250 to 500 mg daily (the *BNF* advocates 1 g daily)
- tetracycline 1 g daily

Treatment should be changed to another antibacterial if there has been no improvement in the first 3 months. Maximum improvement is said to occur after 3 to 6 months, but treatment may need to continue for 2 or more years.

Minocycline has been reported to have superior antibacterial activity against *P. acnes* and a reduced incidence of resistance compared with tetracycline;[1] it has also been reported to be more effective than erythromycin against oxytetracycline-resistant acne.[2] However, a later randomised study[3] found minocycline to be comparable in efficacy to oxytetracycline, topical erythromycin with benzoyl peroxide, and topical benzoyl peroxide alone in the treatment of mild to moderate acne; in another randomised study[4] lymecycline also showed comparable efficacy and safety. Moreover, minocycline can cause skin pigmentation and may be associated rarely with immunologically-mediated reactions.[5] Although the usual dose of minocycline is 100 mg daily in one or two divided doses some patients may need up to 200 mg daily.[6]

For the use of doxycycline in subantimicrobial doses in patients with acne, see Administration, Subantimicrobial Doses, p.268.

1. Eady EA, *et al.* Superior antibacterial action and reduced incidence of bacterial resistance in minocycline compared to tetracycline-treated acne patients. *Br J Dermatol* 1990; **122:** 233–44.
2. Knaggs HE, *et al.* The role of oral minocycline and erythromycin in tetracycline therapy-resistant acne—a retrospective study and a review. *J Dermatol Treat* 1993; **4:** 53–6.
3. Ozolins M, *et al.* Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: randomised controlled trial. *Lancet* 2004; **364:** 2188–95.
4. Bossuyt L, *et al.* Lymecycline in the treatment of acne: an efficacious, safe and cost-effective alternative to minocycline. *Eur J Dermatol* 2003; **13:** 130–35.
5. Ferner RE, Moss C. Minocycline for acne. *BMJ* 1996; **312:** 138.
6. Goulden V, *et al.* Safety of long-term high-dose minocycline in the treatment of acne. *Br J Dermatol* 1996; **134:** 693–5.

PEMPHIGUS AND PEMPHIGOID. Corticosteroids are generally given to control the blistering in pemphigus and pemphigoid (p.1582), although there have been reports[1-8] suggesting that a tetracycline (often minocycline) may be of value in controlling the lesions associated with various types of pemphigus and pemphigoid.

1. Sawai T, *et al.* Pemphigus vegetans with oesophageal involvement: successful treatment with minocycline and nicotinamide. *Br J Dermatol* 1995; **132:** 668–70.
2. Poskitt L, Wojnarowska F. Minimizing cicatricial pemphigoid orodynia with minocycline. *Br J Dermatol* 1995; **132:** 784–9.
3. Kolbach DN, *et al.* Bullous pemphigoid successfully controlled by tetracycline and nicotinamide. *Br J Dermatol* 1995; **133:** 88–90.
4. Loo WJ, *et al.* Minocycline as a therapeutic option in bullous pemphigoid. *Clin Exp Dermatol* 2001; **26:** 376–9.
5. Amato L, *et al.* Successful treatment with doxycycline and nicotinamide of two cases of persistent pemphigoid gestationis. *J Dermatol Treat* 2002; **13:** 143–6.
6. Assmann T, *et al.* Therapieresistenter pemphigus vulgaris: Kombinationstherapie mit Methylprednisolon und Doxycyclin. *Hautarzt* 2003; **54:** 979–81.
7. Kakurai M, *et al.* Localized pemphigoid (pretibial type) with IgG antibody to BP180 NC16a domain successfully treated with minocycline and topical corticosteroid. *Clin Exp Dermatol* 2007; **32:** 759–61.
8. Carrozzo M, *et al.* Minocycline in combination with mycophenolate mofetil in oral mucous membrane pemphigoid. *Eur J Dermatol* 2008; **18:** 198–200.

ROSACEA. Tetracyclines are commonly used in the treatment of rosacea (p.1583). Long-term treatment is usually necessary.

Tetracycline and doxycycline have also been shown to improve ocular manifestations of rosacea.[1] However, a review[2] of the literature concluded that the treatment effect and optimal dose and duration of these 2 drugs have yet to be established; oxytetracycline was found to be of moderate benefit.

For the use of doxycycline in subantimicrobial doses in patients with rosacea, see p.268.

1. Frucht-Pery J, *et al.* Efficacy of doxycycline and tetracycline in ocular rosacea. *Am J Ophthalmol* 1993; **116:** 88–92.
2. Stone DU, Chodosh J. Oral tetracyclines for ocular rosacea: an evidence-based review of the literature. *Cornea* 2004; **23:** 106–9.

Preparations

BP 2008: Tetracycline Capsules; Tetracycline Tablets;
USP 31: Tetracycline Hydrochloride and Nystatin Capsules; Tetracycline Hydrochloride Capsules; Tetracycline Hydrochloride for Injection; Tetracycline Hydrochloride for Topical Solution; Tetracycline Hydrochloride Ointment; Tetracycline Hydrochloride Ophthalmic Ointment; Tetracycline Hydrochloride Ophthalmic Suspension; Tetracycline Hydrochloride Oral Suspension; Tetracycline Hydrochloride Tablets; Tetracycline Oral Suspension.

Proprietary Preparations (details are given in Part 3)

Arg.: Ciclotetryl; Tancilina†; ***Austral.:*** Achromycin V†; Achromycin†; Latycin; Tetrex; ***Austria:*** Achromycin†; Actisite; Latycin; ***Braz.:*** Ambra-Sinto T; Aureciclina; Biotrex†; Cinatrex; Infex; Multigran†; Prociclina; Statinclyne†; Telexin†; Teraciton†; Tetraben; Tetracilil; Tetracina; Tetraclin; Tetragel; Tetramax†; Tetramicin†; Tetraspir†; Tetraxil; Tetrex; Tetrib†; ***Canad.:*** Apo-Tetra; Novo-Tetra†; Nu-Tetra; ***Cz.:*** Tetrachel†; ***Fin.:*** Apocyclin; Oricyclin; ***Ger.:*** Achromycin; Imex; Supramycin†; Tefilin; Tetralution†; ***Gr.:*** Cliten; Hostacyclin; Imex; Muvito; Tetrac; Tracyclin; ***Hong Kong:*** Medocycline; ***India:*** Achromycin; Hostacycline; Resteclin; Subamycin; Tetrabact; ***Indon.:*** Cetacycline-P; Conmycin; Corsatet; Dumocycline; Ikacycline; Indocycline; Licoklin; Sanlin; Spectrocycline; Super Tetra; Tetra; Tetrarco; Tetrin; ***Irl.:*** Topicycline; ***Israel:*** Recycline; Tevacycline; ***Ital.:*** Actisite†; Ambramicina; ***Malaysia:*** Beatacycline; Dhatracin; Latycyn†; Tracyne†; ***Mex.:*** Acromicina; Ambotetra; Berciclina; Biotricina; Cortigrin†; Dibaterr; Educiclina; Forciclina†; Istix†; Laur†; Miciclin; Neoprobal; Ofticlin; Oxi-T; Profalin CPS; Quimocyclar; Senociclin; Solclin; Te-Br; Teclizima; Terrakal; Terranumonyl†; Tetra; Tetra-Zil; Tetrapar; Tetrapres; Tetrerba†; Tetrex; Tetrim; Traplicina†; Triclin†; ***Philipp.:*** Moncycline; ***Port.:*** Ciclobiotico†; Neociclina†; ***Rus.:*** Polcortolon TC (Полькортолон ТС); ***S.Afr.:*** Tetrex; ***Singapore:*** Beatacycline; Biotine; ***Spain:*** Actisite; Quimpe Antibiotico; Tetra Hubber†; ***Switz.:*** Actisite†; ***Thai.:*** Achromycin†; Boramycin; Hydromycin†; Lenocin; Pantocycline; Tetra Central†; Tetralim†; Tetrana; Tetrano; ***Turk.:*** Imex; Tetra; Tetralet; Tetramin; Vitasilin; ***UK:*** Topicycline; ***USA:*** Achromycin V†; Actisite†; Bristacycline; Sumycin; Tetrex; ***Venez.:*** Alfaciclina; Clincor†.

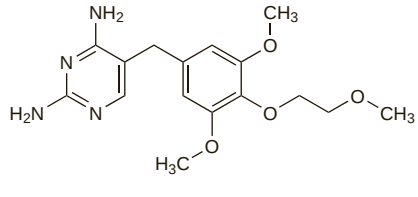
Multi-ingredient: ***Arg.:*** Dresan Biotic†; Eubetal Biotic†; Febrimicina†; Papasine; Solustres; ***Austria:*** Eftapan Tetra; Fluorex Plus; Mysteclin; ***Braz.:*** Anfoterin†; Gino-Teracin; Monocetin; Novasutin; Parenzyme Tetraciclina; Talsutin; Tericin AT; Tricangine†; Tricocilin B; Trinotrex†; Vagiklin; ***Chile:*** Talseclin†; ***Fin.:*** Helipak T; ***Fr.:*** Amphocycline; ***Ger.:*** Mysteclin; Polcortolon TC; ***Hong Kong:*** Talsutin; ***Hung.:*** Polcortolon TC; ***Indon.:*** Epicortyn; Talsutin; ***Ital.:*** Alfaflor; Betafloroto; Colbiocin; Eubetal Antibiotico; Flumeciclina; Flumetol Antibiotico†; Mictasone; Pensulvit; Vitecaf; ***Malaysia:*** Talsutin†; ***Mex.:*** Berciclina Enzimatica; Pharbrix; Quimotrip; Solfrancol; Trecloran; Urovec; ***Philipp.:*** Vagimycin; ***Pol.:*** Polcortolon TC; ***Port.:*** Ciclobiotico†; ***Rus.:*** Colbiocin (Колбиоцин); ***S.Afr.:*** Riostatin; Tetrex-F; Tritet; Vagmycin; ***Spain:*** Bristaciclina Dental; Gine Heyden†; Nasopomada; Sanicel; ***UK:*** Deteclo†; ***USA:*** Helidac; Pylera; ***Venez.:*** Talsutin†.

Tetroxoprim *(BAN, USAN, rINN)*

Tetroxoprima; Tétroxoprime; Tetroxoprimum. 5-[3,5-Dimethoxy-4-(2-methoxyethoxy)benzyl]pyrimidine-2,4-diyldiamine.

Тетроксоприм

$C_{16}H_{22}N_4O_4$ = 334.4.
CAS — 53808-87-0.



NOTE. Compounded preparations of tetroxoprim may be represented by the following name:

- Co-tetroxazine (*BAN*)—tetroxoprim 2 parts and sulfadiazine 5 parts (see p.257).

Profile

Tetroxoprim is a dihydrofolate reductase inhibitor similar to, but less active than, trimethoprim (p.355). It has been used, with sulfadiazine, as co-tetroxazine (p.257).

Tetroxoprim embonate has been used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)

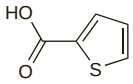
Multi-ingredient: ***Ger.:*** Sterinor†; ***Venez.:*** Esterinor†.

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.

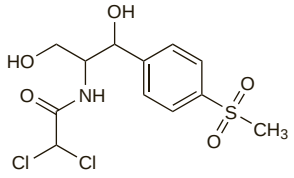
Multi-ingredient: ***Fr.:*** Glossithiase; Trophires; Trophires Compose; ***Spain:*** Trophires†.

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.

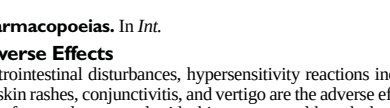
Multi-ingredient: ***Spain:*** Flumil Antibiotico; ***Thai.:*** Fluimucil Antibiotic.

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