Pharmacokinetics

The pharmacokinetics of tinidazole resemble those of metronidazole although the half-life is longer.

Tinidazole is rapidly and almost completely absorbed after oral doses and, typically, a peak plasma concentration of about 40 micrograms/mL is achieved 2 hours after a single 2-g dose, falling to about 10 micrograms/mL at 24 hours and 2.5 micrograms/mL at 48 hours; concentrations above 8 micrograms/mL are maintained by daily maintenance doses of 1 g. Comparable concentrations are achieved with equivalent intravenous doses. The plasma elimination half-life of tinidazole is 12 to 14 hours.

Tinidazole is widely distributed and concentrations similar to those in plasma have been achieved in bile, breast milk, CSF, saliva, and a variety of body tissues; it crosses the placenta readily. Only 12% is reported to be bound to plasma proteins. An active hydroxy metabolite has been identified.

Unchanged drug and metabolites are excreted in the urine and, to a lesser extent, in the faeces.

◊ References.

1. Wood BA, *et al.* The pharmacokinetics, metabolism and tissue distribution of tinidazole. *J Antimicrob Chemother* 1982; **10** (suppl A): 43–57.
2. Karhunen M. Placental transfer of metronidazole and tinidazole in early human pregnancy after a single infusion. *Br J Clin Pharmacol* 1984; **18:** 254–7.
3. Evaldson GR, *et al.* Tinidazole milk excretion and pharmacokinetics in lactating women. *Br J Clin Pharmacol* 1985; **19:** 503–7.
4. Wood SG, *et al.* Pharmacokinetics and metabolism of C-tinidazole in humans. *J Antimicrob Chemother* 1986; **17:** 801–9.

Renal impairment. Single-dose studies indicate that the pharmacokinetics of tinidazole in patients with chronic renal failure are not significantly different from those in healthy subjects and that no modification of tinidazole dosage is necessary. However, tinidazole is rapidly removed by haemodialysis.[1,2]

1. Flouvat BL, *et al.* Pharmacokinetics of tinidazole in chronic renal failure and in patients on haemodialysis. *Br J Clin Pharmacol* 1983; **15:** 735–41.
2. Robson RA, *et al.* Tinidazole pharmacokinetics in severe renal failure. *Clin Pharmacokinet* 1984; **9:** 88–94.

Uses and Administration

Tinidazole is a 5-nitroimidazole derivative. It has the antimicrobial actions of metronidazole and is used similarly (see p.839) in the treatment of susceptible protozoal infections and in the treatment and prophylaxis of anaerobic bacterial infections. It has also been used in regimens for the eradication of *Helicobacter pylori* in peptic ulcer disease.

Tinidazole is usually given as a single daily oral dose with or after food; it is also given by intravenous infusion and as vaginal pessaries.

In invasive **amoebiasis**, tinidazole is usually given with a luminal amoebicide. In intestinal amoebiasis, a single daily dose of 2 g is given orally for 2 or 3 days; in hepatic amoebiasis, 1.5 to 2 g as a single daily dose may be given for 3 days or occasionally up to 6 days. Children are given 50 to 60 mg/kg daily for 3 or 5 days respectively.

A single dose of tinidazole 2 g is given orally in the treatment of **giardiasis**, **trichomoniasis**, and acute necrotising **ulcerative gingivitis**; 50 to 75 mg/kg as a single dose is given to children with giardiasis or trichomoniasis. It may sometimes be necessary to repeat this dose once. In trichomoniasis, sexual partners should also be treated.

In **bacterial vaginosis**, a single 2-g dose of tinidazole is usually given orally, although higher cure rates have been achieved with a 2-g dose on 2 successive days or 1 g daily for 5 days.

For the treatment of most **anaerobic bacterial infections**, tinidazole is given orally, usually for 5 or 6 days, in an initial dose of 2 g followed on subsequent days by 1 g daily or 500 mg twice daily. If oral therapy is not possible, tinidazole may be given intravenously, 800 mg being infused as 400 mL of a 2 mg/mL solution at a rate of 10 mL/minute; this initial dose is followed by 800 mg daily or 400 mg twice daily until oral therapy can be substituted. For the *prevention* of postoperative anaerobic bacterial infections, 2 g is given by mouth about 12 hours before surgery. Alternatively 1.6 g is given as a single intravenous infusion before surgery.

In regimens for the treatment of **peptic ulcer disease**, tinidazole 500 mg twice daily has been given with clarithromycin and omeprazole for 7 days.

◊ Reviews.

1. Manes G, Balzano A. Tinidazole: from protozoa to Helicobacter pylori—the past, present and future of a nitroimidazole with peculiarities. *Expert Rev Anti Infect Ther* 2004; **2:** 695–705.
2. Fung HB, Doan TL. Tinidazole: a nitroimidazole antiprotozoal agent. *Clin Ther* 2005; **27:** 1859–84.
3. Nailor MD, Sobel JD. Tinidazole for bacterial vaginosis. *Expert Rev Anti Infect Ther* 2007; **5:** 343–8.

Administration in renal impairment. The elimination of tinidazole is largely unchanged in patients with impaired renal function (see under Pharmacokinetics, above) and dosage adjustment is not generally considered necessary. However tinidazole is removed by haemodialysis, and patients may need additional doses to compensate.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Fasigyn; Gynormal; Ladylen Duo; ***Austral.:*** Fasigyn; Simplotan; ***Belg.:*** Fasigyn; ***Braz.:*** Amplium; Facyl; Fasigyn; Ginosutin; Pletil; Tinoral; Trinizol†; ***Chile:*** Fasigyn; Triconidazol†; Troxxil; ***Fr.:*** Fasigyne; ***Ger.:*** Simplotan†; ***Gr.:*** Fasigyn; ***Hong Kong:*** Fasigyn; ***India:*** Amebamagma; Enidazol; Fasigyn; Tiniba; Tinidafyl; Tinidol†; Tinifas; Tinvista; ***Indon.:*** Fasigyn; Flatin; ***Israel:*** Fasigyn; Protocide; ***Ital.:*** Fasigin; Trimonase; ***Malaysia:*** Fasigyn†; Tindol; ***Mex.:*** Amebysol; Ametricid†; Estovyn-T; Fasigyn; Induken†; Trinigyn; Triseptil; ***Neth.:*** Fasigyn†; ***NZ:*** Dyzole; ***Port.:*** Fasigyn; ***Rus.:*** Fasigyn (Фазижин); Tiniba (Тиниба); ***S.Afr.:*** Fasigyn; ***Singapore:*** Fasigyn; ***Spain:*** Tricolam; ***Swed.:*** Fasigyn; ***Switz.:*** Fasigyne; ***Thai.:*** Asiazole-TN; Fasigyn; Funida; Idazole; Sporinex; Tinazole; Tini†; Tonid; Trichonas; Tricogyn; Tricozone; Trigyn†; ***UK:*** Fasigyn; ***USA:*** Tindamax; ***Venez.:*** Cinabel†; Fasigyn; Pangamil.

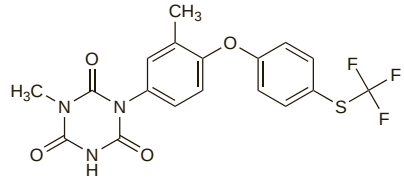
Multi-ingredient: ***Arg.:*** Aduar; Fasigyn Nistatina; Gynormal; Helmint Compuesto; Ladylen; Mebutar Compuesto; Nistinol; Tru Compuesto; ***Braz.:*** Amplium-G; Anfugine; Cartrax; Colpolase; Duozol; Facyl M; Ginec†; Gino Pletil; Ginometrim Oral†; Ginosutin M; Gynomax; Gynopac; Poliginax; Seczol; Takil; Tizonil M†; Travogyn; Trinizol M†; ***Chile:*** Doxifen; Famidal; Famidal Ad†; Ginecopast; Ginecopast Dual; Ginedazol; Ginedazol Dual; Medidos; Mizonase; ***India:*** Biocip-TZ; Bioflox-TZ; Candizole-T; Cipgen TZ; Ciplox TZ; Ciptini; Citizol; Entrolate†; Forcan TZ; Genflox TZ; Helipac; Nor T; Norflox TZ; Normax TZ; Ofler-TZ; Oflox TZ; Olfi TZ; OTC HP Kit; Parabact; Pylokit; Tinidafyl Plus; Tinvista-CF; Tinvista-NF; Wotinex; ***Indon.:*** Fasigyn-Nystatin; ***Ital.:*** Fasigin N; ***Malaysia:*** Pylobact Combi; ***Mex.:*** Afumix; Fasigyn VT; Mebeciclol; ***Rus.:*** Pylobact (Пилобакт).

Toltrazuril *(BAN, USAN, rINN)*

Bay-Vi-9142; Toltrazurilo; Toltrazurilum. 1-Methyl-3-(4-{*p*-[(trifluoromethyl)thio]phenoxy}-*m*-tolyl)-*s*-triazine-2,4,6(1*H*,3*H*,5*H*)-trione.

Толтразурил

$C_{18}H_{14}F_3N_3O_4S$ = 425.4.
CAS — 69004-03-1.
ATC Vet — QP51AJ01.



Profile

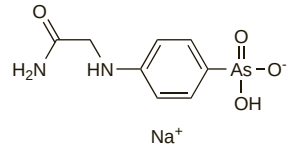
Toltrazuril is an antiprotozoal used in veterinary practice for the treatment of coccidiosis in poultry and piglets, and for the treatment of isosporiasis in piglets.

Tryparsamide *(rINN)*

Glyphenarsine; Triparsamida; Tryparsam.; Tryparsamidum; Tryparsone. Sodium hydrogen 4-(carbamoylmethylamino)-phenylarsonate hemihydrate.

Трипарсамид

$C_8H_{10}AsN_2NaO_4 \cdot H_2O$ = 305.1.
CAS — 554-72-3 (anhydrous tryparsamide); 6159-29-1 (tryparsamide hemihydrate).



(anhydrous tryparsamide)

Profile

Tryparsamide, a pentavalent arsenical compound, is a trypanocide which penetrates into the CSF and has been used with suramin in the treatment of late-stage African trypanosomiasis due to *Trypanosoma brucei gambiense*, as an alternative to melarsoprol or eflornithine (see p.827). However, because of its toxicity, especially the risk of blindness resulting from damage to the optic nerve, melarsoprol or eflornithine are preferred.

For the adverse effects of arsenic and their treatment, see Arsenic Trioxide, p.2260. Like melarsoprol, tryparsamide can cause encephalopathy.

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tory-tract RSV infection, days of hospitalisation and short-term outcomes have not been affected.[2,15] Due to the small number of patients enrolled in these studies, evaluation of the effects has been difficult. Also, there are some difficulties in giving the drug, and concerns about occupational health and safety, and the high cost. Routine use is not recommended;[6,7] but it may be used for selected infants and children at risk of severe disease and complications. If used, ribavirin should be started early in the course of the disease.[2,3,6]

Antibacterials, although often used in the management of bronchiolitis, are not routinely recommended.[6,7] The results from three small studies[16] suggest that *surfactant* may reduce duration of ventilation and length of intensive care stay.

Prevention of RSV infection involves good infection control practices and use of *RSV immunoglobulin* and a human monoclonal antibody to RSV, *palivizumab*. Both RSV immunoglobulin and palivizumab can be given during an RSV outbreak to prevent serious complications of infection in infants and children considered at high risk. The effectiveness of RSV immunoglobulin[17] and palivizumab[18] were tested in randomised, placebo-controlled clinical studies involving high-risk infants and children (history of prematurity or with bronchopulmonary dysplasia). A 41% overall reduction in hospital admissions was reported in those given RSV immunoglobulin prophylaxis. Prophylaxis with palivizumab resulted in a 55% overall reduction in hospitalisation; reduction rates were 39% and 78% in those with and without bronchopulmonary dysplasia respectively. Respiratory severity scores, hospital days, days of oxygen requirement, and the rate of intensive care admission were also significantly lower in the palivizumab group than for the placebo group. Prophylaxis with palivizumab was also found to reduce post-bronchiolitic wheezing in premature infants.[19] It is recommended by some expert groups for prophylaxis in infants and children at high risk of severe RSV infections.[6,7,20] Vaccines to prevent RSV infection are currently under development.

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SARS

Severe acute respiratory syndrome (SARS)[1,2] is a respiratory illness caused by a newly identified coronavirus (SARS-CoV). SARS presents primarily in previously healthy adults although there have been some cases reported in children. SARS-CoV is transmitted by contact or droplets and transmission mainly occurs during the second week of illness. The incubation period for SARS is usually 2 to 10 days but may be as long as 16 days. The disease manifests initially as flu-like prodromal symptoms, usually characterised by fever, malaise, myalgia, headache, and rigors. Cough (initially dry), dyspnoea, and diarrhoea may be present in the first week but are more commonly present in the second week of illness. Severe cases develop rapidly progressive respiratory distress and hypoxia and up to about 20% of patients may require intubation or mechanical ventilation. About 20% of patients develop large volume, watery diarrhoea. The overall fatality rate during the 2002–2003 SARS outbreak was about 9.5%.

There is currently no consensus on the optimal treatment for SARS and treatment recommendations are based on the experience gained during the 2002–2003 SARS outbreak. Guidelines for the **surveillance and management** of SARS have been developed by WHO.[3] In the UK guidelines[4] have been issued for the hospital management of adults with SARS, and others have also been developed by clinicians involved in the SARS outbreak in Hong Kong.[5] Because SARS is indistinguishable from pneumonia caused by viral and bacterial pathogens, empirical antibacterial treatment in accordance with local guidelines for severe community-acquired pneumonia (p.186) is recommended. Fluids and oxygen therapy should be given as required. Other treatments tried have included corticosteroids, ribavirin, interferons, normal immunoglobulins, and the co-formulated HIV-protease inhibitor ritonavir-boosted lopinavir. Corticosteroids, usually with ribavirin, were widely used and the timely use of high-dose corticosteroids may decrease fever, improve radiographic appearances, and reduce oxygen requirements.[6-8] There is, however, concern that high-dose and long-term use of corticosteroids may suppress the patient's immune system resulting in increased viral replication and possible bacterial or fungal superinfection. The UK guidelines recommend that their use be considered in moderate doses in severely ill patients with increased oxygen requirements.[4] Additionally there is no convincing clinical evidence that the use of ribavirin alters clinical outcome and the UK guidelines state that its routine use is not recommended.[4] Although interferon beta shows greater *in-vitro* antiviral activity against SARS-CoV, most experience during the 2002–2003 outbreak was with interferon alfa with or without normal immunoglobulins.[6] An open study[9] using interferon-alfacon-1 and high-dose pulse methylprednisolone reported more rapid improvement in radiographic appearance and oxygenation than corticosteroids alone. Better clinical improvement was reported in patients treated with daily interferon alfa plus high-dose corticosteroids than in those given interferon plus low-dose or limited corticosteroids.[8] The UK guidelines state that no recommendation can be given regarding the use of interferons.[4] Although normal immunoglobulins have been used in SARS their effectiveness cannot be established as they were usually given with other therapies.[6] A preliminary open study[10] with ritonavir-boosted lopinavir in 41 patients with probable SARS and receiving the local standard treatment of ribavirin and corticosteroids, reported an improved outcome at 21 days and reductions in viral load, corticosteroid dose, and the incidence of nosocomial infections.

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Warts

Warts are caused by human papillomaviruses. The lesions present in several different forms and can affect any skin site although the hands, feet, and anogenital areas are most frequently affected. Anogenital warts are known as condylomata acuminata. Treatment generally relies on some form of local tissue destruction (see p.1584). Interferons have also been used (see p.891).

Abacavir *(BAN, rINN)*

Abacavirum; Abakaviiri; Abakavir. {(1*S*,4*R*)-4-[2-Amino-6-(cyclopropylamino)-9*H*-purin-9-yl]cyclopent-2-enyl}methanol.

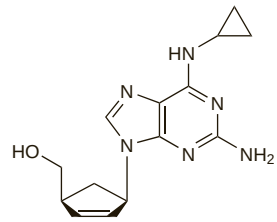
Абакавир

$C_{14}H_{18}N_6O$ = 286.3.

CAS — 136470-78-5.

ATC — J05AF06.

ATC Vet — QJ05AF06.



NOTE. The code 1592U89 has been applied to abacavir but is more properly reserved for abacavir sulfate.

Abacavir Succinate *(BANM, USAN, rINNM)*

Abacavir, Succinate d'; Abacaviri Succinas; Succinato de abacavir.

Абакавира Суксинат

$C_{14}H_{18}N_6O,C_4H_6O_4$ = 404.4.

CAS — 168146-84-7.

ATC — J05AF06.

ATC Vet — QJ05AF06.

NOTE. The code 1592U89 has been applied to abacavir succinate but is more properly reserved for abacavir sulfate.

Abacavir Sulfate *(USAN, rINNM)*

Abacavir, Sulfate d'; Abacavir Sulphate *(BANM)*; Abacaviri Sulfas; Sulfato de abacavir; 1592U89.

Абакавира Сульфат

$(C_{14}H_{18}N_6O)_2,H_2SO_4$ = 670.7.

CAS — 188062-50-2.

ATC — J05AF06.

ATC Vet — QJ05AF06.

NOTE. The code 1592U89 and its abbreviated form, 1592, have also been applied to abacavir and abacavir succinate.

Adverse Effects

The most significant adverse effects associated with antiretroviral regimens containing abacavir are severe hypersensitivity reactions, sometimes fatal, that may occur in up to 9% of patients given abacavir, especially (but not exclusively) during the first 6 weeks of treatment, or during intermittent therapy. Symptoms of hypersensitivity often include fever, rash, cough, dyspnoea, lethargy, malaise, headache, myalgia, and gastrointestinal disturbances, particularly nausea and vomiting, diarrhoea, and abdominal pain. Anaphylaxis has occurred. Caution is needed as hypersensitivity