CHAPTER - III

DRUG PROFILE

3.0 Drug Profile

3.1 Itraconazole (ITR)

Introduction

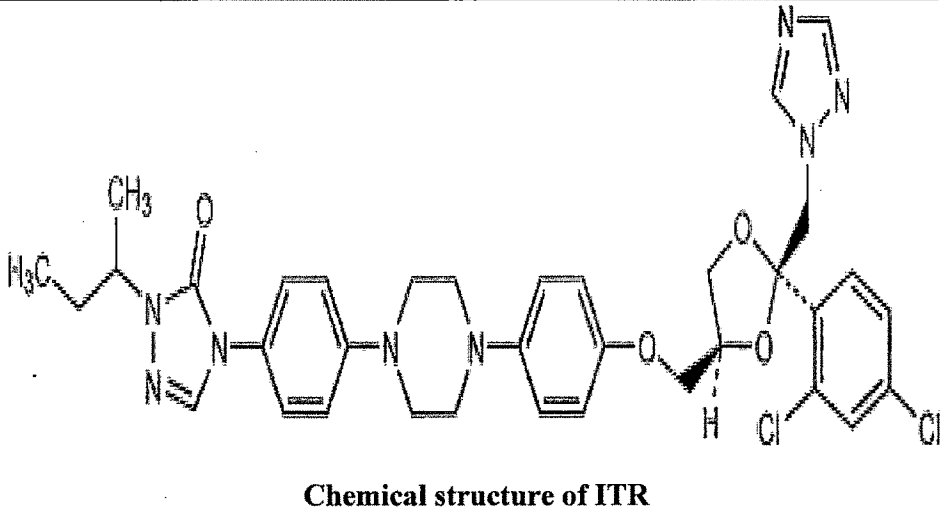
ITR is a fat soluble synthetic triazole antifungal drug. It has the same mechanism of action as all azoles and *prevents the formation of ergosterol necessary for the cell walls of fungi.* Studies with ITR commenced in 1984 and the drug was licensed in *1991.* It was discovered and developed by Janssen Pharmaceutica.

Proprietary Names

Canadiol ;Hongoseril; Itrizole; Sempera; Siros; Sporanox; Triasporin

Chemical Name

4-[4-[4-[4-[[2-(2,4-Dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one



Chemical structure of ITR

Chemical formula: $C_{35}H_{38}Cl_2N_8O_4$

Appearance: A white to off-white powder.

Solubility: It is soluble in dichloromethane; sparingly soluble in tetrahydrofuran; practically insoluble in water and dilute acidic solutions.

Physicochemical Properties	
Molecular weight	705.64
Partition coefficient	Log P > 5
Ionization constant	4.0
Melting point	166°C
Solubility in water (pH 7)	~ 1 ng/mL
Solubility in 0.1 N HCl	4 µg/mL

Pharmacokinetics

ITR is slowly but well absorbed after oral administration with peak concentrations reached in approx. 4 h. Absorption is enhanced in the presence of food and in an acidic intragastric environment. It is metabolized, mainly via oxidative pathways, to inactive metabolites which are excreted via bile and in urine. Over 30 metabolites have been isolated and most are biologically inactive including a hydroxy metabolite (bioactive) and hydroxyitraconazole. Both the drug and hydroxyitraconazole are inhibitors of the CYP3A4 enzyme system. The drug is widely distributed throughout the body with small amounts detected in most body fluids and accumulation occurring in tissues. The drug is extensively protein bound and therefore does not get into urine or cerebrospinal fluid. ITR has also been detected in skin, hair and nail but it does not easily redistribute in these tissues 3 to 18 % is excreted in the faeces as unchanged drug.

Toxicity: The serum toxic concentration is 6 mg/L (sum of ITR and its hydroxy metabolite).

Bioavailability: Dose dependent, increases with increasing dosage; 55% after a 100 mg dose (as solution)

Half life: 20 h (following a 100 mg single dose); increases to 30 h on multiple dosing.

Volume of distribution: 10.7 L/kg; also reported as 561 L

Protien binding: Approx. 99.8 %, albumin

Dose: 100 to 400 mg daily depending on indications and severity. For example, 2 doses of ITR (100mg) are sufficient for vaginal thrush.

Quantification

Ultraviolet spectrum: Aqueous acid - 263nm, Methanol – 262nm

High performance liquid chromatography: Column: RP C_{18} (RsiL C18HL, 150 × 2.1 mm i.d., 5 µm). Mobile phase: water:acetonitrile (40:60), 0.5 mL/min flow rate. UV detection (λ=254 nm). Retention time: ITR, 4.3 min; [R. Woestenborgh *et al.,J. Chromatogr., 1987*,413, **Biomed. Appl.**, 332–337.

Column: RP C_{18} (Hypersil, 100 × 4.5 mm i.d., 3 µm). Mobile phase: water: acetonitrile (40:60) containing 0.03% diethylamine, pH 7.8 with dilute orthophosphoric acid, 1 mL/min flow rate. UV detection (λ=254 nm). [D. Law *et al.,Antimicrob. Agents Chemother.*, 1994, **38**(7), 1561–1566.

Bioasay in serum: In serum—D. Law *et al.*, *Antimicrob. Agents Chemother.*, 1994, **38,** 1561–1566.

Antimicrobial Activity

ITR is one of the most broad spectrum antifungals which produce activity against *Aspergillus, Blastomyces Candida* (all species including many fluconazole resistant isolates) *Coccidioides, Cryptoccocus, Histoplasma, Paracoccidioides, Scedosporium apiospermum* and *Sporothrix schenkii.* It is also active against all skin fungi. It is not active against Mucorales or *Fusarium* and a few other rare fungi. Resistance to ITR is described in *Candida*, although less often than with fluconazole and also in *Aspergillus.*

Drug/drug Interaction

There are numerous drug/drug interactions with ITR which is one of its limitations. The absorption of capsules is reduced if given with antacid drugs but increased if the solution is used. If enzyme inducing drugs such as rifampicin, phenytoin or carbamazepine are used, there is a marked reduction in the blood levels of ITR and treatment may fail. ITR also prevents some drugs being metabolised, in particular terfenadine, astemizole and cisapride, which can lead to serious heart arrhythmias. These drugs should not be given with ITR. Certain sedatives will have prolonged action if given with ITR, in particular midazolam and triazolam. ITR may also increase the blood levels of digoxin, cyclosporin and warfarin and these drugs and their effects should be carefully monitored. Anticancer therapy with the drug vincristine given together with ITR may have prolonged action and cause neurological damage, which is usually temporary but can be very problematic.

Side Effects

ITR is well tolerated; the commonest side effects are nausea and sickness, occasional abdominal discomfort and constipation. Abnormal liver function tests occasionally occur and in rare cases severe liver disease or jaundice. Occasionally adrenal gland suppression, low blood potassium and raised blood pressure can occur.

Dose & Delivery

Until 1997 capsules only were available. Capsules are better absorbed taken with food. A liquid form was then introduced, particularly for the management of fluconazole resistant oral thrush in patients with AIDS and an Intravenous formulation has recently received FDA approval.

The oral liquid is typically used in patients with oral thrush, especially AIDS, and in the prophylaxis of fungal infections in leukaemia or after bone marrow transplantation. Suspension is better absorbed taken on an empty stomach.

Intravenous ITR is usually given a dose of 5mg per kg twice a day and is used when patients are unable to take oral medication or are very ill.

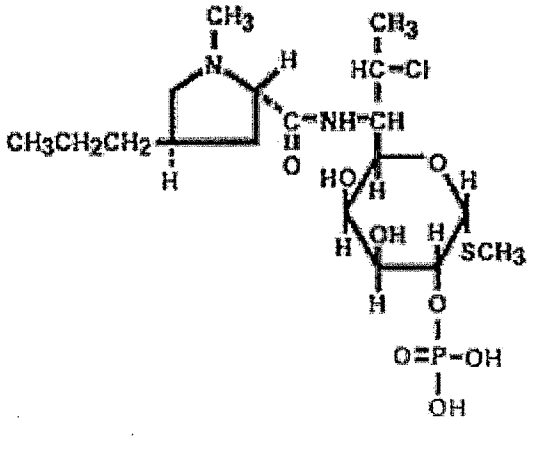
3.2 Clindamycin Phosphate (CL)

Introduction

CL is a water-soluble ester of the semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin. [Meyers B.R. *et al.* (1969). *Appl Microbiol* **17** (5): 653–657]. It is official in European pharmacopoeia 5.0 and US pharmacopoeia.

Chemical Name

Methyl 7-chloro-6, 7, 8-trideoxy-6-(1-methyl-*trans*- 4-propyl-L-2-pyrrolidine-carboxamido)-1-thio-L-*threo*-a-D-*galacto*-octopyranoside 2- (dihydrogen phosphate). The structural formula is represented below



Chemical Formula

$C_{18}H_{34}ClN_2O_8PS$

Physical and Chemical Properties
Molecular weight

504.96 g/mole

Appearance

A white or almost white powder, slightly hygroscopic in nature. It shows polymorphism

Solubility

Freely soluble in water, very slightly soluble in alcohol, practically insoluble in methylene chloride

Taste: BITTER

pH (1% w/v in water): pH of the solution is 3.5 to 4.5

Melting Point: Decomposes.

Ionization constant (pKa): 6.06 [Kipp JE et al. 1991, *Int. J. Pharm.* 74, 215-220]

Specific optical rotation: + 115 to + 130

Pharmacokinetics

Approximately 90% of an oral dose of clindamycin is absorbed from the gastrointestinal tract, and it is widely distributed throughout the body, excluding the central nervous system. Adequate therapeutic concentrations can be achieved in bone. There is also active uptake into white blood cells, most importantly neutrophils. Clindamycin is extensively metabolised in the liver, probably by CYP3A4; some of its metabolites are active, such as *N*-dimethyl clindamycin and clindamycin sulfoxide. Clindamycin is primarily eliminated by hepatic metabolism; after an intravenous dose of CL, about 4.5% of the dose is excreted in urine as clindamycin and about 0.35% as the phosphate salt. The metabolites are excreted primarily in the urine

Bioavailability: Route of administration dependent, more (about 90%) with oral administration, while less (4-5%) with topical administration. Borin M. T. *et al.* (1995) reported that systemic exposure of CL from intravaginal administration is minimal.

Half life: 2-3hr

Protein binding: Approx. 90%

Excretion: Biliary and renal (around 20%)

Antimicrobial activity

Clindamycin inhibits bacterial protein synthesis at the level of the bacterial ribosome. The antibiotic binds preferentially to the 50S ribosomal subunit and affects the process of peptide chain initiation. Clindamycin is an antimicrobial agent active in vitro against most strains of the following organisms that have been reported to be associated with bacterial vaginosis:

- *Bacteroides* spp
- *Gardnerella vaginalis*
- *Mycoplasma hominis*
- *Peptostreptococcus* spp
- *Mobiluncus* spp

Drug Interactions

CL has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, it should be used with caution in patients receiving such agents.

Dose & Delivery

The recommended dose of CL is 100 mg per day for 3 consecutive days. Clindamycin preparations for oral administration include capsules (containing clindamycin hydrochloride) and oral suspensions (containing clindamycin palmitate hydrochloride). It is also available for topical administration, in gel form and in a foam delivery system (both containing CL) and a solution in ethanol (containing clindamyin hydrochloride) Clindamycin is available as a generic drug, for both systemic (oral and intravenous) and topical use

Side Effect

Common adverse drug reactions (ADRs) associated with clindamycin therapy include: diarrhea, pseudomembranous colitis, nausea, vomiting, abdominal pain or cramps, rash, and/or itch. High doses (both intravenous and oral) may cause a metallic taste, and topical application may cause contact dermatitis, menstrual disorder, dysuria, pyelonephritis, vaginal discharge, and vaginitis/vaginal infection rash and urticaria. Jaundice and abnormalities in liver function tests have been observed during CL therapy.

The following adverse reactions and altered laboratory tests have been reported with the oral or parenteral use of clindamycin:

Gastrointestinal: Abdominal pain, esophagitis, nausea, vomiting, diarrhea and pseudomembranous colitis.

Hematopoietic: Transient neutropenia (leukopenia), eosinophilia, agranulocytosis, and thrombocytopenia have been reported. No direct etiologic relationship to concurrent clindamycin therapy could be made in any of these reports.

Hypersensitivity Reactions: Maculopapular rash, vesiculobullous rash, and urticaria have been observed during drug therapy. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported.

Liver: Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy.

Musculoskeletal: Rare instances of polyarthritis have been reported.

Renal: Although no direct relationship of clindamycin to renal damage has been has been established, renal dysfunction as evidenced by azotemia, oliguria, and/or proteinuria has been observed in rare instances.