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Sertaconazol; a review of antifungal agent.

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ABSTRACT:
Sertaconazol is an effective type of fungal agent that has shown considerable in vitro activity against pathogenic fungi. Various studies are carried out in animal models,clinical and toxicological trials have confirmed the value of sertaconazol in the topical treatment of mycoses in dermatology and gynecology. The recent approval of the molecule by US food and drug administration, and the appearance of a new formulation of sertaconazol for the treatment of onychomycoses on a weekly administrative basis are all relevant to the process of marketing the product. Sertaconazol known for its antifungal activity, anti-inflammatory effect. Sertaconazol has broad spectrum of antifungal activity against dermatophytes of trichophyton,Epidermophyton and microsporum genera,and yeast of genera candida and cryptococcus;additionally,it is effective against opportunistic filamentous fungi and gram-positive bacteria.

Keywords; antifungal activity, fungi, dermatophytes, gynecology, sertaconazol.

I. INTRODUCTION:

Sertaconazol it is the drug (Dermofix,Ertaczo,Ginedermofix,Monazol,Mykosert or Zalain),an imidazole antifungal agent,inhibit the synthesis of the ergosterol,an essential cell wall components of fungi.it is indicated in EU for treatment of the superficial skin mycoses(including tineacorporis,tineacruris,tineamanus,tineabarbae,tineapedis),cutaneous candidiasis,seboeeheoicdermatitits of scalp,pityriasis versicolor.

Sertaconazol it is FDA approved small molecule,it having the synonym like sertaconazole,sertaconazolum,sertaconazol.

Structure: sertaconazol nitrate(FI-7545)(nitrate salt of 7-choloro-3-[1-(2,4-dicholorophenyl)-2-(1H-imidazol-1-yl)erthoxy-methyl]benzo[b]thiophene) (C20H10O4CL3S),molecular weight 500.8Da,CAS99592-32-2)is a topical azole derivative associated with benzothiophene matrix. This represents an important difference compared with azoles used in the treatment of mycoses. It is practically insoluble in water and the lipophilic part of molecule soluble in organic solvents such as choloroform(1.5%),acetone(0.95%),ethanol(1.7%)it is slightly soluble in N-octanol(0.069%).

ANTIFUNGAL ACTIVITY OF SERTACONAZOL

Mechanism of action: due to its mix structure,sertaconazol is capable for direct damage to the C.albicans cell membrane. This is very important,effect on the fungicidal effect against C.albicans.

PHARMACODYNAMICS

Sertaconazol is an imidazole type of antifungal drug. It is highly selective inhibitor of fungal cytochrome P-450 sterol C-14α demethylase. This enzyme converts lanosterol to ergosterol,which is required in fungal cell wall synthesis,subsequent loss of normal sterols correlate with the accumulation of 14-α-methyl sterols infungi and may be partly responsible for fungistatic activity of flucoconazol. Sertaconazol exhibits the in vitro activity against cryptococcus neoformans and candida spp.

MECHANISM OF ACTION

Sertaconazol interacts with the 14-α-demethylase,a cytochrome p-450 enzyme which one is needed for conversion of lanosterol to ergosterol which is an essential component of fungal cell membrane,inhibition of synthesis results in increased cellular permeability causing leakage of cellular content.The drug also inhibits the endogenous respiration,interact with membrane phospholipids,inhibitthe transformation of yeast to mycelial forms,inhibit purine uptake,and impair phospholipid biosynthesis.

CLINICAL EFFICACY

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ANTI-INFLAMMATORY EFFECT OF SERTACONAZOL

It has been shown to have the anti-inflammatory activity when administered at a dose of 2%.

DERMATOLOGY

The cream formulation was effective in a double-blind study carried out with a group of patients suffering from the dermatophytosis such as tinea cruris,tinea pedis,tinea manuum, tinea barbae)the efficacy of formulation of cream of sertaconazol in a multicentre phase III,randomized and comparative study with miconazole in patients infected by microsporum canis,C.albicans and other dermatophyte fungi, reached ranges of 98.3 versus 94.3%, respectively,after 4 weeks treatment.[4]

GYNECOLOGY

The comparison study of sertaconzol done with the drugs clotrimazole and econazole for the treatment of candida vulvovaginitis excellent efficacy of sertaconazol was demonstrated.[5]

SAFETY PROFILE OF SERTACONAZOL

ACUTE TOXICITY STUDIES

Sertaconazole's acute toxicity was determined after administration of single dose of drug by the oral route,subcutaneous and intra peritoneal route in rats and mice with median lethal dose i.e.(LD_{50})being higher than 8000 mg/kg in all cases. Sertaconazol having the reduced absorption,administration is safe even in the event of accidental overdose or indigestion.[6]

SUBACUTE TOXICITY AND MAXIMUM TOLERATED DOSE

After repeated administration of the sertaconazol over a period of 28 days with the subacute and dermal doses i.e.50,150,3000mg/kg and maximum tolerable doses on a geometric progression of 50,75,11205,168,250mg/kg of sertaconazol revealed a reduced no of the toxic effects that are not possible to reproduce after the administration of single doses. Histopathological changes were not founded in any cases.[7]

CHRONIC TOXICITY STUDIES AFTER ORAL ADMINISTRATION

Among the all derivatives sertaconazol is also common for treatment of the mycoses,were detected at dose of 50mg/kg in chronic toxicity studies after repeated and sustained administration by oral routes doses are 50,150,300mg/kg in rats and ferrets. The accumulative effect,which did not produce any associated mortality,was observed in the group treated with bifonazole(10mg/kg), ketoconazole (60mg/kg) miconazole(100mg/kg). There was a low increase in body weight in animals treated with 300mg/kg over 11 weeks(ferrets) the histo-pathological findings are similar to those produced by other imidazole's and consisted of changes in pattern of microvacuolization in the hepatocyte cytoplasm related to induction of microsomal enzymes.[8]

TOXICITY STUDIES IN REPRODUCTION

Low toxicologic risk associated with the administration of sertaconazol compared to others ketoconazole,bifonazole or miconazole,the drug has been demonstrated by teratologic studies in rats,rabbits and also in peri-and postnatal rats.[9]

GENOTOXICITY

There was no evidence of induction of signs of mutagenicity,promutagenicity, clastogenicity or interference with the process of chromosomal segregation caused by DNA damage. Neither have genotoxicity studies carried out with sertaconazol demonstrated any increases in the frequency of bacterial retro-mutation or lethal mutations in spermatozoa or spermatids.[10]

SKIN TOLERANCE AND PHOTOTOXICITY

There is no risk of phototoxicity after the administration of the 2% creams formulation of sertaconazol in guinea pigs. Trials are carried out to detect skin tolerance demonstrated the absence of any irritation. Sertaconazol may be administered safely without possible existence of degradation by-products caused by direct exposure to sunlight.[11,12]

PHARMACOKINETIC OF SERTACONAZOL

Sertaconazol penetrates the horny layer of the skin where some pathogenic fungi are capable of developing their effect,and the therapeutic concentration may be found there during a long period of time,which is of interestin clinical practice.

High concentration of sertaconazol cannot be reached in the lower layers of skin,thus avoiding the potential risk of systemic absorption. In precilinical study the concentration of the sertaconazol in plasma found below 0.011% 5 h after bigining application of 2% cream to the skin.

No hematologic,cardiac or body temperature changes were observed at 13 days,neither was there any alteration of the blood testosterone levels,thus it provides good safety profile. The various types of vaginal forms are available such as tablets,pessaries and cream for vulvovaginitis make it possible to

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reach concentration above the required dose to inhibit the development of different species of the genus Candida spp. With dose of 300 or 500 mg. in addition,this concentrationare maintained in vaginal secretion for several days after a single administration without there being any systemic absorption, thus resolving its necessary presence and persistence in the vaginal mucous membrane.
Fecal and the renal routes are main route of elimination of the product(61 an 4%,respectively,for endovenous administration:30 and 0.4% for administration and 17 and 0.6% for the skin.[13]

TOLERABILITY STUDIES

Tolerability studies for sertaconazol carried out using animal models and healthy human volunteer showed the absence of evidences of adverse effects associated with the administration of total amount of 98 of antifungal agents during 13 days. It was also show with healthy volunteer's and other therapeutically available antifungal agents such econazole,bifonazole,clotrimazole,miconazole,keto conazole produces the adverse effect. There were no differences between sertaconazol and placebo in regards to photosensitivity.[14]

administration					
	cutaneous				
	Iv solution	cream	solution	powder	gel
Absorption %		1.47	1.97	0.665	0.885
C_{max}(µg/ml)		0.011	0.01	0.0033	0.0042
T_{max}(h)		5	5	18	18
$t_{1/2}$	7.276				
AUC (0-24) (µm/ml/h)	7.559	0.1114	0.1493	0.0503	0.0668
AUC (0-24) AREA UNDER CURVE OVER 24 HR; CMAX: MAX. CONC.T1/2; HALF LIFE; TMAX: TIME MAX. CONC.					

MARKET OF SERTACONAZOL

Sertaconazol is available in worldwide in different dermal and gynecological formulations. It include's topical gel,2% topical cream(approved recently in the USA under the brand name Ertaczo®),solution and powder. In the gynecology;pessaries,vaginal cream and vaginal tablets.

EVOLUTION

In period (1996-2001),there was report of reduced % percentage of possible adverse effect of different formulations of sertaconazol. It is 0.5% per 100,000 patients. A total of 88.7%of these reported the adverse effect of the drug preparation of 2% cream and consisted exudation,urticaria,erythema,maculopapular rash,contact dermatitis,pruritus,burning,flush,wetting,vesication ,swelling pain,hyperpigmentation and also discoloration. The earlier discussed adverse effects are observed same after the application of other azole derivatively.

In vitro antifungal activity shown against the dermatophyte fungi,which produces infextion to the nails,higher than inhibitory concentration reached in the nails,are the basis for the development of a formulationfor the onchomycoses consisting patches that contain concentration of 1.65 mg/cm2 of sertaconazol.

Some topical antifungal agents are available for the treatment of superficial fungal infection, sertaconazol offers an antifungal activity that occurs at concentrations that reached and exceeded after topical administration. Dermal formulation of sertaconazol is retained for a long time in stratum corneum and other qualities of drug such as anti-inflammatory activity, antibacterial activity, good tolerance, safety profile are helpful for the management of mixed infections.

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