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TREATMENT OF SUPERFICIAL MYCOSES

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ABSTRACT:

Superficial fungal infection of the skin is treated with the help of systemic and topical medicaments. Commonly used drugs include griseofulvin, Ketoconazole and terbinafine. The drugs have undergone a wide research. In the following these drugs have been discussed.

INTRODUCTION

GRISEOFULVIN:

It is a metabolic product of *Penicillium griseofdvun* and other *Penicillium* species first described by Oxford *(1939).* It was not effective against bacteria so the topic was kept untouched. Brian *et al.* (1946) found a substance in *Penicilliun janczewski* which showed shrinking and stunting of fungal hyphae. This substance was named "Curling factor", later on it was found to be griseofulvin. Within ten years time this antibiotic was widely used in the treatment of fungal infections in plants, and ring worm of the cattle.

Gentles (1958) worked on fungal infections of the feet of Scottish miners and observed that griseofulvin cured experimentally produced mycotic diseases of guinae pig after that the drug became available for trials and was introduced to market.

General properties:

Griseofulvin forms massive colourless, rhombic crystals by slow deposition from ethanol MP 218-219 without decomposition, it is sparingly soluble in chloroform, ethylacetate, benzene, toulene, ethanol, acetone and dioxane. it is quite insoluble in water.

Metabolism of griseofulvin:

Barnes and Boothroyd (1961) worked on metabolism of griseofulvin by performing experiments on rabbit and rat.

Antifungal activity:

Gentles (1958) administered the drug orally to guinae pigs infected with *Trichophyton mentagrophytes* and resulted in to be markedly fungistatic to many fungi. Williams *et al.,* (1958) worked on griseofulvin and reported that its toxicity was very low. Blank *et al.* (1959) performed trials on 200 cases of superficial fungus infection and confirmed favourable observation. The species of *Trichophyton, Microsporum* and *Epidennophyton* responded well to this drug. Patients having nail involvement responded well where as lesions of the palms and soles cleared slowly.

Blanks (1965) considered it to be fungistatic and fungicidal in the light of biological activity. Growing cells of the fungi were killed and cells not growing were restrained. Accordingly the antibiotic was both fungistatic and fungicidal under the circumstances.

According to Blank and Roth (1959) concluded that mycoses caused by various species of dermatophytes showed uniform favourable response. *Malassezia fufur* and *Blastomycoses dermatitis* were not responding to the treatment. Goldfarb and Sulzberger (1960) after trial on different sites of the body infected by fungus showed that it needed 3-4 weeks to cure. Stevenson and Wahiszwile (1961) treated 50 patients of Onychomycosis *Trichophytone* ashram, according to them this treatment was unsatisfactory. Burgoon and Keiper (1961), showed useful results and inferred cent percent success. Anderson (1965) described in details the biology and clinical usefulness of giseofulvin. Biochemical analysis of human tissue griseofulvin to be concentrated in fat, liver, skeletal muscles, nail hair shaft and newly formed keratin in epidermis. Peak blood levels could reach between 4-5 hours. it was detected at the junction of stratum corneum and stratum mucosum 48-72 hours after daily dose of 1 g.

Toxicity:

Macleod and Nelson (1960) examined at weekly Intervals the semen of 22 human subjects who received 2g griseofulvin *every* day for six months and found no adverse effects. Alexander (1962) observed the lesions similar to lupus erythematosus and the effects included urticaria, angioneurotic edema, erythema multiforme, photosensitivity, Lichen planus, anorexia, nausea, vomitting, glossitis, angular stomatitis, headache, blurred vision, disorientation, virtigo, temporary leucopaenia, granulocytopaenia, thrust, fatigue and mailase. Osment (1969) described many effects of griseofulvin and it was also found to relieve spasm of peripheral arterial vessels. Coronary arteries of animals were found dilated.

Barich *et al.* (1962) described that griseofulvin was co-carcinogen to methyl cholantherene and tumors in mice when both the drugs given together. Paget and Walpole (1960 showed colchicine like effects in rats after intraperitoneal and intravenous administration.

Enzyme inducing effects:

Griseofulvin is an enzyme inducer. Hepatic microsomal enzyme is produced by the giseofulvin and it also stimulates metabolism of certain drugs. Griseofulvin may also alter prothrombin activity by inducing enzyme and so heparin is required to maintain the anticoagulant effect as described by Cullen and Catalano (1967).

Allen et al., (1973) performed an experimental study on griseofulvin in prevention of human dermatophytoses. In this trial 12 individuals were selected and a group of them was given prophylactic griseofulvin and another control group was given placebo. The results of the trial proved not much satisfactory outcome in the subject of griseofulvin as prophylactic measure. Priestly and Brown (1978) tested griseofulvin for its effects on morphology, proliferation and metabolism of fibroblast cultured from human skin and it was resulted that griseofulvin depressed proliferation. Beury *et al.,* (1982) reported two children suffering from epilepsy and were on phenobarbitone therapy. They were also having Tinea corporis and were taking long treatment. The disease was cured on discontinuation of phenobarbitone. It means that griseofulvin has metabolic interference with phenobarbitone.

Fungal resistance and comparison with other drugs:

Kidava and German (1981) performed an experimental study in which Gris Peg (an ultramicro crystalline solid state disperson of griseofulvin in polyethylene glycol) was compared with griseofulvin F.P. The Gris Peg formulation provides plasma levels of 1.6 ug/ml in four hours when administered to fasting adults as half the dose of micronize form.

Hay and Clayton (1982) treated patients with Ketoconazole who failed to respond to griseofulvin. Mitchell et al., (1973) performed experimental study and concluded that griseofulvin has immunosupressive effect in mice and in rats it leads to liver tumor formation.

Drug interaction:

Griseofulvin when administered on fatty diet gives better results as the study performed by Crounse (1961). Cullen and Cata la no (1967) mentioned that griseofulvin interfered with warferin but healthy volunteers had no effect on giving combination. Udall (1970) had decreased prothrombin time. It is suggestive that any patient taking anticogulant along with griseofulvin should be wached. Griseofulvin level falls down when given alongwith phenobarbitone as mentioned by Burns (1964). Jamali and Axelson (1978) performed study regarding interaction of phenobarbitone with griseofulvin Busfield *et al.,* (1964) experimented that animals who were previously fed on phenobarbitone and later on griseofulvin had low level of plasma griseofulvin may be due to increased rate of griseofulvin metabolism rather than impaired alimentary absorption. Efficacy of griseofulvin is reduced on taking it with phenobarbitone (Riegelman 1970).

Absorption distribution and excretion:

Platt (1970) concluded that griseofulvin can be given as a single oral dose without loosing efficacy. Shah a al., (1972) determined griseofulvin in skin, plasma and sweat. Epstein and Riegelman (1972) showed that griseofulvin level in stratum corneum can be dtected in eight hours. Knight (1974) worked on the activity of various topical preparations and appearance of oral griseofulvin in stratum corneum.

Preparation, route of administration and dosage:

Sande and Mandell (1980) recommonded daily oral dose as 10 mg/Kg for children and 500 mg-1g daily dose for adults.

Untoward effects of griseofulvin:

Untoward effects have been described by Nater and Groot (1983) as nausea, diarrhoea anorexia, vomiting, abdominal cramps, fatigue, dizziness, drowsiness, confusion, depression, irritability, insomnia, headache, impaired coordination, visual disturbances and peripheral neuritis.

On skin various types of rashes as cutaneous vasculitis, photosensitivity, fixed drug eruption, angioneuritic edema, porphyria like eruptions, and drug induced systemic lupus erythematosus have been reported. Griseofulvin interferes with porphyrin metabolism, oral symptoms include angular stomatitis, disturbance of

taste, glossodynia, black hairy tongue. In children it may produce estrogen like effects. Similar studies were done by Levan (1960), and Paget and Walpole (1960).

Demattis and Rimington (1963) performed experiments on animals and noted prompt rise of faecal excretion of protoporphyrin and coproporphyrin, survey was done by Rimington et al., (1963) about griseofulvin administration and porphyrin metabolism.

Delman and lenbuscher (1963) noticed transient macular edema due to griseofulvin therapy. Stegall (1963) reported severe reaction to griseofulvin. Hurst and Paget (1963) reported severe reaction to griseofulvin. Hurst and Paget (1963) gave griseofulvin to mice and noticed cirrhosis, hepatomata in the liver of mice. Redeker et al., (1964) *gave* griseofulvin to patients who had history *of* acute intermittent porphyria. The administration of griseofulvin was followed by marked increase of pyrrole excretion in urine. Chang (1965) described a case who developed early transient discrete macules. Fogan (1971) reported a case developing dysgeusia after griseofulvin administration. Hankin (1970 also admitted that griseofulvin may produce dysgeusia. Lastinic (1974) reported a case developing psychotic symptoms. Alexander (1962) noticed lupus erythematosus in two patients on griseofulvin. Chirput *et al.,* (1976) found intrahepatic cholestasis after griseofulvin therapy. Savage (1977) reported fixed drug eruptions to griseofulvin. Thyagarajan et al., (1981) reported another case of fixed drug eruptions after griseofulvin therapy.

Trial of griseofulvin indifferent diseases:

Griseofulvin has been tried in treatment of gout Wallace and Nissen (1062). It shows that griseofulvin has antiinflammatory effect. Cohen *et al.,* (1960) tried griseofulvin for treatment of shoulder hand syndrome. De Pasquale *et al.,* (1963) tried for angina pectoris Rubin (1963) performed experiments on dogs coronary blood flow and it was found increasing coronary blood flow. Charles et al.,(1970) noted subjective and objective improvement in 6 patients of raynauds disease on griseofulvin.

Hasker (1970) also tried griseofulvin in Raynauds disease and improvement was noted in three days time. Sehgal (1974) tried griseofulvin in herpes progenitalis with better results. Singh and Kamar (1977) treated five cases of moluscum contagiosum with griseofulvin. Massa and Rogers (1981) tried griseofulvin in therapy of Lichen planus. Sehgal *et al,* (1980) performed histopathological evolution of griseofulvin therapy in Lichen planus. Meyrick *et al,* (1983) treated patients of erosive Lichen

planus with griseofulvin. Giordano *et al.* (1980) treated a case of eosinophilic facilities with griseofulvin, clinical manifestations improved considerably. Thomson (1981) treated two cases of mycosis fungoides with tetracycline and griseofulvin. shelley (1981) also treated mycosis fungoides with demethyle tetracycline and griseofulvin. In vitro study was performed by Priestely and Brown (1981) and they noted that griseofulvin in vitro inhibitted the proliferation of scleroderma skin fibroblast.

Therapeutic uses:

Fungus diseases of the skin, hair and nail due to *Microsporum,Trichophyton* or *Epidermophyton,* the infection of hair caused by *M. canis, M.* audouni, *T. scoenleni, T. verrucosum,* ring worm of the glabrous skin, *Tinea cruris* and Tinea *corporis* caused by *M. canis T. rubrum, T. verrucosum. Tinea* of the hands and beard. it is also effective in atheletes foot and eidermophytosis involving skin and nails.

Symptomatic relief occurs within 48-96 hours. Treatment into he continued for 4 to 6 weeks. Duration of treatment depends upon the site of involvement, finger nails require long treatment nearly for 6 months because the growth of the finger nail is completed in 4 months and toe nail in 6 months, treatment for toe nail infection requires 6 to 12 months. Dose. 500 mg daily adult dose.

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Ketoconazole

Ketoconazole belongs to the imidazole group of antifungal compounds. The first substance developed was miconazole which appeared in the early 1970s, miconazole was the first broad spectrum antimycotic active agent against all pathogenic yeasts and other fungi. Ketoconazole has similar spectrum of activity, has advantages that it is active when taken orally.

It is suitable for the treatment of superficial fungal diseases those localized on the skin or mucous membrane. it is used for the treatment of tinea capitis, faints, pityriasis versicolour and candidal infections at various sites which include oral thrush, vaginal candidosis and chronic mucocutaneous candidiasis.

Mode of action:

Ketoconazole attacks fungal cells in a number of different ways. Even small concentration of Ketoconazole produces changes in the plasma membrane and cell walls of candida albieans when the fungus is in the budding yeast form. Growth of fungal hyphae is also prevented. At higher concentration Ketoconazole produces complete necrosis of the fungal cell contents. The changes take place are initially due to drug induced suppression of sterols that are essential for the maintenance of fungal cell membrane so cellular contents begin to leak out, fluid moves in and cell expand because of osmotic pressure. At higher concentrations the enzymes that break down hydrogen per oxide inside fungal cells are inhibited. The toxic peroxide accumulates and the cell contents are destroyed.

Pharmacokinetics:

After taking 200 mg tab the drug is absorbed from the first part of the duodenum and rapidly appears in blood stream. The absorption is greater when it is taken with or just before meal. it is widely distributed in the body, appears in liver, kidney and is also predent in more superficial subcutaneous regions and in a variety of glandular tissue. It is transported to stratum corneum through sweat, to hair and nails.

Side effects:

G.I.T disturbances, pruritus, nausea, and vomiting. It also acts by altering steroid synthesis in the fungal cell wall and therefore may show some effect on production

of human steroids such as testosterone, however the synthesis, readily recovers as described by Pont et al., (1982). Gynaecomastia and decrease in libido has also been reported.

Comparative study:

Hay and Clayton (1982) treated patients with Ketoconazole who failed to respond to griseofulvin therapy. this study shows the drug resistance to Ketoconazole. Hay *et al.,* (1985) *carried a* comparative double blind study of Ketoconazole and griseofulvin in dermatophytosis. Ketoconazole appeared to act more rapidly in curing Tinea corporis and griseofulvin was found superior in interdigital infections. Thiers (1988) described about Ketoconazole being effective in systemic treatment of dermatophtoses in addition in treatment of certain systemic fungal and yeast infections, however although Ketoconazole achieved cure rates against dermatophytes in excess of those reported with griseofulvin, its use was somewhat limited by the discovery of some rare incidence of hepatotoxicity as reported by Janssen (1983).

Dosage and administration:

Adults:

Vaginal candidosis: two tab (400 mg) once daily for 5 days. All other conditions:

One tab (200 mg) once daily untill atleast one week after the symptoms have disappeared. Usual duration given in the following.

Oral thrush 10 days.
Mycosis of the skin and hair 1 to 2 months.
Onychomycosis and chronic mucocutaneous candidosis 6 to 12 months.

Children:

Children upto 15 kg 1ml of oral drops (20 mg) three times adults. Children from 15 to 30 Kg 100 mg or 1/2 tab daily. Children above 30 Kg. 10 ml oral drops (200 mg or 1 tab daily).

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TERBINAFINE

Terbinafine is the drug used in the treatment of fungal infections. it is allylamine derivative (Petranyl *G et al,,* 1984). It interferes with the integrity of the cytoplasmic membrane of fungi by blocking membrane sterol synthesis (Ryder NS 1985) and accumulation of squalene in the fungi induces fungicidal action.

Terbinafine is effective in the treatment of superficial fungal infections and can be given both topically and orally.

Mode of action:

It is broad spectrum antifungal drug and is fungicidal against most organisms. It is non toxic to mammalian cell. It interferes with cytoplasm, membrane synthesis at an early step of sterol metabolism. it leads to marked accumulation of squalene within the fungi which in turn exerts a fungicidal effect and it is specific for fungal squalene epoxidase.

Pharmacokinetics:

1% cream applied to the skin, approximately 5% is absorbed into systemic circulation. On oral administration the drug is well absorbed, rapidly distributed to lipophilic tissue, slowly eliminated from tissue compartment, cimetidine inhibits its

metabolism and rifampicin induces its metabolism. It is concentrated in epidermis and subcutaneous fat tissue. It is rapidly carried to stratum corneum, nails and hairs through sebum.

Efficacy and tolerability:

Clinical studies have shown it to be having high degree of efficacy. Many skin conditions like Tinea corporis and Tinea pedis, cutaneous yeast infections, candidiasis and pityriasis versicolour infection of the skin appendages such as hair and nail. Topical application of 1% cream has been shown to be highly effective in short duration treatment.

According to trial performed by Evans (1993) to compare is efficacy with clotrimazole, it was found that Terbinafine is more effective. A double blind comparative study of the efficacy and tolerability of Terbinafine with itraconazole was done by Vora Vutinon (1993). In this study two weeks treatment with terbinafine at a dose of 250 mg/day is safe and is equally effective as four weeks use of itraconazole at a dose of 100 mg/day in treatment of tinea pedis.

Widyanto, *et al.,* (1993) performed double blind comparative study of terbinafine Vs griseofulvin in tinea pedis and concluded at the end of treatment, a complete cure was seen in 19 terbinafine treated patients out of 22, on the other hand a complete cure 21 patients was seen with griseohtivin and no adverse reaction was reported in each case. According to the study performed by Roa, *et al.,* (1993) terbinafine at a dose of 250 mg once daily is an effective safe and well tolerated drug in the treatment of extensive and chronic tinea corporis and cururis.

The study results demonstrated by Chang and Yang (1993). Oral Terbinafine is an effective and safe therapy for dermatophyte only chomycosis.

Overview:

Griseofulvin is the oldest of antifungal agents, it has made a new way in the treatment of dermatophytoses. Its contribution in the aspect of treatment of dermatophytes should note be understimated. For treatment of nail fungal infection long term therapy is required. A few interactions with other drugs have also been noted.

Ketoconazole was introduced in 1970, it was the first orally effective imidazole agent. Its spectrum of activity is broad and is effective against trichophyton, and microsporum and the yeast candida spp and m. furfur. It is active against certain others such as cryptococcus, pathogens, histoplasma and blastomyces implicated in deep mycosis. Although Ketoconazole gained importance in treatment of dermatophytes but its use was somewhat limited by the discovery of a rare incidence of hepatotoxicity.

Terbinafine:

It is a useful agent having potent activity against dermatophyte. It is effective in dermatophytosis, sporotrichosis, blastomycosis and histoplasmosis.

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