Oral Antifungals in Perspectives: from Petridish to Patients

Speaker: Dr. P. De Doncker

The therapeutic efficacy of antifungal agents depends on the spectrum of activity, bioavailability of drug and its availability at the site of infection. Different antifungals have their own mechanism of actions. Allylamines inhibit the conversion of squalene to squalene epoxide. After two weeks of allylamine, the drug can remain in the stratum corneum for about four weeks. The drug remains effective in the nail for up to six months after three months of treatment. Azoles inhibit the formation of ergosterol from lanosterol. The therapeutic level of itraconazole remains up to four weeks in the stratum corneum and nine months in the nail after one week and three months of treatment respectively. Pulse itraconazole of 400 mg daily can achieve fungicidal level. It is a breakthrough in the conventional antifungal treatment which is usually administered continuously.

The spectrum of antifungal activity varies slightly among different agents. Itraconazole, fluconazole and terbinafine are all effective against the dermatophytes. The two azoles are active against candidal infection of the skin, nail and mucosa. Terbinafine is not active against candidal infection of skin and mucous membrane and its results in candidal nail infection are controversial. Oral terbinafine is not effective in pityriasis versicolor whilst both itraconazole and fluconazole are active in this disease. In treating dermatophyte skin infection, such as tinea cruris or corporis, one week of itraconazole 200 mg daily is equivalent to two weeks of terbinafine 250 mg daily. Pulse itraconazole therapy is as effective as continuous terbinafine therapy.

Pulse therapy is more safe than continuous treatment. One in 500,000 develops symptomatic hepatitis in patients on pulse itraconazole but 1 in 54,000 in those on terbinafine. It is recommended that monthly liver function monitoring is necessary in both drugs when administered in continuous fashion. Liver function monitoring is not needed in pulse therapy. According to the reports in the literature, drug interaction is more common in the azole than terbinafine.

To date, new options of antifungal agents available include terbinafine, pulse itraconazole and Sunday pill for fluconazole. Usually three pulses of itraconazole is recommended for toe nail infection. However, if there is less than 50% improvement in the diseased nail, a fourth pulse could be given at sixth month. Combination treatment of terbinafine and itraconazole is now under investigation.

Learning points:
Three pulses of itraconazole is recommended for toe nail infection. If the clinical improvement is less than 50%, a fourth pulse could be given at sixth month.
Intermittent Pulse Therapy of Itraconazole in Onychomycosis: Local Experience in Hong Kong
Speaker: Dr. W. Y. M. Tang

This is a study conducted in the Social Hygiene Service to evaluate the efficacy of three weekly-pulses of daily 400 mg itraconazole in treating finger and/or toe nail onychomycosis. Previous studies had already demonstrated that continuous regimen of daily 200 mg itraconazole for three months was an effective way of treating onychomycosis but there may be a problem of drug compliance. Forty-four Hong Kong Chinese with 10 fingernail and 42 toenail onychomycoses diagnosed clinically and mycologically were recruited in this study. They were given three pulses of itraconazole with each pulse of 200 mg bd in the first week of three consecutive months. The progress was monitored by measuring the normal nail length from the proximal nail fold and the proportion of the diseased area of the target nail at week 0, 5, 9, 12, 24 and 36. Liver function tests were monitored both before and after treatment. The pathogens isolated were mostly dermatophytes (Trichophyton rubrum and mentagrophytes). The clinical cure rate, positive clinical response rate and mycological cure rate were 70%, 90% and 90% for fingernail onychomycosis; 35%, 81% and 68% for toenail onychomycosis. Five patients dropped out because of adverse effects or defaulted for unknown reason. The tolerability to treatment was rated as good or excellent. Minor side effects reported included epigastric pain, dyspepsia, diarrhoea and urticaria. No deranged liver function tests were detected at the end of treatment. It was concluded that pulse itraconazole therapy was an effective and safe treatment for both fingernail and toenail onychomycoses.

Erbium-Yag Laser Therapy
Speaker: Dr. R. S. C. Leung

Erbium-Yag laser is one of the new laser technology used in skin resurfacing. The mechanism of skin resurfacing includes regeneration of epidermis and dermis, collagen remodelling and shrinkage. Other resurfacing lasers include Ultrapulse, Nova pulse, silk-touch and feather-touch carbon dioxide lasers. Erbium-Yag laser has a wavelength of 2940 nm. It has the characteristics of precise depth control and less thermal necrosis, thus, wound healing is faster. Epidermal reepithelialization takes 7-14 days and dermal repair takes around 90 days. It causes less erythema, less pigmentation and the procedure requires less anesthesia.

Skin resurfacing is a potent stimulant of herpes simplex infection. To minimise the risk of herpes simplex infection, prophylactic antiviral agent can be given 24 hours preoperatively, such as Acyclovir 400 mg tds, Famiclovir 250 mg qd or Valaclovir 500 mg tds. Broad-spectrum antibiotics is prescribed on the day of operation to reduce bacterial infection. The preoperative use of topical retinoid to reduce pigmentation is still controversial. After resurfacing, mild non-greasy moisturiser should be used. Sunscreen and 1% hydrocortisone are prescribed to reduce the inflammatory reaction and sun-induced pigmentation. Post-operative hyperpigmentation occurs two to four weeks after the procedure. It affects dark skin person more than fair skin. Topical 2% to 4% eldoquin can be applied as prophylaxis after reepithelialization. More attention should be paid to postoperative erythema. Focal erythema indicates impending scarring which requires immediate action with topical steroid and/or silicone gel occlusion. Diffuse erythema usually represents normal reaction.

Learning points:
Local study in Social Hygiene Service evaluating forty-four patients also concluded that pulse itraconazole with 400mg daily for one week per month for three months was an effective and safe treatment for onychomycoses.
Syphilis: Revival of an Old Disease

Speaker: Dr. K. H. Lau

Syphilis: an Old Disease
Syphilis is a disease of more than 500 years old and it was believed to be acquired by Columbus' Spanish crew from the New World natives in 1490. The world-wide incidence of syphilis reached an all-time high during the World War II. With the introduction of penicillin, the incidence had decreased significantly. In Hong Kong, with the introduction of comprehensive control programme and penicillin treatment in late 1960's, the incidence of syphilis reported in Social Hygiene Service fell from around 1400 new cases per year during 1970's to the all-time low of around 300 cases in 1991. Congenital syphilis decreased from over 100 new cases annually in early 1970's to no reported cases in 1991.

Revival of Syphilis in its Early Infectious Forms
Recently, however, the Social Hygiene Service has witnessed a significant re-emergence of syphilis. From 1991 to 1997, the total incidence of the disease in the Service has increased more than two times (reported new cases increased from 310 in 1991 to 744 in 1997). This recent increase in incidence in syphilis was part of the general increasing trend in all sexually transmitted diseases seen in recent years in Hong Kong.

The majority of these new syphilitic patients in Social Hygiene Service suffered from early infectious syphilis: over the last six years, there has been a tremendous increase in primary syphilis of more than 14 times; a significant increase of secondary syphilis of six times; and a moderate increase of early latent syphilis of four times. Furthermore, congenital syphilis has reappeared in recent years.

Medico-social Causes for the Rise
There are numerous causes for the recent increase of syphilis in Hong Kong. The change of attitude and behaviour towards liberal sexual contact, the lack of public awareness towards the disease, the increasing population moving in and out of Hong Kong, and the presence of reservoirs of sexually transmitted disease around our territory are important social factors to account for the increase. Medical factors also play an important role in the rapid rise of syphilis. The inadequate awareness of syphilis among the unwary doctors, the inadequate resource on public health education on STD, as well as the inability of the STD service to reach the high risk groups (e.g. prostitutes and frequent travellers) all weakened the control of the disease. Various strategies dealing with these adverse medico-social factors are being implemented by the Government in hope of halting the rising trend of syphilis. However, the ultimate mean of control of the current problem depends on the cooperated effort among specialists working in the private and the public sectors.

Syphilis & HIV Infection
In USA, the rise of early infectious syphilis in early 1980's was met with a subsequent epidemic spread of HIV infection in late 80's. Various studies in USA had confirmed that genital ulcerative disease such as syphilitic chancre is an important co-factor for HIV infection. Local data in Social Hygiene Service has also confirmed the close association between the two diseases. Patients with positive syphilitic serologies had three times the risk of being co-infected with HIV, when compared with other STD patients whose VDRL were negative. In addition, almost one tenth of our HIV positive patients had concomitant syphilis. Almost half of these patients had early infectious syphilis. Whether we will face an epidemic rise of HIV infection in the coming year after the present increase of early infectious syphilis is an important issue which should be monitored very carefully. Although the direct extrapolation of the American experience to local population may not be totally feasible, we are encountering more and more patients who have syphilis as well as HIV infection. Managing syphilis in these HIV positive patients will definitely pose a great challenge to physicians and venereologists in the coming years.

Learning points:
The incidence of syphilis in Hong Kong has increased significantly as reflected by the two times increase of the annual incidence of the disease in Social Hygiene Service in the last six years. The majority of these new syphilitic patients suffered from early infectious syphilis.
Atopic eczema is a very common skin disorder which usually runs a protracted course, causes great discomforts and adversely affects the life of the patient.

**New Insight in Immunopathogenesis of Atopic Eczema**

In the symposium, various speakers gave a comprehensive overview of the most up-to-date advances in the immunopathogenesis and treatment of this common condition.

Dr. Cooper showed that the immune system of patients with atopy is tuned to respond to an antigenic challenge with a type 2(Th2) rather than with a type 1(Th1) T helper cell response. Type 2 response in these antigen-reactive T cells produce mainly IL-4, IL-5 and IL-10, which stimulate the humoral arm of immune system with antibody IgE production. Equilibration of this dysbalance with IFN-gamma or IL-2, which is an essential part of type 1 T helper cell response, can exhibit an inhibitory effect on type 2 response and thus may be a promising treatment strategy for such patients.

It is well recognized that increase in IgE is frequently associated with atopic disease and particularly pronounced in patients with skin manifestation as atopic eczema. As a result, the increase of IgE has all alone been regarded as a diagnostically helpful parameter only. Paradoxically, atopic eczema does not result from type I hypersensitivity reactions. The immunological response is rather similar to type IV immune response.

The new concept of a pathogenetic role of IgE in the aetiology of atopic eczema was introduced in the meeting. The theory began with an observation that the cutaneous antigen-presenting cells such as Langerhans cells and dermal dendritic cells of atopic individual frequently display anti-IgE reactivity. And in lesional skin, Langerhans cells and other dendritic antigen-presenting cells express surface-bound IgE. It is now clear that binding of monomeric and perhaps also, complexed IgE to these antigen presenting cells mainly occurs via their high affinity IgE receptor FcεR1. Dr Maurer showed that antigens and allergens are much more efficiently processed and presented to T cells when taken up by these IgE bound antigen presenting cells. The enhanced allergen or antigen presentation to T cells greatly amplified the subsequent Th2 response seen in patient with atopic eczema. In vivo, this FcεR1- IgE-facilitated allergen presentation may critically lower atopic individuals' threshold to mount allergen-specific T cell responses and thus, be responsible for the perpetuation of the disease.

These serum IgE-defined exogenous protein are not always the main disease precipitating allergen. Recent observation found that patients with atopic dermatitis have serum IgE against, not only exogenous allergens, but also self proteins. A newly defined cytoplasmic protein, Ara 1, has been very recently characterized as the autoantigen targeted by IgE in atopic eczema. This suggests that autoimmunity is a major component of allergic tissue inflammation in atopic individuals. Hence, scratching in atopic eczematous patients, on the one hand, introduces exogenous allergen into antigen presenting cells in skin, and on the other hand, disrupts some epidermal keratinocytes, releasing Ara 1 autoantigen. In this way, two feedback loops are established which perpetuate the inflammation.
**New Investigation in Atopic Eczema**

IgE-facilitated allergen presentation may also be operative in the newly introduced investigative procedure in patients with atopic eczema: Atopy Patch Test. Dr. Ring demonstrated that aeroallergens such as pollen and house dust mite best prepared in petrolatum base, applied under occlusive conditions on tape-stripped non-lesional skin during period of disease remission, can elicit delayed-type hypersensitivity reactions. This is introduced as a clinical method of evaluating the relevance of IgE-mediated sensitization due to exogenous allergen in patients with atopic eczema. Avoidance strategy of the identified allergen, such as house dust mite, becomes a very important step in managing those patients who are atopy patch test positive.

**New Treatment Modalities**

The symposium concluded by presentations of Drs. Reitamo and Van Leent's results on the use of topically applied immunosuppressive macrolides which may provide an effective therapeutic alternative to the conventional corticosteroids treatment.

Topical Tacrolimus (FK506) ointment was first used to treat patients with atopic eczema in 1994. Dr. Reitamo shared his experience on this new form of topical treatment. The action of the drug is similar to cyclosporin which blocks the inflammatory cytokines production. Clinical improvement is noticed as early as three days after treatment, with a maximum response seen after one week of treatment. Concentration of 0.3% topical tacrolimus shows better response than the weaker strength of 0.03%. The topical treatment is also effective in treating atopic eczema in children, even in lichenified forms involving the flexure. No serious side effect was reported except the significant increase of local burning, especially in first and second day of treatment. Systemic absorption of tacrolimus did not reach therapeutic concentration, hence no systemic immunosuppressive effect was noted. The absence of skin atrophy, in particular, may make this new form of treatment a good alternative to topical steroids.

Another emerging anti-inflammatory drug introduced by Dr. Van Leent is SDZ ASM 981 (Ascomycin). The drug is a macrolactam derivative. A recent study comparing topical 1% ascomycin with vehicles in the treatment of atopic eczema for a period of three weeks showed a 37.7% of improvement on once daily regime. Clinical improvement rose to 71.9% in twice daily regime. Only very low concentration of ascomycin was detectable in patients' serum which had no clinical effect. No serious side effects were reported except the feeling of warmth or burning, occasional folliculitis and dry skin.

**Learning points:**
The use of topically applied immunosuppressive such as topical Tacrolimus & SDZ ASM 981 may provide an effective therapeutic alternative to the conventional corticosteroids treatment in the management of atopic dematitis.
Scientific Meetings

New Insight in Immunopathogenesis & Clinical Features of Leprosy

The clinical features of leprosy can be boiled down to the presence of anaesthetic skin lesions, thickened nerves and the demonstration of bacilli in these lesions. This clinical spectrum of leprosy is now redefined in the light of immunopathogenesis and various cytokine profile: M. leprae detected in the body are presented to T helper cell by the antigen presenting cells through HLA class II epitope. The subsequent T helper cell response is predominantly a type 2 response with the production of IFN-gamma and TNF-beta. It is believed that the degree of this type 2 T helper response in relation to the type 1 T helper response determines the position in the clinical spectrum at which the patient stands. In tuberculoid end, the type 2 Th response predominant while type 1 Th response prevails in lepromatous end of leprosy. In addition, host susceptibility to M. leprae infection has been clarified by genetic studies. Tuberculoid leprosy has been linked with HLA DR2 &3, while lepromatous leprosy associated with HLA DQ1. The clinical manifestation of neuropathy is believed to be due to immunological damage targeting to Laminin alpha 2 in neural tissue. The whole genome sequence of M. leprae has almost been worked out completely. With a better understanding of the organism from the point of view of its DNA blueprint and subsequent protein makeup, a new area of research is opened: the development of possible vaccine and serological tests basing on the immunological response to the antigenic component of the organism.

Advance in Treatment

Treatment of leprosy has greatly affected the prevalence of the disease. The latest figure (June 1997) from WHO shows that the number of leprosy patients registered for chemotherapy has fallen from 5.4 million in 1985 to 0.88 million. One of the reasons for the dramatic fall in the number of patients over the past three years is the result of the cleaning up of old registers and also because many countries have adopted fixed duration chemotherapy. The global coverage of multidrug therapy (MDT) is currently about 97%. The information available from a number of WHO control programme for the Elimination of Leprosy shows that the relapse rate is very low (0.1% per year for paucibacillary and 0.06% per year for multibacillary leprosy on average).

Recently four more new drugs have shown bactericidal activity against M. leprae. These are sparfloxacina and ofloxacin (fluoroquinolones), minocycline (a tetracycline) and clarithromycin (a macrolide). Several experimental and clinical studies have demonstrated that these drugs either alone or in combination with other antileprosy drugs have significant bactericidal activity. Furthermore, synthetic drug in the form of an analogue to thalidomide is being developed. This drug shows similar anti-TNF and T cell stimulating activity as thalidomide does, but hopefully the bio-engineered chemical structure can dissociate its therapeutic effects from the side effect of tetratogenicity as seen in thalidomide. Hopefully, the recent molecular advance in understanding of M. leprae and the improved effectiveness of chemotherapy against leprosy may achieve the goal of eliminating leprosy as a public health problem by the year 2000.

Learning points:
Sparfloxacina, ofloxacin, minocycline & clarithromycin have demonstrated significant bactericidal activity against M. leprae & can be used alone or in combination with other anti-leprosy drugs.

Leprosy in the Year 2000
Speakers: Dr. K. P. W. J. McAdam & P. Sampoonachot

According to the report by the WHO at the beginning of June 1997, there were 1,150,000 estimated cases of leprosy in the world. Over half of the leprosy patients were in SE Asia. More than 85% of all registered cases are found in 6 countries: India, Brazil, Indonesia, Myanmar, Nigeria and Bangladesh. Although there has been a global decline in the number of case of leprosy, there are still countries in which the control of leprosy is suboptimal. The number of case in Bangladesh is increasing while that in India and Phillipines static. The number of case in China is decreasing. On the other hand, the global incidence of new case showed no similar decrease as the general trend, but remained static.
Acne formation is a multi-factorial and complex process. During puberty, the augmented secretion of male sex hormone increases sebum secretion from the pilosebaceous units, which sets the stage for acne formation.

The Propionibacterium acnes colonizing the pilosebaceous ducts converts the sebum into irritant and comedogenic free fatty acids. These substances are chemotactic for inflammatory cells and induce the release of cytokines causing the inflammatory reaction.

Failure of the epidermis lining the follicular duct to keratinize properly leads to hypercornification at the poral opening, thus blocks the secretion from the pilosebaceous ducts and further aggravates the process.

The enlarged follicular lumen containing the inspissated keratin and lipid debris forms the clinical whitehead (closed comedome). When its content is released through the poral opening, it forms the blackhead (open comedone). On the other hand, its content may break into the dermis, provoking a foreign body response, forming the inflammatory papules, pustules and nodules of acne.

Topical treatment of acne vulgaris comprises two main categories of drugs: the comedolytic agents and the anti-bacterial agent.

Retinoids are comedolytic agents, that significantly reverse abnormal follicular differentiation, enhance epithelial cell turnover, and decrease cohesion of keratinized cells. Tretinoin, one of the earliest retinoids, suffers from the drawback of causing local irritation, erythema and pustular flaring of the acne in the early stage of treatment.

Recently a new agent, Adapalene was introduced. It differs from the previous retinoids in that it is a naphthoic acid derivative with potent retinoid-like pharmacological activity, but with increased chemical and light stability. Unlike tretinoin which binds to cytosolic retinoic acid-binding proteins and nuclear retinoic acid receptors (RAR), Adapalene has a characteristic binding profile. It binds very poorly to RAR alpha but exhibits good affinity for RAR beta and gamma. The selectivity of adapalene for RAR gamma is likely associated with activity in the terminal differentiation process. It also rapidly penetrates the pilosebaceous units when applied topically. According to a US multicenter study, it was equally effective as tretinoin but caused less dryness, scaliness, erythema and burning sensation. It can either be used as monotherapy or in combination with topical anti-bacterial agent.

The second group of topical agent comprises the anti-bacterial agent: the benzoyl peroxide and topical antibiotics.

Benzoyl peroxide, being an anti-bacterial agent, has an addition anti-inflammatory action. However, irritancy and bleaching of skin are its main drawbacks. Topical erythromycin and clindamycin are less effective than benzoyl peroxide in inhibiting P. acne, yet they are less irritant. Recently, the development of resistant strain of P. acnes to these topical agents is of concern.

**Learning points:**
For those who require topical Retinoids and yet are unable to tolerate its side effects, Adapalene may be tried as monotherapy or in combination with anti-bacterial agent.
In the first part of the meeting, Dr. John Berth-Jones discussed on the use, efficacy and safety of cyclosporin A microemulsion in the treatment of moderate and severe atopic dermatitis and psoriasis. He had conducted various studies on these aspects, and had found that cyclosporin A was very effective and had an excellent safety profile. The drug was used at a dosage ranging from 2.5mg to 5mg/kg/day.

In his study on severe atopic dermatitis, disease activity was monitored using the six-areas (head and neck, trunk, hands, feet, arms, legs), six-signs (erythema, exudation, excoriation, dryness, cracking, lichenification) score. Pruritus and sleep disturbance were assessed using four-point scales. Cyclosporin A was found to produce rapid and highly significant improvement in all indices of disease activity. Blood pressure and serum creatinine tend to increase slightly with cyclosporin A, but the increase tends to be mild, seldom requiring withdrawal of the drug, and these parameters all return to the baseline level after discontinuation of the drug. However, most patients relapsed after cessation of treatment, but in his experience there was no rebound. He had noted a small number of patients actually did go into remission of their atopic dermatitis after treatment with cyclosporin A, raising the possibility that the drug might modify the natural history of the disease, although it remained debatable as some patients would go into natural remission even after treatment with placebo. The results indicate that cyclosporin has a place in the long-term treatment of severe atopic dermatitis provided that appropriate patients are selected and careful monitoring is performed.

Cyclosporin has also been used for treatment of severe psoriasis for more than 13 years, and the clinical efficacy has been confirmed. The drug is found to be beneficial to all aspects of this disease. Dr. Jones had studied on the use of continuous against intermittent short course of cyclosporin A in treatment of psoriasis vulgaris. Both modalities of treatment were found to be effective. With continuous treatment, the efficacy tends to be marginally better. With intermittent short course treatment, there were statistically significant increases in mean serum creatinine and blood pressure, but which did not rise after further successive treatment periods, and these parameters returned to their baseline levels after the drug was discontinued. The overall drug dosage consumption tends to be less. He concluded that intermittent short courses of cyclosporin may be the more appropriate approach to treatment of psoriasis. According to the speaker, there is no satisfactory predictive factor as to which group of patients will be less responsive to cyclosporin therapy or who will relapse quicker after treatment.

In the second part of the meeting, Dr. Henry Ho shared with the audience the local experience of using cyclosporin A microemulsion in the treatment of patients with severe atopic dermatitis. The study was an open trial conducted in three Social Hygiene Clinics. Twenty-six patients were studied. They received Cyclosporin A for a period of eight weeks at a dosage between 3-5mg/kg/day, and were put on a further four
weeks reduction period at half of the maximum dose. The drug was then stopped and the patients were observed for a further eight weeks. Significant improvements were seen in the extent of the disease, the disease severity, pruritus and sleep disturbance during the study period. Overall the drug was well tolerated except in one patient whose serum creatinine level was raised by 42% at week 12, which returned to the baseline level shortly after the drug was stopped. As seen in Dr. Jones' patients, relapse was commonly seen shortly after cessation of treatment. Dr. Ho concluded that short course treatment with cyclosporin A microemulsion was fast acting and effective for severe refractory atopic dermatitis in adolescents and adults. However relapse occurs commonly after 12 weeks treatment. Side effects do occur and close monitoring according to guidelines is mandatory.

**Learning points:**
Local study also showed that short course treatment with cyclosporin A microemulsion was fast acting and effective for severe refractory atopic dermatitis in adolescents & adults. But relapse after treatment occurs commonly.