

Editorial/Van die Redaksie

Ketoconazole and systemic mycoses

Ketoconazole (Nizoral; Janssen) is the most recent imidazole derivative to be introduced as an antifungal agent, and differs from others in being readily absorbed when given by mouth. It has already established itself as an effective treatment for the dermatophytoses and for candidiasis,¹ but recently interest has been focused on the more severe fungal infections.

Patients with chronic mucocutaneous candidiasis have persistent or recurrent candidial infections of the mucous membranes, skin and nails and often show impaired cell-mediated immunity, so that they are difficult to treat. In a double-blind controlled trial by Petersen *et al.*,² 12 of these patients were given a 6-month course of either ketoconazole (usually 200 mg by mouth daily) or a placebo. Results were greatly in favour of ketoconazole, almost all symptoms and signs disappearing. No patient on ketoconazole had any oral lesions left after 6 months, although 1 had positive oral cultures for *Candida*. All skin lesions improved greatly, nail lesions less rapidly; again there were occasional isolations of *Candida*.

A more serious systemic disorder is disseminated coccidioidomycosis, in which there are skin lesions, soft-tissue abscesses, osteomyelitis and miliary pulmonary disease due to the fungus *Coccidioides immitis*.

Two clinical trials of ketoconazole in this disorder were published last year.^{3,4} Catanzaro *et al.*³ treated 29 patients with disseminated coccidioidomycosis for at least 6 months with 200 - 600 mg ketoconazole daily. Results were hard to assess but objective improvement was noted in 7 of 8 cases of synovitis, 3 of 8 cases of osteomyelitis, 8 of 10 cases of soft-tissue abscess, and 6 of 9 cases of skin lesions. The authors called for a comparative clinical trial of the drug with amphotericin B and miconazole, but so far none has been published. Ross *et al.*⁴ treated 21 patients with chronic pulmonary coccidioidomycosis, a very difficult condition to manage, and found clinical and objective signs of improvement even in cases of chronic cavitory disease (9 out of 16).

This year has seen the publication of a collaborative study of treatment of systemic mycoses with ketoconazole under the auspices of the US National Institute of Allergy and Infectious Diseases.⁵ Altogether 52 patients were collected from a number of centres in the USA, including cases of blastomycosis, non-meningeal coccidioidomycosis, histoplasmosis, non-meningeal cryptococcosis and sporotrichosis. Patients received doses of 200

mg/d, stepped up where necessary to 400 mg/d and later 600 mg/d, and the investigators claimed cure or marked improvement in 27 out of the 52. The duration of therapy ranged from 1 month to 22 months, and the effect was most obvious in histoplasmosis and non-meningeal cryptococcosis.

The authors claim that ketoconazole shows promise as an effective alternative to amphotericin but point out that it is a fungistatic rather than a fungicidal agent, as shown by the frequent relapses which occur after apparent cure or improvement, especially after discontinuation of the drug. Unfortunately, results cannot be predicted from *in vitro* studies of susceptibility of the micro-organism, nor can failure or relapse be attributed to resistance to the agent.

This study can only be regarded as a preliminary to in-depth studies, and it has come in for criticism on a number of points in an editorial by Hoepfich.⁶

In general, one pleasing feature of these studies of systemic mycoses has been the comparative rarity of side-effects, the commonest being nausea, vomiting or anorexia, although serious adverse effects have been signalled in other studies. In the *FDA Drug Bulletin*⁷ last year, a warning was issued about the hepatotoxic potential of ketoconazole. Three cases of fatal, massive hepatic necrosis and 20 cases of liver damage had been reported, but in the studies mentioned above the only effect on liver function seems to have been an occasional elevation of levels of such liver enzymes as aspartate transaminase in the serum. Gynaecomastia has developed in some men treated with ketoconazole, and Pont *et al.*⁸ reported inhibition of cortisol response to adrenocorticotrophic hormone in some healthy volunteers, suggesting that the drug blocks steroid synthesis.

To sum up, while the efficacy of ketoconazole in treating the commoner fungal infections of the skin has been amply demonstrated and its toxicity is in general low, the place of the drug in the treatment of the dangerous systemic mycoses has yet to be established, as has its place in the prevention of fungal infections in immunocompromised patients. In a British trial it certainly gave significantly greater protection against fungal disease than a combination of oral amphotericin B plus nystatin in 72 severely immunocompromised patients who had not had transplants.⁹

1. Levine HB. *Ketoconazole in the Management of Fungal Diseases*. Auckland: Adis Press, 1981.
2. Petersen EA, Alling DW, Kirkpatrick CH. Treatment of chronic mucocutaneous candidiasis with ketoconazole: a controlled clinical trial. *Ann Intern Med* 1980; **93**: 791-795.
3. Catanzaro A, Einstein H, Levin B *et al*. Ketoconazole for treatment of disseminated coccidioidomycosis. *Ann Intern Med* 1982; **96**: 436-440.
4. Ross JB, Levine B, Catanzaro A *et al*. Ketoconazole for treatment of chronic pulmonary coccidioidomycosis. *Ann Intern Med* 1982; **96**: 440-443.
5. Dismukes WE, Stamm AM, Graybill JR *et al*. Treatment of systemic mycoses with ketoconazole: emphasis on toxicity and clinical response in 52 patients. *Ann Intern Med* 1983; **98**: 13-20.
6. Hoepflich PD. Ketoconazole in systemic mycoses. *Ann Intern Med* 1983; **98**: 105.
7. Anon. Hepatotoxic potential of ketoconazole under investigation. *FDA Drug Bull* 1982; **12**: 11-12.
8. Pont A, Williams PL, Loose DS *et al*. Ketoconazole blocks adrenal steroid synthesis. *Ann Intern Med* 1982; **97**: 370-372.
9. Hann IM, Prentice HG, Corringham R *et al*. Ketoconazole versus nystatin plus amphotericin B for fungal prophylaxis in severely immunocompromised patients. *Lancet* 1982; **ii**: 826-829.

Wat het van mediese geheimhouding geword?

Wanneer daar oor mediese geheimhouding of mediese vertroulikheid gepraat word, gaan 'n mens se gedagtes onwillekeurig terug na die welbekende paragraaf in die Hippokratiese eed. Maar is hierdie paragraaf nie in die praktyk al net so uitgediend soos ander bepalings nie, soos bv. dié aangaande die seuns van jou leermeester wat jy as jou broers sal beskou, of dat jy nie 'n aborsie mag bemiddel nie, of selfs om 'kuis en godsdienstig' in praktyk te wees nie?

Die Britse Mediese Vereniging is tans besig om oor 'n klousule in die voorgestelde Polisie en Kriminele Getuienis-wetsontwerp te protesteer wat blykbaar aan houe die reg verleen om dokters te dwing om vertroulike mediese inligting aan die polisie te verskaf, ongeag of die pasiënt voorheen skuldig bevind is. Dit is net nóg 'n byvoegsel tot die baie maniere waarop die Britse pasiënt se versoek dat sy vertroulike mededelings gerespekteer sal word, in die afgelope paar jare geskaad is deur die onversadigbare passie van die burokrasie vir rekordhou, die groeiende skakel tussen mediese en sosiale dienste, en die toenemende behoefte aan spanwerk in geneeskunde.

Menings verskil wat die kwesbaarheid van gerekenariseerde verslae aanbetref. 'n BMV-beplannings-eenheid meen dat hierdie verslagsisteme veiliger is as ouer sisteme, maar die Wêreld Mediese Vereniging is gedurig bekommerd oor die vertroulikheid van gerekenariseerde verslae sedert hulle in 1973 'n besluit daaromtrent aangeneem het.

Maar in the meeste menslike aangeleenthede word die geheime deur die dokters self uitgelap, en dit lyk inderdaad asof dokters deesdae meer geneig is om hulle pasiënte se sake te verkondig as vroeër. Wyle Lord Moran het die toon aangegee toe hy 'n breedvoerige relaas oor sy mees vernaam pasiënt, Winston Churchill, geskryf het en gevolglik daartoe aanleiding gegee het dat mediese verenigings 'n klousule tot die etiese kodes bygevoeg het wat bepaal het dat geheimhouding nie met 'n pasiënt se dood eindig nie.

Sedertdien word ons gereelde slae toegedien deurdat uitvoerige beskrywings van die mediese behandeling van pasiënte (waarvan sommige vernaam is en ander slegs bekendheid verwerf het as gevolg van 'n nuwe lyn van behandeling) gegee word. Daar word gewoonlik aangevoer en gearchumenteer dat hierdie publisiteit (met sy gepaardgaande perskonferensies en televisie-

verskynings) in die publiek se belang is, maar dieselfde argument is al aangevoer om publieke teregstellings te regverdig.

In die lig hiervan, klink 'n onlangse artikel deur 'n Switserse advokaat, professor H. Schultz,¹ oor die regte van die pasiënt, eg Viktoriaans. Hy voer aan dat die Switserse wet (en Franse ook, sover dit aangaan) bepaal dat mediese geheimhouding ook op kollegas van toepassing is. Dit is, om die waarheid te sê, onwettig in sekere lande om 'n pasiënt se mediese geheime met 'n kollega te bespreek sonder die pasiënt se toestemming. Die feit dat almal deur dieselfde geheimhoudingskode gebind is, maak nie hierdie feit ongeldig nie. Die pasiënt maak nie die inligting aan die hele profesie bekend nie, maar slegs aan 'n lid daarvan. Volgens Switserse wet kan die verslae van pasiënte vir navorsing gebruik word, maar slegs as die pasiënt self nie geïdentifiseer word nie.

Die dokter kan ook slegs gegewens aangaande 'n pasiënt aan 'n wetenskaplike vergadering bekend maak mits die pasiënt anoniem en onidentifiseerbaar bly. Per slot van rekening, nie alle wetenskaplike vergaderings word deur slegs dokters bygewoon nie. In Switserland kan 'n pasiënt op wie se privaatheid daar inbreuk gemaak is deur 'n skending van hierdie vereistes, 'n klag aanhangig maak teen die oortredende dokter. Daar kan selfs 'n kriminele aksie teen die skuldige dokter ingestel word vir skending van geheimhouding.

Sommige mag dink dat hierdie tipe wetgewing heeltemal uit pas is met moderne mediese praktykvoering, maar is dit regtig? Klaarblyklik is die Switserse pasiënte tevrede daarmee om die wet net so te laat bly soos dit is.

Die Suid-Afrikaanse wet is minder onbuigsaam, maar dit verleen nogtans 'n groot mate van beskerming aan die pasiënt in hierdie opsig, soos ook die Etiese Gedragsreëls wat deur die Suid-Afrikaanse Geneeskundige en Tandheelkundige Raad uitgevaardig is. Daar is egter 'n sekere mate van buigsaamheid in die bewoording van Reël 16 waarin die dokter verbied word om 'mondeling of skriftelik enige inligting aangaande 'n pasiënt se siekte bekend te maak indien hierdie besonderhede *nie geopenbaar behoort te word nie*, behalwe as sodanige bekendmaking met die toestemming van die pasiënt of sy voog geskied'. Die vryspringgedeelte '*nie geopenbaar behoort te word nie*' dek natuurlik enige statutêre verpligtings om inligting bekend te maak. Vir 'n

gedetailleerde bespreking van die implikasies behoort lesers die standaardwerk van Masters en Shapiro² oor mediese geheimhouding te raadpleeg.

Bogenoemde vryspringgedeelte kan nouliks as 'n regverdiging vir sommige van die verhoogkunsbenaderings tot pasiënt-behandeling waarop ons die afgelope paar jare vergas word, geïnterpreteer word.

Of kan dit? Wil die publiek hê ons moet in die openbaar

oor hulle siektes en behandelings praat? En is die Switsers en Franse net 'n klomp ou vitsiekes? Alles is 'n bietjie verwarrend.

1. Schultz H. Droits des personnes et démonstrations avec des patients. *Schweiz Aerztezeitung* 1983; **64**: 165.
2. Masters NC, Shapiro HA. *Medical Secrecy and the Doctor-Patient Relationship*. Cape Town: A A Balkema, 1966.

News and Comment/Nuus en Kommentaar

The water babies

From Texas comes the news that babies held upside-down in water can drown (*Tex Med* 1982; **78**: 6). This blinding glimpse of the self-evident was nearly tragically proved correct by a mother who took her 6-month-old baby to a 'water baby' course designed to teach infants to swim, part of which involves blowing in the baby's face, holding him upside down in the water by the heels and then releasing him in the hope that he will learn to swim by paddling back to the surface. Mothers are warned that during this manoeuvre, not surprisingly, babies will swallow a great deal of water and may urinate more profusely afterwards. In the case described, the baby swallowed so much water that he became hyponatraemic, which produced respiratory arrest and epileptiform seizures. Luckily, he survived.

Systemic effects of eye drops

Very few warnings have appeared in the literature about toxic effects of eye drops or ointments, and few doctors consider systemic absorption of eye drops as a possible cause for unexplained cardiovascular, pulmonary, autonomic or central nervous system dysfunction.

Yet systemic reactions do occur, as Adler *et al.* (*Arch Intern Med* 1982; **142**: 2293) point out, and a national registry of possible drug-induced ocular side-effects in the USA is currently collecting information on these.

For example, a drop of 2% adrenaline solution in each eye could result in the introduction of over 2,5 mg adrenaline into the conjunctival sac; with 10% absorption, a dose of 0,2 - 0,3 mg could reach the circulation and produce cardiac effects. The registry mentioned above has details of 33 cases of adverse effects from 10% phenylephrine eye drops, including 15 myocardial infarctions (11 fatal) as well as severe hypertensive reactions (diabetics with autonomic neuropathy or patients on reserpine or guanethidine are particularly at risk).

Serious cardiopulmonary adverse reactions such as acute bronchospasm, congestive cardiac failure or syncope have been recorded after the use of timolol eyedrops for glaucoma, while topical pilocarpine has caused severe symptoms (vomiting, colic, diarrhoea, and respiratory distress).

The anticholinesterase agents used in treatment of primary open-angle glaucoma may also cause colic, diarrhoea, sweating and weakness through accumulation of acetylcholine, and ecotiopate drops even caused a cardiac arrest. Symptoms may be delayed for days or weeks and the doctor may fail to connect them with the therapy.

Topical atropine, particularly in children, has led to alarming CNS reactions with confusion, hallucinations and dysarthria, and another anticholinergic agent, cyclopentolate, has caused severe symptoms including mental deterioration. Among a miscellany of toxic reactions, one must not forget bone marrow aplasia after prolonged use of chloramphenicol eye drops, and suppression of plasma cortisol levels by steroid eye drops.

Doctors are now well aware of the need to enquire about drug ingestion if peculiar symptoms appear; don't forget that eye drops are also a possible cause.

Coagulopathy associated with moxalactam

Moxalactam is a new β -lactam antibiotic with a broad spectrum of action, and considered by some to be a third-generation cephalosporin. Other broad-spectrum antibiotics have been known to deplete body stores of vitamin K and thus interfere with blood coagulation, and it now seems that moxalactam must be added to the list. Pakter *et al.* (*JAMA* 1982; **248**: 1100) report 2 cases of postoperative abdominal infection treated with intravenous moxalactam in which a coagulopathy developed with hypoprothrombinaemia. This yielded rapidly to vitamin K administration, and the manufacturers recommend prophylactic use of supplemental vitamin K whenever moxalactam is used, especially in debilitated patients.

The empty chair syndrome

According to the American Dental Association, it seems that American dentists are suffering from the empty chair syndrome (*AMA News*, 26 November 1982, p. 3). In other words, they are doing what doctors should be aiming at, namely working themselves out of jobs. While dental school enrolment has fallen, the actual number of dentists will increase for some years, and there is not enough work for them.

Demands for dental services have decreased, partly because of the recession, partly because the widespread fluoridation of water supplies in the USA instituted some 20 years ago seems to be having a remarkable effect on caries rates, as is the emphasis on preventive dentistry and the advent of more and more hygienists.

Yet services to the elderly and the rural poor remain inadequate, while more dentists are turning to specialties, foremost being oral and maxillofacial surgery and orthodontics. In true American fashion, the dentists are now organizing to advertise and market their services.