TODAY'S DRUGS

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Griseofulvin

This drug is marketed by Glaxo Laboratories under the name Grisovin and by I.C.I. Ltd. under the name Fulcin-Forte.

History

Griseofulvin, a metabolic product of a mould, was discovered in 1939 in England by Oxford, Raisinick, and Simonart. In 1947 Brian and Grove and McGowan showed it was responsible for a curling action on certain fungi, and it was found to be effective in protecting plants from fungal infection. After another 10 years Gentles showed that oral griseofulvin was effective in the treatment of experimental ringworm infections in guinea-pigs, and Williams, Marten, and Sarkany reported its successful use in superficial fungus infection in man. Griseofulvin has since become very widely used and has represented a major breakthrough in the management of various types of ringworm infection. More and more information about its action and use is being learnt, and it is useful at this stage to reassess its value.

Pharmacology

The molecular formula is C₃₁H₄₁O₁₃Cl. The drug is insoluble in water but slightly soluble in various organic solvents. Its fluorescent properties are utilized in quantitative measurements.

In vitro, griseofulvin is active against all ringworm fungi, but it has little or no effect on bacteria, candida, Malassezia furfur, aspergillii, and other fungi included in the group of deep mycoses. Its action is to impair the normal development of terminal hyphae, producing distortion and curling. Although fungicidal, its main effect is fungistatic. Griseofulvin does not diffuse through the stratum corneum but moves out with the cells from the prickle layer. Fungus can no longer grow on keratin which has developed while the patient is on an adequate dose of griseofulvin. As the drug does not destroy fungus growing in the outer layers of keratin, cure is obtained only when the particular keratin structure infected has completely grown out. Thus the treatment time will be 3 to 4 weeks for skin, 6 to 8 weeks for hair, and 6 to 18 months for nails. Resistance of various fungi to griseofulvin has been demonstrated, but it is very uncommon and usually not complete.

Griseofulvin is absorbed from the gastrointestinal tract, and the blood levels in patients have shown considerable variation after a standard dose. When the drug has been administered after a meal with a high fat content the serum levels may be double those obtained with controls. In recent years it has been shown that barbiturates administered at the same time reduce considerably the effect of griseofulvin, perhaps because the barbiturate stimulates destructive chemical processes in the liver which are also active against griseofulvin. This is an important consideration, as barbiturates may well be given to patients on prolonged courses of griseofulvin, when the effect of the drug will be reduced. The fine particle preparation is absorbed more readily and allows the required dosage to be halved. Although the fine particle preparation has superseded the older form of griseofulvin, the latter is still available as tablets of 250 mg., and confusion has arisen. Unless otherwise stated in a prescription the fine particle preparation is dispensed. Divided doses maintain higher blood levels, and for adults the common dose scheduled is 250 mg. (two tablets) twice per day. Some authorities recommend twice the dose, and this could certainly be used in the treatment of severe ringworm, or when there is a possibility of partial resistance or poor absorption. The relative amount of griseofulvin required for children is higher, and 125 mg. (one tablet) twice per day is required in most cases. A number of special dosage schemes have been tried. A single large dose such as 2 to 3 g. in children has been successfully used in microsporum infections of the scalp, and a once-weekly dose has also been found to be effective. However, it seems that a more certain response is obtained by the usual twice-daily administration.

There have been a number of trials of griseofulvin and its newer analogues applied topically, but these have shown that it has little or no value in the treatment of human ringworm.

Side-effects and Toxic Reactions

Remarkably few side-effects have been reported. Urticarial, morbilliform, and other rashes occasionally occur, but most of these disappear despite continued therapy. A photosensitizing action with subsequent eruption in light-exposed areas has been reported. Headache, gastrointestinal upsets, thirst, and other minor symptoms may occur, but are rarely severe enough to demand stopping treatment. A curious feeling of distension and fullness in the epigastrium, neck, and face has also been recorded.

Griseofulvin may have some effect on porphyria metabolism, and Rimmington et al. demonstrated an abnormality in porphyrins in 21 out of 50 patients on treatment. This, however, seems to be of little practical significance, and does not give rise to any symptoms.

It has recently been shown that griseofulvin has an anti-inflammatory effect, which is in the region of one-third to one-tenth of that of cortisone acetate. This may account for some of the effects which have been claimed on diseases other than ringworm infections.

Clinical Applications

As griseofulvin will act on all ringworm fungi the clinical use can best be considered according to the site involved.

Scalp.—Treatment of scalp ringworm has been revolutionized and x-ray epilation has become a thing of the past. A period of six to eight weeks' treatment is often required, and in small-sphere ringworm the hair distal to that laid down while on griseofulvin can still be seen to fluoresce under Wood's light. The cutting off of this distal hair over the infected patches may well stop cross-infection. The natural course of cattle ringworm causing the kerion reaction is to clear after two to three months, but with griseofulvin the treatment time and the severity of the reaction are greatly reduced.

Skin.—Small patches and large areas of infected skin respond to topical fungicides, but griseofulvin will greatly shorten the period of treatment, and perhaps the most dramatic cases treated are where Trichophyton rubrum infection has involved large patches, including the hands and feet. However, this is the type of case which often responds to topical fungicides, and recently Davies et al. have questioned the use of griseofulvin in smooth skin infections.

Toe-web.—Ringworm involving the skin of the toe-webs is often not cleared by griseofulvin, and in many cases after months of treatment the fungus can still be cultured from the sites. It would seem, therefore, that it should not be used to treat ringworm which has remained localized to the toe-webs.

Nails.—Finger-nails infected with ringworm will take about six months to clear, or longer in older patients. To prevent relapse it is important to treat coincidental ringworm of the
toe-nails with topical fungicides at the same time. Toe-nails will often require one to two years to clear completely, and even after such a period of treatment many are still infected or relapse when treatment is stopped. Particularly in older patients with dystrophic toe-nails it is probably inadvisable to attempt treatment with griseofulvin. Nails infected with *T. mentagrophytes* do not respond quite as well as those infected with *T. rubrum*.14

Failure of Treatment

Perhaps the commonest cause of failure is the treatment of conditions other than ringworm infection. The differential diagnosis of ringworm from some cases of eczema and psoriasis may be difficult, and mycological examination of scrapings is very important before treatment with griseofulvin is started.

Similarly, fungi known not to respond to griseofulvin may be treated, and in particular candida infection associated with chronic paronychia and *Malassezia furfur* infections (*Tinea versicolor*) are not affected.

The tablets may not have been taken regularly or the drug may not have been sufficiently absorbed. It is worth while stressing the importance of fat increasing the absorption, and the tablets should always be taken after meals. The simultaneous use of other drugs, particularly barbiturates, will reduce the effect of griseofulvin, and this may well have accounted for some reports of failure of treatment.

Resistance of ringworm fungus to griseofulvin is a very unlikely cause of lack of response.

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**Any Questions?**

We publish below a selection of questions and answers of general interest.

Susceptibility to Infectious Hepatitis

Q.—Is a recent attack of tonsillitis likely to make a girl who is to work in a nursery school where there is an outbreak of infectious hepatitis among the staff more open to infection? Is it possible to predict an individual person’s proneness to contract infectious hepatitis, and are there any factors which, if taken into account, might make it possible to predict the severity of the illness?

A.—Infectious hepatitis is an acute disease ascribed to one or more viruses whose biological characters have not been precisely determined. The evidence so far is that they are enteroviruses with mainly faecal excretion of variable duration. The mode of infection is the faecal-oral route, and there is a probability that a proportion of those infected do not show overt disease. Children suffer less from the disease in this way than adults, though they may constitute the main source of continuing infection.1

The number of unknown factors makes it impossible to say whether a recent attack of tonsillitis renders a person more open to infection. This would surely depend on close contact with persons excreting the virus at the time and on the actual infecting dose of virus transmitted. Contact with school staff and children and the handling and use of common objects, including crockery, would provide opportunities for infection.

There is no way of predicting nonspecific resistance to infectious hepatitis, and, at present, no suitable laboratory method for measuring specific immunity arising from past infection, inapparent or overt.

In some outbreaks it has been noted that the illness is more severe when there is initial high pyrexia before jaundice develops and when the interval between this pyrexial stage and the appearance of jaundice is short.

REFERENCE


Booster Doses of Rabies Vaccine

Q.—A child who was bitten by a rabid dog has completed a therapeutic course of rabies vaccine. Should subsequent booster doses be given, and, if so, how often?

A.—A child who has been bitten by a rabid dog and has completed a therapeutic course of rabies vaccine will not as a rule require any subsequent booster dose. Exceptions to this are when the bite has been caused by a wild animal or when the bites have been severe. In these cases booster doses should be given on the 10th and 20th day after the completion of a full course of vaccine. Vaccines of non-nervous tissue origin, if available, should be used in booster doses.

REFERENCE


Other Uses

Griseofulvin has been reported to be of value in gout, shoulder-hand syndrome, angina pectoris, psoriasis of the nails, and other conditions. The effect is often slight or unproved, and there does not appear to be any clear clinical application other than in ringworm infections.

The basic N.H.S. cost of 100 tablets of 125 mg. is 26s. 3d.

Tests for Connective Tissue Diseases

Q.—What is the relative value of the antinuclear-factor, L.E.-cell, and L.E.-latex tests in the diagnosis of systemic lupus erythematosus and other diseases of connective tissue? What proportion of false-positive and false-negative reactions are obtained when these tests are used for diagnosis of these diseases?

A.—The antinuclear-factor (A.N.F.) test is positive in many forms of connective tissue disease other than systemic lupus erythematosus, and is therefore of little value in the positive identification of that condition. The L.E.-cell test, on the contrary, is highly specific for systemic lupus erythematosus (S.L.E.), with few false-positive reactions apart from certain cases of drug hypersensitivity and of liver disease. Cassils, Friou, and Teague have, however, described a form of nuclear staining characterized by diffuse irregular fluorescence spreading out from the nuclear margin which is much more closely correlated with S.L.E.

The sera from many cases of S.L.E. give precipitin or complement-fixing reactions with D.N.A. and D.N.A.-protein. The L.E.-latex test detects these sera because the latex particles used are coated with D.N.A.-protein. The results with this reagent are more specific for S.L.E. than is the A.N.F. test, but its lack of sensitivity makes it unsuitable as a substitute for either the A.N.F. or L.E.-cell test.

REFERENCE


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*References*