was also carried over into the hospices' perception of themselves as essentially "technical" if there was a full-time consultant or "non-technical" if there was not. Following the Royal College of Physicians' recognition of palliative medicine as a new specialty it is likely that these differences will increase with the advent of a generation of "accredited hospice consultants," who will displace the "enthusiastic amateurs" of the past.

We thank all the respondents to the survey and the nurses at the Leicestershire Hospice for their interest and willing participation, Dr Carol Jagger for statistical help, and Miss K Jeffery for preparing the typescript.

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New Drugs

New antiviral and antifungal drugs

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Currently licenced indications for treatment with acyclovir

Considerable advances have been made in treating viral and fungal diseases since the last series of reports was published in 1983; several new drugs have been introduced and new clinical data on older drugs collected. This review aims at giving general clinicians a guide to changes since 1983 in licenced antiviral or antifungal treatment in the United Kingdom and briefly discusses when specialist advice about experimental treatment should be sought. Vaccines are not considered.

Antiviral drugs

Nine drugs are currently licenced for antiviral treatment in the United Kingdom: seven (acyclovir, amantadine, ganciclovir, idoxuridine, tribavirin, vidarabine, and zidovudine) have direct effects on viral replication, and two (inosine pranobex and interferon alfa) act by modulating the immune system. Except for amantadine, the drugs with direct antiviral activity are

nucleoside analogues that interfere with viral DNA or RNA replication and may also affect mammalian nucleic acids. The newest drugs (acyclovir, ganciclovir, and zidovudine) achieve greater antiviral specificity because they are inactive until phosphorylated by enzymes that are preferentially synthesised by virally infected cells.

ACYCLOVIR

Acyclovir (Zovirax, Wellcome) was available in 1983 but there have been substantial recent changes in the licenced indications, notably approval of high dose oral treatment for shingles. The manufacturers have recently produced a detailed monograph with 211 references, which is an excellent source of information.¹

Indications, doses, and costs

These are summarised in the table. The clinical indications for the use of this drug continue to expand as experience grows. In particular, long term (3-4 year)

Formulation	Licenced indications	Recommended dose	Cost a day (BNF prices)	Comments
Cream	Primary herpes labialis or genitalis in immunocompetent patients Herpes simplex keratitis	Application five times a day	£1.07-£3.23	Much less effective for secondary than for primary infections. Treatment is unlikely to be effective unless new lesions are still forming
Ointment		Application five times a day	About £1.05	Little difference between acyclovir, idoxuridine, and vidarabine for superficial disease but acyclovir is probably superior for deep infections. Experimental combinations of acyclovir with interferon alfa have been reported to be superior to acyclovir alone <i>Unlicensed use:</i> often used for ophthalmic shingles, but probably adds little to systemic treatment
Tablets and suspension	Primary or secondary herpes labialis or genitalis in immunocompetent patients	200 mg five times a day	£5.00	<i>Unlicensed use: treatment in pregnancy</i> Much less effective for secondary than for primary infections. Does not eliminate vaginal carriage so delivery by caesarean section is recommended to avoid neonatal herpes infection
	Recurrent herpes in immunocompetent or immunocompromised patients	200 mg four times a day (prophylaxis)	£4.00	A controlled clinical trial showed that 200 mg four times a day was more effective than 400 mg twice or 800 mg once a day to prevent recurrent genital herpes in immunocompetent hosts. Reduction of daily dose to 200 mg three to two times a day should be considered after 2-3 months of maintenance ²
	Shingles	800 mg five times a day	£25.00	Treatment must be started within 72 hours of onset to be effective and should be reserved for patients with severe pain. Efficacy in preventing postherpetic neuralgia is controversial. ^{3,4}
Injection	(a) In immunocompetent patients Herpes simplex encephalitis	10 mg/kg three times a day	£50.00	Treatment must be started as soon as diagnosis is made. ⁵ Delayed treatment is much less effective. Neonatal treatment is less effective for type 2 than type 1 herpes simplex virus. ⁶
	Severe herpes genitalis	5 mg/kg three times a day	£25.00	Unlikely to be more effective than oral treatment.
	Severe shingles	5 mg/kg three times a day	£25.00	Unlikely to be more effective than oral treatment.
				<i>Unlicensed use:</i> Anecdotal evidence for efficacy against chickenpox pneumonia, which is a life threatening condition even in immunocompetent patients
	(b) In immunocompromised patients Herpes simplex or shingles	10 mg/kg three times a day (treatment or prophylaxis)	£50.00	

BNF = British National Formulary.

continuous administration is being used in specialist centres to prevent recurrent infection, particularly in immunocompromised patients. Alternatively, patient initiated treatment at the earliest suspicion of symptoms may abort recurrences of herpes simplex or herpes zoster. Specialist advice should be sought on the management of recurrent herpes infections, particularly in immunocompromised patients.

Pharmacokinetics

Acyclovir is available as an eye ointment, a skin cream, an oral suspension, a tablet, and an intravenous infusion.¹ Systemic absorption from the eye ointment or skin cream is minimal but, in contrast to older drugs such as idoxuridine or vidarabine, application of acyclovir eye ointment does result in therapeutic drug concentrations penetrating through the cornea and into the aqueous humour. In adult patients with normal renal function the terminal half life of acyclovir after intravenous administration is 2.9 hours; peak and trough serum concentrations are essentially similar in neonates and adults in the dose range 5-10 mg/kg. The suspension provides plasma concentrations adequate to treat infants and children with herpes simplex.⁷ Most (73%) of the drug is excreted unchanged in the urine, the remainder is cleared by metabolism. The half life is increased by about 18% by administering probenecid concurrently. Binding to plasma proteins is minimal (9-33%). Acyclovir is widely distributed in body tissues; concentrations in cerebrospinal fluid are 50% of plasma concentrations. The bioavailability of the oral formulation is only about 20% and some evidence exists that bioavailability decreases with increasing oral dose. Clearance of acyclovir is reduced in patients with renal failure, and the manufacturer's data sheet contains dosing recommendations. Acyclovir is cleared by haemodialysis, and a supplementary dose is recommended at the end of each dialysis treatment. Only about 13% of a dose of acyclovir is cleared by peritoneal dialysis; patients receiving chronic ambulatory peritoneal dialysis do not require supplementation after dialysis.

Adverse effects

Acyclovir is highly selective for virally infected cells and, unlike ganciclovir, zidovudine, and interferon, has no dose related effect on human bone marrow in the recommended dose range. The eye ointment has been associated with superficial punctate keratopathy (in 9.8% of patients), although that may be related to the disease, and with burning or stinging after application (in 4%).¹ Transient burning sensation has also been reported after application of skin cream. Intravenous and oral acyclovir have been associated with mild gastrointestinal symptoms (nausea, vomiting, diarrhoea, and abdominal pain), rashes, and transient increases in liver enzyme activity. Headache and transient neuropsychiatric reactions have been reported, particularly in patients with renal failure who have received inappropriately high doses of intravenous acyclovir.⁸ Intravenous acyclovir should be infused for one hour because more rapid administration is associated with reduced glomerular function. Local extravasation of intravenous acyclovir results in severe tissue inflammation or necrosis.

Use in pregnancy and lactation

Acyclovir is not teratogenic or mutagenic in animals and there are several reports of its safe administration to pregnant women. The manufacturers do not encourage its use in pregnancy, however, and it should be reserved for severe symptomatic infections. Acyclovir does pass into breast milk but as it is licensed for use in neonates this is of doubtful clinical importance.

GANCICLOVIR

Indications, doses, and cost

Ganciclovir (Cymevene, Syntex), formerly known as DHPG (9-[(1,3-di-hydroxy-2-propoxy)methyl] guanine), is active against all the herpes viruses including herpes simplex virus, herpes zoster virus, Epstein-Barr virus, and cytomegalovirus. Because of its toxicity it has been used to treat severe cytomegalovirus infections in immunocompromised patients alone, and this is currently the only licensed indication. The results of several large clinical trials have recently been published with details of its pharmacology, pharmacokinetics, and adverse effects.⁹ Clinical resolution of cytomegalovirus infection without virological relapse has been achieved after 14 days of ganciclovir treatment in recipients of transplants in whom immunosuppressive treatment could be reduced. In contrast, patients who must continue intensive immunosuppressive treatment or who have AIDS require long term maintenance treatment to prevent relapse. In both categories of patients treatment gives an initial response in 70-90% with retinitis, hepatitis, and colitis but in only 30-50% with pneumonitis.

The recommended dose is initially 5 mg/kg every 12 hours. If maintenance treatment is required a dose of 30 mg/kg a week should be given either as 6 mg/kg for five days a week or as 5 mg/kg for seven days a week. As a 500 mg phial of ganciclovir costs £17.15 the daily cost for an 80 kg adult is £34.30 initially and about £17.15 for maintenance treatment.

Pharmacokinetics⁹

Ganciclovir is available for reconstitution only as an intravenous infusion. After an infusion of 5 mg/kg for one hour the terminal plasma half life in patients with normal renal function is 3.6 hours. About 70% of an administered dose is recovered unchanged from urine; there is evidence that ganciclovir is excreted into the urine by tubular secretion as well as by glomerular filtration. Protein binding is minimal (1-2%, manufacturer's data sheet). Twice daily administration of 5 mg/kg for two weeks does not result in drug accumulation. Clearance of ganciclovir is reduced in patients with renal failure and doses should be modified (see data sheet). Serum concentrations of ganciclovir are reduced by about half after a four hour period of haemodialysis. There are no data about clearance by peritoneal dialysis.

Adverse effects⁹

Ganciclovir has dose related cytotoxic effects on uninfected mammalian cells at therapeutic concentrations. Neutropenia occurs in about 30% of patients who receive ganciclovir, and treatment should not be started if the neutrophil count is less than 500/ μ l. Combination with other drugs that are myelotoxic, such as cytotoxic drugs, amphotericin B, 5 flucytosine, interferon, pentamidine, or zidovudine, should be avoided if possible. Other less common and less important adverse effects reported from clinical trials include thrombocytopenia (19%); rash (6%); nausea (6%); fever (6%); infusion site reactions, vomiting, diarrhoea, anaemia (4% each); and eosinophilia, confusion, seizures, and abnormal mentation (3% each).⁹ The risk of convulsions may be increased by administering concurrently with imipenem or cilastatin (ganciclovir data sheet).

Neutropenia occurs early in treatment and its incidence does not appear to be related to the daily dose of ganciclovir or to the neutrophil count before treatment. In contrast, the incidence of thrombocytopenia is greater in patients with low platelet counts before treatment. Neutropenia is usually transient, but

death from sepsis secondary to irreversible neutropenia has been described.

Inhibition of spermatogenesis occurs in animals but clinical data have not been obtained about this side effect. Intravenous ganciclovir will probably result in temporary or permanent inhibition of spermatogenesis in men and in permanent infertility in women (data sheet).

Pregnancy and lactation

Treatment with ganciclovir carries a high risk of damage to fetuses, and ganciclovir should not be given to pregnant women. Men and women should use effective contraception during ganciclovir treatment, and men should continue using barrier contraception for 90 days after treatment is completed (data sheet). There are no data about penetration of the drug into breast milk, but breast feeding should not occur until 72 hours after the last dose of ganciclovir (data sheet).

TRIBAVIRIN

Indications, dose, and cost

Tribavirin (Virazid, Britannia) has been used experimentally for over 10 years but was not licensed in the United Kingdom until 1987. The only licensed indication is severe respiratory syncytial virus bronchiolitis, although successful aerosol treatment of influenza and other viral respiratory infections has been reported,^{10 11} and oral or intravenous formulations have been used experimentally against a wide variety of viral infections.^{10 11}

The recommended regimen for respiratory syncytial virus bronchiolitis is a solution of tribavirin 20 mg/ml administered through a small particle aerosol generator for 12-18 hours a day for at least three days. The daily cost is about £195.

Pharmacokinetics

Negligible amounts of tribavirin are absorbed systemically after inhalation treatment.

Adverse effects

No serious adverse effects of tribavirin administered by aerosol or nebuliser have been reported.

Pregnancy and lactation

Using tribavirin during pregnancy and lactation is not recommended; this is somewhat academic as respiratory syncytial virus infection is essentially a paediatric problem and the drug is only licensed for use in children.

ZIDOVUDINE

Indications, dose, and cost

Zidovudine (Retrovir, Wellcome) was licensed in 1987 for treating people with serious manifestations of infection with human immunodeficiency virus (HIV). A clear beneficial effect has been shown in patients with AIDS or with severe constitutional symptoms of HIV infection, such as night sweats or weight loss.¹²

Experimental uses of zidovudine include treating patients with other symptoms of HIV infection, such as lymphadenopathy or disease of the central nervous system, treating asymptomatic patients with HIV infection, and prophylaxis of health care workers after needle stick injury.^{13 14} Zidovudine treatment in these cases is possibly ineffective or even harmful, and in general such treatment should be given only as part of a controlled clinical trial.

The recommended dose of zidovudine is 200 mg every four hours, including a night time dose. There are innumerable experimental variations on this dose and interval but no unequivocal comparative data. Similarly, no convincing data exist about combining

zidovudine with acyclovir. The data sheet recommends dose reduction or temporary interruption of treatment if gastrointestinal or haematological side effects become too severe.

The cost of zidovudine is £13.75 a day.

Pharmacokinetics

Zidovudine is only available in capsule form. Its bioavailability is 60-70% after oral administration. Clearance from plasma is rapid, with a half life of about one hour; 50-80% of a dose is excreted in the urine as the 5'-glucuronide. No data exist about the pharmacokinetics of zidovudine in children, the elderly, or patients with renal or hepatic impairment. Binding to plasma proteins is slight (34-38%). Zidovudine concentrations in cerebrospinal fluid are half those in plasma. No specific doses are recommended for patients with renal or hepatic impairment, but zidovudine is principally eliminated by glucuronidation in the liver and excretion of the glucuronide and unchanged drug by the kidney. Particularly careful monitoring for haematological adverse effects of zidovudine is recommended for patients with renal or hepatic impairment.

Adverse effects

Nausea, vomiting, anorexia, abdominal pain, headache, and myalgia are common at the start of zidovudine treatment but diminish or disappear with continued administration.^{15 16} Dose reduction or transient interruption of treatment and reintroduction of a reduced dose may be required to allow tolerance to develop (data sheet). The main adverse effects are anaemia, neutropenia, and leucopenia. These are most common in patients with advanced disease or pre-existing haematological abnormalities. In one trial administering paracetamol with zidovudine was associated with increased haematological toxicity.¹⁶ Only limited data exist about other drug interactions with zidovudine, and combination treatment should be avoided if possible, particularly with drugs that affect hepatic metabolism, are nephrotoxic, or myelotoxic.

Pregnancy and lactation

Neither embryotoxic nor teratogenic effects have been shown in animals, but potential toxicity must be weighed against probable clinical benefit for pregnant women with HIV infection. Zidovudine probably penetrates into breast milk, though no data about this exist. Breast feeding should therefore be discouraged in women taking zidovudine.

INOSINE PRANOBEX

Indications, dose, and cost

Inosine pranobex (Imunovir, Leo) is licensed for treating people with mucocutaneous lesions caused by herpes simplex virus types I and II and as an adjunct to podophyllin or carbon dioxide laser treatment for genital warts. The drug has no direct antiviral activity but has been reported to have several effects on the immune system that allegedly result in useful stimulation of the host's immune response to viral infection. A recent clinical trial showed that it was unequivocally inferior to acyclovir for treating people with primary genital herpes and that combination with acyclovir was no better than acyclovir alone.¹⁷ Until further evidence from controlled clinical trials is produced it is difficult to see a role for this agent as an antiviral drug.^{10 18 19}

The recommended dose of inosine pranobex is 1 g four times a day; the cost is £1.49 a day.

Pharmacokinetics

Remarkably little has been published on the pharmacology of inosine pranobex and the data sheet contains no pharmacokinetic data whatsoever. The

drug is available only in tablet form. No specific data exist about pharmacokinetics in renal or hepatic impairment. The data sheet states that there are no known contraindications to use but that inosine pranobex should be used with caution in patients with renal impairment because there is a risk of uric acid accumulation.

Adverse effects

The inosine component of inosine pranobex is metabolised to uric acid. Increased serum and urine concentrations of uric acid have been reported in normal subjects, and inosine pranobex should be used with caution in patients with renal failure, gout, or hyperuricaemia. No other adverse reactions have been reported.

Pregnancy and lactation

No teratogenic or mutagenic effects have been reported, but use when pregnancy is suspected or confirmed should be avoided (data sheet). No data exist about secretion into breast milk.

INTERFERONS

Indications, doses, and cost

Three interferon preparations are currently licensed in the United Kingdom: interferon alfa-2b (Intron A, Kirby-Warrick); interferon alfa-2a (Roferon-A, Roche) and interferon alfa-N1 (Wellferon, Wellcome). All three preparations are licensed for treating people with hairy cell leukaemia. Although clinical trials suggest that the other preparations are also effective, only interferon alfa-2a (Roche) is currently licensed to combat Kaposi's sarcoma in patients with AIDS. Antiretroviral activity of interferon alfa has been documented in patients with AIDS and may be partly responsible for its efficacy against Kaposi's sarcoma in these patients.^{20,21} None of the interferons, however, is currently licensed to combat the primary HIV infection in patients with AIDS.

All the interferons have substantial adverse effects, and their role as systemic antiviral drugs will probably always be limited to combating or preventing severe infections.²² Clinical trials in patients with AIDS are continuing, and interferon will possibly be used to treat patients with chronic hepatitis B infection. Topical application of interferon is still experimental but has shown some promise in the management of genital warts²⁵ and, in combination with acyclovir, in treating patients with severe ophthalmic herpes simplex infections.¹⁸

The recommended dose of interferon alfa-2a (Roche) to combat Kaposi's sarcoma in patients with AIDS is 36 million units a day for 4-10 weeks followed by an indefinite maintenance dose of 36 million units three times a week. The cost of 36 million units of interferon alfa-2a is £203.54.

Pharmacokinetics

Interferon alfa-2a is available only as a powder for reconstitution for intramuscular or subcutaneous injection. More than 80% of an intramuscular dose is absorbed. The elimination half life in healthy men is about five hours after intravenous administration. No specific recommendations exist about doses for patients with renal or hepatic impairment, but interferon alfa-2a is not recommended for patients with severe renal or hepatic disease; in patients with milder impairment close monitoring of renal and hepatic function and periodic neuropsychiatric monitoring are recommended.

Adverse effects

Dose related adverse effects include influenza like symptoms and neuropsychiatric symptoms.^{20,21,23}

Psychiatric effects have been described as reminiscent of the postviral fatigue syndrome.²³ They are mainly non-psychotic symptoms, such as fatigue, impaired concentration, anxiety, and depression, which reverse after discontinuation of treatment is stopped or the dose reduced. Neurological effects are rarer but include paraesthesia, numbness, neuropathy, tremor, convulsions, or severe somnolence. A history of convulsions or compromised central nervous system function are contraindications to treatment (data sheet). Anorexia is common and may be severe enough to lead to weight loss. Transient hypotension or cardiac arrhythmias occur; more severe cardiovascular adverse effects have been reported only rarely but severe pre-existing cardiac disease is a contraindication to treatment (data sheet). Neutropenia and thrombocytopenia occur, particularly in patients with pre-existing myelosuppression, but are usually transient.

Pregnancy and lactation

Abortifacient effects of high dose interferon have been reported in monkeys; teratogenic or mutagenic effects have not been reported but interferon alfa-2a is not recommended in pregnancy. No data exist about its penetration into breast milk or effects on lactation.

THE FUTURE

Several experimental regimens exist for treating people with herpes virus infections,^{19,24} retroviruses including HIV,^{13,14} and other viruses including chronic infection with hepatitis B.^{11,26} Clinicians should seek expert advice about treating people with any severe viral infections that are not covered by existing product licences, particularly immunocompromised patients, because advances in management will continue to be rapid.

New antifungal drugs

The new antifungal drugs reviewed in 1983 were all nitroimidazoles; a new imidazole, tioconazole (Trosyl, Pfizer), has been marketed recently as have fluconazole (Diflucan, Pfizer) and itraconazole (Sporanox, Janssen), the first members of the triazole antifungal agents to be licensed in the United Kingdom.

TIOCONAZOLE

Indications, dose, and cost

Tioconazole has broad antifungal activity,²⁷ but the only marketed formulation is a solution for topical application to combat nail infections caused by dermatophytes and yeasts. This is a 28% solution of tioconazole in undecylenic acid, a fatty acid that facilitates penetration of tioconazole into nails. No other topical imidazole preparations have proved effective in combating fungal nail infections. The only previously available treatments were oral griseofulvin or oral ketoconazole. Enthusiasm for ketoconazole has waned because of hepatic necrosis and the disruption of synthesis of human endocrine steroids.²⁸ Hepatic necrosis occurs in patients treated for more than two weeks and prolonged treatment for nail infections is difficult to justify, particularly as ketoconazole is ineffective in most patients.²⁹ In an open study tioconazole alone cured 22% of patients with fungal nail infections, although appreciable improvement was seen in a further 40%.³⁰ Treatment with topical tioconazole and oral griseofulvin led to remission in 69% of patients compared with 39% treated with griseofulvin and placebo nail paint.³¹

The recommended duration of treatment with tioconazole is six to 12 months. The cost of one 12 ml phial of tioconazole nail solution is £25.

Pharmacokinetics

Systemic absorption of tioconazole is negligible after local application of the nail solution.

Adverse effects

Local irritation is the only reported adverse effect. Tioconazole should not be given to patients with histories of hypersensitivity to imidazoles.

Pregnancy and lactation

Despite negligible systemic absorption the manufacturer's data sheet states that tioconazole is contraindicated in pregnancy because of the prolonged duration of treatment. No specific recommendations exist about its use by breast feeding mothers but any risk to suckling infants is unlikely.

FLUCONAZOLE

Indications, dose, and cost

Fluconazole was the first triazole antifungal drug to be licensed in the United Kingdom. The triazoles are structurally similar to imidazoles but have a wider range of antifungal activity. The intravenous and oral formulations of fluconazole have been successful in treating people with a wide range of severe systemic fungal infections, including cryptococcal meningitis, and the licensed indications include vaginal candidiasis, mucosal candidiasis in normal or immunocompromised patients, systemic candidiasis, and cryptococcal meningitis. Bioavailability of fluconazole after oral administration is 94% and absorption is not affected by food.³² The plasma half life in normal patients is about 25 hours. Unlike ketoconazole, fluconazole is not extensively metabolised; nearly 80% of a dose is excreted unchanged in urine and the prolonged half life suggests that fluconazole is reabsorbed from the urine. Binding to plasma proteins is minimal (12%). Fluconazole is widely distributed in tissues, cerebrospinal fluid concentrations are 57-93% of plasma concentrations, and fungicidal concentrations are achieved in nails, vaginal tissue, and saliva.^{32, 33}

Fluconazole is available in three capsule strengths: 50 mg capsules are recommended for treating people with oral or mucosal candidiasis, 150 mg capsules as a single dose treatment for vaginal candidiasis, and 200 mg for treating people with systemic candidiasis or cryptococcosis. A 200 mg intravenous formulation is also available. Most patients with oral candidiasis respond to local treatment, but fluconazole provides an effective second line treatment for unresponsive infections, particularly in patients with underlying immune defects, who often experience a relapse after treatment with standard regimens and may need prolonged maintenance treatment.

The cost of fluconazole 50 mg is £16.61 a week.

The recommended regimen for vaginal candidiasis is a single dose of 150 mg. A multicentre trial of 369 patients compared this dose with 200 mg clotrimazole applied intravaginally daily on three consecutive days. Clinical success at 5-16 days was similar (99% of those receiving fluconazole *v* 97% of those receiving clotrimazole were cured), but relapse rates were significantly higher for clotrimazole than fluconazole (16% *v* 7%).³⁴ Similar results with fluconazole were found in an open non-comparative multicentre trial of 180 patients.³⁵ A comparative trial of 183 patients showed that a single oral dose of 150 mg fluconazole was as effective as 200 mg oral ketoconazole given twice a day for five days.³⁶ The most probable explanation for the differences between systemic and local treatment of vaginal candidiasis is that systemic treatment cures rectal infection, and rectal carriage is one cause of relapse after local treatment.³⁷ Surveys in the United Kingdom suggest that women have a preference for

oral treatment for vaginal candidiasis.³⁸ Oral treatment is substantially more expensive, however, and although no serious adverse effects have yet been reported it will take many years to assess adequately the safety of fluconazole. At present oral fluconazole should probably be reserved for patients who do not respond to local treatment, although other causes for relapse should be considered, such as steroid contraceptive use, pregnancy, or infection of sexual partners.³⁹

The cost of fluconazole 150 mg is £7.12 (compared with £2.64 for six clotrimazole 100 mg vaginal tablets, £1.55 for 15 nystatin pessaries 100 000 U, and £8.86 for triple pack of nystatin, containing tablets, gel, and pessaries).

For patients with candidaemia, disseminated candidiasis, other invasive candidal infections, or cryptococcosis the recommended treatment is 400 mg on the first day followed by 200-400 mg a day depending on clinical response. Prolonged treatment for these infections is often required, for example 6-8 weeks treatment is recommended for cryptococcal meningitis. After completing primary treatment patients with AIDS require indefinite treatment to prevent relapse: the recommended dose is at least 100 mg a day.

Dosage regimens for children are 1-6 mg/kg depending on indication, but fluconazole should be used in children aged under 16 only when antifungal treatment is imperative and no suitable alternative exists.

The cost of 200 mg oral fluconazole is £76.40 for one week; the cost of intravenous fluconazole 200 mg is £235.92 for one week including the initial 400 mg loading dose.

Adverse effects

The most common adverse effects reported with fluconazole are nausea (in 2-2% of patients), headache (in 1-6%), and abdominal pain (in 1-4%). Controlled clinical trials in patients with oral or vaginal candidiasis showed similar incidences of adverse events for fluconazole and the comparator. There is less experience with prolonged treatment, but no appreciable effect on liver function was found in 737 patients who received 50 mg a day for up to 42 days for dermal mycoses or in immunocompromised patients who received 400 mg a day for six weeks or 200 mg a day for up to six months (data on file, Pfizer). Unlike ketoconazole, fluconazole does not inhibit hepatic drug metabolism⁴⁰ or the synthesis of steroids in man.⁴¹

Pregnancy and lactation

Adverse fetal effects have been seen only in animals at doses that were many times higher than recommended therapeutic doses, but fluconazole is not recommended for use in pregnancy or in women of childbearing potential unless adequate contraception is practised. No data exist about penetration into breast milk, but the manufacturers recommend that fluconazole should not be given to nursing mothers.

ITRACONAZOLE

Indications, dose, and cost

Itraconazole is a triazole antifungal that has recently been licensed in the United Kingdom to treat patients with vaginal candidiasis, tinea infections of the skin, or pityriasis versicolor. Itraconazole is currently available only in an oral formulation. It is well absorbed, but unlike fluconazole it undergoes extensive hepatic metabolism.⁴² Increases in plasma concentrations are not proportional to dose after oral treatment with 100 and 200 mg, which suggests that itraconazole undergoes saturable first pass metabolism in the liver.⁴³

Important differences exist between itraconazole and fluconazole. Itraconazole shows promising activity against *Aspergillus* spp in vitro and in experimental infection whereas fluconazole, like the earlier

imidazole antifungals such as ketoconazole and miconazole, is not effective against these infections. Further clinical trials are required to assess the role of itraconazole in systemic aspergillosis. Although it does not penetrate the brain or the cerebrospinal fluid in therapeutic concentrations, itraconazole has been used in combination with flucytosine to combat cryptococcal meningitis in patients with AIDS and it appears to be effective in preventing relapse.⁴¹ Trials comparing itraconazole with fluconazole are required.

Open clinical trials have shown that itraconazole is effective against the infections for which it is licensed. Too few data from comparative clinical trials are available, however, to compare itraconazole with standard topical drugs or griseofulvin. Like fluconazole, itraconazole should be reserved for patients with infections that fail to respond to standard drugs.

The cost of itraconazole is £5.71 for four 100 mg tablets, which is the recommended dose to combat vaginal candidiasis. Patients with nail infections may require treatment with 200 mg a day for several months,⁴³ though itraconazole is not currently licensed to combat nail infections.

Adverse effects

Like fluconazole, itraconazole is highly specific for fungal cytochrome *P450* and has no effect on mammalian steroid biosynthesis or hepatic drug metabolism. Unlike ketoconazole, these new triazoles do not appear to alter pituitary-testicular-adrenal function.⁴² Itraconazole has been well tolerated in clinical trials; as with fluconazole, mild gastrointestinal intolerance is experienced by a few patients.

Pregnancy and lactation

Itraconazole is not currently recommended for pregnant or lactating mothers.

THE FUTURE

Fluconazole and itraconazole are only two of several triazole antifungals that have been developed.⁴²⁻⁴³⁻⁴⁵ In addition to these new drugs the range of licensed and experimental indications for fluconazole and itraconazole will expand rapidly. The role of these new drugs in patients with local infections remains to be established, but until further comparative trials are published the drugs should be reserved for infections that fail to respond to standard topical treatment. A review of current treatment for systemic mycoses has been published recently.⁴⁶ This is a rapidly advancing field and clinicians should seek expert advice about managing any systemic fungal infection.

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