given miscalculated doses of common drugs (morphine, digoxin) is reflected by reports in the medical literature suggesting an increase in drug errors.[6] Most paediatricians have at least second hand experience of incidents in which a child's care has been compromised by medication errors. The difficulties of using medicines formulated in adult dose volumes are often compounded by complex dilutions and rate calculations (such as µmol/kg/min) being performed by tired medical staff.[7] Medication errors could be reduced by the use of software programmes such as those in use in general practice,[8] but such systems are seldom evident on paediatric wards. Reports emphasise the need for a systematic approach to avoid such events, including close attention to prescription writing, pharmacy dispensing, and nursing processes.[9]

In an attempt to improve this situation the European Agency for the Evaluation of Medicinal Products has given guidance to pharmaceutical companies on the need to conduct clinical trials in children. This states that there is a shared responsibility to ensure that children are not denied timely access to safe and effective medicines which have accurate, scientifically justified prescribing information.

In a more robust directive the Food and Drug Administration in the United States has declared that new drugs likely to be used to treat children must be tested by pharmaceutical companies for their effects in children.[10] Existing drugs used off label may also be required to have their licences amended if there is substantial use in childhood.[10] The National Institutes of Health have established a paediatric pharmacology unit, based in seven centres, which provides a base for clinical trial coordination by paediatric pharmacologists. A similar centre should be developed in the European Union. To encourage the development of orphan drugs, the Australian Therapeutic Goods Administration has waived its evaluation fee for orphan drugs. Orphan drug legislation in Europe is awaited.

In the United Kingdom the Royal College of Paediatrics and Child Health has produced a formulary, *Medicines for Children*, published last week. This formulary is divided into three sections: a therapeutics section, a drug monograph section (with information on licensed, unlicensed, and off label use of drugs), and a dietary section on borderline substances. The secondary aims of this initiative are to establish a database on the efficacy and safety of medicines given to children that can be used by those who make, test, market, prescribe, dispense, and administer medicines for children. A nation's children are its investment in the future. There must be further progress in the development and prescribing of medicines for children to ensure that children do not remain therapeutic orphans.[11]

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Skin and nail fungi—almost beaten

Don't get confused by the "evidence"

Papers p 79

Dermatophyte infections occur often either between the outer toes or in the toenails. It is now possible to eradicate most of these, and more widespread fungal infections, with the new generation of antifungal agents. Competing claims are made for systemic terbinafine and itraconazole, and up to now it has been hard to sort out the science from the marketing. The recent paper by Evans et al[1] and the systematic review in this issue by Hart et al (p 79)[2] attempt to point ways through the evidence. Other problems remain in treating children and non-responders.

The conclusions reached in the systematic review by Hart et al are undermined by the limited questions asked. It is legitimate to review the evidence for topical treatments for superficial fungal infections of the skin, but common sense must be applied to the results. Use of topical drugs in the community is not necessarily the same as in a trial situation. Poor compliance is common because symptoms are rapidly relieved, whether or not there has been mycological cure. Very few applications of topical (fungicidal) terbinafine are needed to produce a cure, whereas fungistatic drugs must be applied until the infected stratum corneum is shed. One week of topical terbinafine therefore gives better cure rates than four weeks of clotrimazole.[3] The implications for community cure rates, recurrence, and spreading of infection to others are obvious and the authors' failure to consider them indicate a naivety in their cost effectiveness conclusions.

Moreover, in considering nail infections it is inappropriate to review the evidence for topical treatment in isolation from that for systemic treatment. In their discussion Hart et al correctly state that evidence on the efficacy of topical treatments for nail infections is sparse, but the summary conclusion ambiguously implies that their conclusions apply to nail as well as the skin.[2] Systemic therapy, with terbinafine, is the treatment of choice for onychomycosis.[1]

BMJ 1999;319:71–2

Today's drugs for treating superficial fungal infections are dramatically more effective than those available 20 years ago. Griseofulvin, introduced in the 1960s, is fungistatic whereas terbinafine is fungicidal even at low concentrations. Fungistatic drugs anaesthetise dermatophytes; fungicidal ones murder them. Griseofulvin therefore has to be taken until all infected tissue is lost through natural turnover—about four weeks for stratum corneum and up to 18 months for infected toenail. In contrast a fungicidal drug, such as the allylamine terbinafine, needs only to be taken for a short time until all the fungi are dead: normal appearance will slowly follow. Itraconazole is a triazole that is primarily fungistatic[1] but which reaches fungicidal levels at 100 times greater concentration than for terbinafine.

Topically applied terbinafine and topical azoles rapidly penetrate the stratum corneum. Pharmacokinetic studies suggest that only a few applications of topical terbinafine will cure a dermatophyte infection.[4] This is particularly useful as a high response rate may still follow low compliance.

Knowledge of the pharmacokinetics of terbinafine and itraconazole have resulted in original, but contrasting, advice over the timing of oral therapy. Both drugs penetrate nail plate rapidly and persist in nail for some time. This persistence has led Janssen to advocate a pulse therapy concept for itraconazole, in which the drug is given for only one week every month, relying on the stored reservoir of drug. Novartis has taken the more traditional approach of uninterrupted therapy for terbinafine: both suggested regimens, of equivalent cost, are for only 12 weeks for toenail disease—long enough for the drug to penetrate and the organisms to be killed. At last there is clear evidence about which regimen is most effective: Evans et al showed that terbinafine gives a 76% mycological cure rate and itraconazole a 38% cure rate in toenail onychomycosis assessed at 72 weeks after each drug had been given for 12 weeks.[1]

Perhaps the most contentious issue in the itraconazole-terbinafine battle has been over *Candida albicans*. Does candida play an important primary pathogenic role in onychomycosis, or is it usually secondary to the primary dermatophyte infection, disappearing when the dermatophyte infection is dealt with? If candida is of prime importance, itraconazole with its broad spectrum of action is indicated. However, it appears that it is only of secondary importance,[5] so terbinafine is appropriate, despite its specific action. In warmer humid climates, however, candida may thrive more easily and play a more important part.

Even in the most optimistic studies, at least 15% of patients with onychomycosis are not cured. How can they be helped? If the organism is identified and known to be sensitive to the drug, presumably the drug is not reaching the organism. Roberts and Evans have suggested the concept of a "dermatophytoma," analogous to an aspergilloma, where the space between the nail plate and the nail bed is invaded and expanded by a mass of dermatophytes, impenetrable to systemic or topical drugs.[6] Other reasons for failure may include a distorted nail plate preventing penetration, and, of course, non-compliance. There is some logic in treating such nails with a combination of oral therapy, removal of infected tissue, and topical therapy—but there is little published evidence on the effectiveness of this approach.

Children, once again, are the losers in these therapeutic advances. The complexities and expense of having drugs licensed for use in children has resulted in oral terbinafine being licensed for children in very few countries, despite a safety profile similar to that in adults[7]; itraconazole is similarly restricted. Griseofulvin is therefore still used in children, for skin and nail infection, despite its side effects and inferior effectiveness. The pharmaceutical industry and licensing authorities must jointly bear the blame for this continuing disadvantage to children (see p 70).

Fungal infection of the hands, body, or scalp is unsightly and uncomfortable. Although many—6.9% estimated prevalence in Ontario[8]—are troubled by the appearance of infected toenails and by the impact on quality of life,[9] most people with localised fungal infections probably are little concerned. Now that effective therapy is available, there are pressures to educate the public about the problem, which is clearly in the interests of the pharmaceutical companies as well as the public. The risks, such as idiosyncratic liver reactions associated with oral therapy,[10] need to be taken into account.

Despite the extensive work represented by this issue's systematic review, I believe that the most effective treatment for a topical dermatophyte infection remains topical terbinafine, and for onychomycosis is oral terbinafine. Why should we recommend inferior therapy to our patients?

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AYF is a member of the UK Novartis Dermatology Advisory Board and has had studies and travel funded by Novartis. He has also contributed to studies funded by Janssen.

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