

MICONAZOLE (Comment)**Safe use of the oral gel in very young infants**

Janssen-Cilag, a Belgian pharmaceutical company, have had a license to market miconazole in Europe as a 20 mg/g oral gel for more than thirty years. The drug is also very widely available as a 2% lotion, cream, spray, powder and vaginal pessary in many countries to treat (or prevent) topical fungal infection. It is not available, however, as an oral gel in the United States. The dusting powder is currently available without prescription in the UK, as are small, 15 gram, quantities of the cream and oral gel, and these cost less than £3.

Until now the company have said that their products are suitable for anyone to use, irrespective of age, although, because use of the oral gel does result in some (limited) intestinal absorption, they have always said that use of the oral gel was contraindicated in patients with 'liver dysfunction'. They have also long warned that, because miconazole affects the action of the Cytochrome P450 enzyme system, oral absorption can affect the way the body handles a range of drugs including cisapride. Full dose systemic treatment with miconazole has also been shown to significantly slow the clearance of carbamazepine and phenytoin, and even topical use has been shown, on occasion, to greatly prolong the half life of warfarin.

However, in a move that caught clinicians by surprise, the company had a change to the Summary of Product Characteristics (SPC) agreed with the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK in April 2008. The new document makes it clear that the company are no longer prepared to recommend the use of the oral gel in any patient less than four months old (and cautions against use in any preterm infant less than six months old). No clear explanation for the change of advice was initially forthcoming, but the decision is now known to have been triggered by a case report published in Dutch in the Netherlands in 2004.¹

That report described a 17 day old child who choked on some of the viscous gel and briefly lost consciousness before recovering rapidly when gel was removed from the back of the throat. The report drew attention to nine other cases of a similar, but less alarming, nature in the Netherlands, all but two occurring in babies less than 2 months old. It is, perhaps, worth offering a translation of the key section of this case report.

" Patient A, a breast fed 17-day old girl born at 36 weeks. A few days after birth a white rash was noted in the mouth of the infant. This was diagnosed as thrush and the following were prescribed [a] Nystatin suspension 100,000 U/ml four times a day for the infant, and [b] miconazole cream to be applied to the nipples of the mother prior to each breast feed. No improvement was noticed after 14 days, and miconazole oral gel (2.5 ml four times a day) was prescribed. The instruction of the pharmacist to the mother was to apply the prescribed amount of gel to the nipple before and after a breastfeed. The mother followed the instructions.

During the next breast feed the patient, now 17 days old suddenly stopped drinking and breathing, became cyanotic and lost consciousness. The mother removed as much of the gel from the infant's mouth as possible, after which the patient recovered within a few minutes. The GP on duty was called out. He carried out a physical examination but found no abnormalities. The miconazole gel was not recommenced, and after some time the thrush disappeared. The patient did not suffer any more incidents after this, and three months later she was still well. "

What is so striking about this, and most of the other nine reports, is that all the mothers had been advised to give a small new born baby the same amount as the manufacturer would recommend for a 1–2 year old child or, in the words of the SP, "half a spoonful (2.5 ml)". Application at the start rather than the end of a feed was obviously inappropriate too (an issue over which the SPC still remains silent) given the clear controlled trial evidence that miconazole gel cures oral infection much better than nystatin drops^{2,3} mainly, one must suspect, because it stays in contact with the fungus for longer before it is swallowed.

Application to the mother's nipple was particularly inappropriate, and bore no relation to the way the manufacturer had said the product should be used. The SPC has always clearly said that "for localised lesions of the mouth, a small amount of the gel may be applied directly to the affected areas with a clean finger" and that, "for topical treatment of the oropharynx, the gel should be kept in the mouth for as long as possible." It has also long said that, in infants and young children, "the gel should not be applied to the back of the throat, and each dose should be divided into smaller portions." However the revised document now only recommends use in infants who are 4 or more months old, and says that "the lower age limit should be increased by 1–2 months for infants who are pre-term, or infants exhibiting slow neuromuscular development".

The continued failure of the manufacturer to recommend the use of a small dose four times a day rather than a large dose twice a day, given that fact that they recommend treatment four times a day in children more than 5 years old, is equally inexplicable. Since it is clearly easier to explain to a child of six that the gel needs to be left in the mouth as long as possible than it is to explain this to a toddler, one would have thought that the manufacturer would be recommending more frequent low dose use rather than less frequent high dose use in the very young child. (Lozenges rather than drops are used when using nystatin to treat oral infection in older patients precisely because this allows the drug to remain in sustained contact with the fungus.

There have been no reports of choking reported to the MHRA in the UK in the last 15 years (although two very young children did become dyspnoeic and a third became agitated). It is not, therefore, entirely clear why the MHRA agreed to the suggestion from the lawyers advising the manufacturer that the appropriate response to these incidents should be to stop recommending all use in children less than 4 months old, rather than providing much clearer advice as to how the gel should be applied, and recommending a much smaller dose for very small babies. A randomised trial in 51 young children in Switzerland by Schaad and Bachmann² back in 1983 had shown that: "Miconazole oral gel therapy [four times a day] resulted in an optimal [culture-validated] cure rate of 100%, and a relapse rate of only 4%, whereas for the nystatin suspension these values were 75% and 22% respectively." Hoppe's overview of the options in 1997³ was equally clear – he found that 5, 8 and 12 days treatment with oral miconazole cured oral thrush in 84.7%, 96.9% and 99.9% of all patients. The equivalent figures for oral nystatin were 21.2%, 37.6% and 54.1%.

Faced with evidence of this sort most clinicians will continue to prescribe oral miconazole rather than oral nystatin when they think that oral infection is the main problem, especially if they can see no need to treat the whole of the alimentary tract. They will accept the point made by Dr. De Vries and his colleagues that asymptomatic signs of thrush do not always call for treatment in the term baby, but they will be rather more reluctant to allow unchecked heavy colonisation with *Candida* in a preterm baby. They will also, hopefully, recommend that the product should only be used in a small baby in the way described in this *Formulary* for the last eight years:

“ **Oral Thrush:** Smear 1 ml of miconazole oral gel round the mouth and gums with a finger after feeds four times a day, and take steps to prevent re-infection as outlined in the monograph on nystatin. Continue treatment for at least 2 days after all the signs of infection have gone (usually 7–10 days in all). “

Having stressed to the family that no drug is safe unless it is given as prescribed, they will then have to explain to the parents *why* they are recommending miconazole gel even though the leaflet that the MRHA requires the manufacturer to issue with each tube of gel tells the parents very clearly “Do not use this medicine ... for an infant under 4 months of age because of the risk of choking”. That risk has been there for thirty years. Why it should suddenly trigger such an abrupt change of advice after all this time is hard to understand.

Even more frustratingly, an aspect of care that had been increasingly passed to Community Practitioner Nurse Prescribers can no longer be managed by them because they are not allowed to prescribe any medicine “off licence”. The same Government that has been trying to get senior and experienced nurses, midwives and health visitors in the UK more involved in supporting parents who are finding their baby reluctant to feed, or having difficulty breast feeding, has now allowed its Agency to deprive them of the authority to prescribe the one *topical* treatment for minor but troublesome thrush that is known to work and either compel them to prescribe a less effective treatment or refer the family to a doctor for treatment. As is so often the case, there has been a lack of joined-up thinking.

What should have resulted in a revision in the advice as to how much to give and how often to give it, and a further warning about the risk of giving an excessive amount, has instead resulted in an inappropriate recommendation that the best known treatment for oral thrush should not be used in children less than four years old. Many experienced paediatricians will ignore the manufacturer's change of advice, but will now have to spend time explaining to parents why they are ignoring that advice.

What is even more puzzling is that a few months before the MHRA took this decision, making it impossible for Community Practitioner Nurse Prescribers to prescribe miconazole gel for use by a baby less than four months old (although it is still an ‘off label’ option for Qualified Nurse Independent Prescribers as long as they take full clinical and professional responsibility for this), the Department of Health recently made a move in the opposite direction by deciding that the prescribing of nystatin *would* be allowed even for babies less than a month old even though the SPC does not support this. An update of the Department's web page headed “Nurse Prescribing FAQ” first posted on 31 July 2007 said:

“**Nystatin – Prescribing off label.** Community Practitioner Nurse Prescribers may exceptionally prescribe nystatin off-label for neonates. Where Community Practitioner Nurse Prescribers are absolutely clear that the diagnosis is one of oral thrush, they may prescribe nystatin in the dose recommended in the Childrens' BNF [100 000 units four times daily after feeds]. An exception for nystatin is allowed on the basis that there is no systemic absorption of the product and the use of the product in treatment of oral thrush is long-established. *This decision is without precedent and there are no other exceptions for off-label prescribing by Community Practitioner Nurse Prescribers.* Community Practitioner Nurse Prescribers who prescribe nystatin off-label must be clear that they accept clinical and medico-legal responsibility for prescribing that medicine. Community Practitioner Nurse Prescribers should only prescribe nystatin ‘off-label’ within their own competence and where they are clear that the diagnosis is one of oral thrush.”

What the thinking behind this decision was is far from clear. Neither is its legal basis. Staff are left knowing that they can prescribe a drug of limited efficacy, but can not prescribe a drug that seems perfectly safe and is much more effective as long as an appropriate dose is applied with a little thought and care.

Topical use of miconazole in pregnancy

The manufacturer's predictable advice to patients is to "Ask your doctor or pharmacist for advice before using this medicine if you are pregnant, think you are pregnant, planning to become pregnant or breast feeding". In fact there is good evidence that vaginal use is very safe in pregnancy. Those running the Michigan Medicaid programme founding, in a study of 229,101 pregnancies, that 3.2% of mothers had used the drug vaginally in the first trimester. A recognisable birth defect was found in 304 of their babies – a proportion that was no different from that seen in a control population (4.2 v. 3.8%).⁴ Given that only about 1% of a vaginally administered dose is absorbed this is not unexpected. Nothing is known about use during lactation, but the dose reaching the baby will be small, and the baby will absorb less than a third of that appears in the milk.

1. De Vries TW, Wewerinke ME, de Langen JJ. Bijna-verstikking van een zuigeling door miconazol orale gel. [Near asphyxiation of a neonate due to miconazole oral gel. *Ned Tijdschr Geneesk* 2004;**148**:1598–600.
2. Schaad UB, Backmann D. Prospektiver vergleich von miconazol-gel und nystatin-suspension in der therapie des mundsoors. *Schweiz Med Wochenschr* 1983;**113**:1356-62. [RCT]
3. Hoppe JE. Treatment of oropharyngeal candidiasis and candidal diaper dermatitis in neonates and infants: review and reappraisal. *Pediatr Infect Dis J* 1997;**16**:885–94. [SR]
4. Briggs GG, Freeman RK, Yaffe SJ. *Drugs in pregnancy and lactation*. 8th ed. Wolters Kluwer| Lippincott Williams & Wilkins: Philadelphia, 2008;1217–8

Comment posted July 2008