Role of itraconazole in haematology/oncology

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The antifungal agents most frequently used in prophylaxis and treatment are amphotericin B (and its new lipid forms) and azoles such as fluconazole, itraconazole, and more recently voriconazole. This review assesses the role of itraconazole in paediatric haematology/oncology practice. Its broader spectrum of activity and availability in oral and intravenous forms allow a flexible approach in the management of fungal infections.

Invasive fungal infections (IFI) are a major cause of morbidity and mortality among neutropenic cancer patients. Their incidence has increased over the past decade because of increasing intensity of chemotherapy regimens and the use of high dose therapy with stem cell rescue. In Europe and North America, candida and aspergillus infections are the most common. The diagnosis of IFI remains elusive and challenging and contrary to the case with bacterial infections, therapeutic intervention has limited success. As a result, prophylaxis and empirical pre-emptive therapy play a key role in patient management.

**PHARMACOLOGY AND PHARMACOKINETICS**

Itraconazole is highly lipophilic and is tightly bound to blood cells and plasma proteins, primarily albumin, leaving only 0.2% unbound. Because of its lipophilic nature, it is extensively distributed in tissues such as liver, lung, and bone where its concentration is 2–3 times higher than in serum. It is metabolised primarily in the liver, and the single dose pharmacokinetics are not affected by renal dysfunction. The erratic absorption and reduced bioavailability of the capsule form has been overcome with the introduction of a liquid formulation in cyclodextrin. The bioavailability of itraconazole oral solution is 60% higher than that of capsules. The absorption of the liquid formulation is enhanced if given under fasting conditions and is not affected by reduced gastric acidity in contrast to the capsule preparation. The capsule formulation requires food for dissolution of the drug from the solid formulation. The capsule preparation has a reduced bioavailability in a fasted state than when administered with food. The oral solution itraconazole is delivered into the stomach already adequately dissolved for maximum absorption. Because the solution does not require the intake of food, it is an important alternative for patients with reduced oral intake, hypoacidity, mucositis, or inability to swallow oral capsules. Use of acidic beverage (cola) aids in absorption of itraconazole capsule formation.

Pharmacokinetic studies in children have shown that plasma levels (measured by HPLC) higher than 250 ng/ml (necessary for effective prophylaxis) may be achieved after three days in 6–14 year old children, and after five days in children under 5 who received 5 mg/kg/day of itraconazole oral solution. In the majority of patients a steady state plasma level is reached after two weeks of itraconazole oral solution at a dose of 5 mg/kg daily. High concentrations have been detected in saliva for about eight hours after single dose of itraconazole oral solution.

In patients at high risk of IFI, such as those post-allogeneic stem cell transplantation procedures, who have severe mucositis or graft versus host disease (GVHD), manifesting as a wide range of upper gastrointestinal abnormalities, oral administration may be difficult and absorption may be reduced. Frequent vomiting or difficulty in swallowing can further hamper absorption and the achievement adequate levels of drug. Antacids may reduce absorption of itraconazole capsule formulation.

Intravenous itraconazole is now available and has helped to overcome these problems; it achieves steady state plasma concentrations in 48–96 hours.

Itraconazole can inhibit the metabolism of drugs used in oncology practice such as warfarin, cyclosporin A, clarithromycin, tacrolimus, and busulphan, resulting in reduced clearance and prolongation of the effects of these drugs. Itraconazole metabolism is increased by carbamazepine, phenytoin, and rifampicin. The combination of itraconazole and vincristine may exacerbate the neurotoxicity of the latter.

**MECHANISM OF ACTION**

Itraconazole is a broad spectrum triazole antifungal agent with three nitrogen atoms, resulting in an increased affinity to, and ultimately inhibition of, fungal cytochrome P450. Fluconazole similarly has three nitrogen atoms, but has a hydrophilic side chain. The inhibition of cytochrome P450 prevents the synthesis of ergosterol, a vital component of the fungal cell membrane. Itraconazole’s main metabolite, hydroxyitraconazole, reaches higher plasma concentrations than the parent compound and has in vitro antifungal activity similar to that of itraconazole.

**Abbreviations:** GVHD, graft versus host disease; IFI, invasive fungal infections
ADVERSE EFFECTS
A recent study in children showed that itraconazole oral solution is generally well tolerated and safe. Some patients experienced diarrhoea secondary to ciclosporin. Other common minor side effects include constipation, abdominal pain, nausea, and headache. 

PROPHYLACTIC USE
The mortality rate of IFI remains very high, despite the availability of many antifungal agents. This has led to the use of pre-emptive therapy in patients at high risk of IFI, such as those with severe prolonged neutropenia and/or impaired cellular immunity. Patients with GVHD on immunosuppressive therapy following allogeneic stem cell transplantation, particularly after mismatched or unrelated transplant, are at particular risk. The most common fungal infections in cancer patients are candida and aspergillus species. Itraconazole is effective against both and would seem an ideal drug for prophylaxis. A recent non-randomised study in children undergoing intensive chemotherapy with or without stem cell rescue suggested that itraconazole 2.5 mg/kg twice daily (median duration of prophylaxis 37 days) was safe and could be used for prophylaxis in high risk children. Randomised trials comparing itraconazole with fluconazole, amphotericin B, or placebo showed that the former is well tolerated and might decrease the incidence of fungal infection in cancer patients. As with other azoles, emergence of itraconazole resistant candida and aspergillus has been reported, particularly following prolonged use.

ITRACONAZOLE IN THE TREATMENT OF PRESUMED OR PROBABLE FUNGAL INFECTION
Itraconazole, with its safety and broad spectrum activity against both aspergillus and candida, is a good alternative to amphotericin B. Other possible indications include:

• Allergic reaction to amphotericin or liposomal amphotericin, or increased potassium requirements
• Deteriorating renal function
• Candidiasis resistant to fluconazole treatment
• Proven systemic aspergillism.

The usual dose schedule is 2.5 mg/kg intravenously twice daily for the first two days to achieve a good plasma concentration followed by once daily dose for the duration of treatment. Oral itraconazole 5 mg/kg/day may be used as an outpatient if a prolonged treatment is required. Blood levels have been recommended in patients on oral therapy or with documented fungal infections to ensure a satisfactory plasma level is achieved.

Prospective economic analysis of intravenous itraconazole compared to conventional and liposome amphotericin B was conducted in six European countries to evaluate the cost and cost-effectiveness of intravenous itraconazole in patients with presumed IFI. It was concluded that itraconazole might be a cost-effective option compared to other agents. At a daily cost of €103 per 200 mg, itraconazole produced savings compared with conventional amphotericin B in Germany, UK, Italy, and Sweden, ranging from €629 to €2201 per patient.

CONCLUSION
Itraconazole has proven record of successful treatment of IFIs. It is better tolerated than amphotericin and cheaper than liposomal amphotericin. Antifungal prophylaxis using itraconazole oral solution may reduce fungal infections in neutropenic patients with haematological malignancies, and has the potential to prevent reactivation of fungal infection in patients with previous fungal infection. There is a need for randomised studies in children to clarify the indications for this drug in haematology practice.

REFERENCES
1 Bodley GP. Infections in cancer patients, a continuing association. Am J Med 1986;81:11-26
IMAGES IN PAEDIATRICS

Craniosynostosis due to premature closing of the sagittal suture

A 7 month old boy was admitted to our paediatric department with a fever up to 40°C and diarrhoea. Physical examination revealed closed anterior fontanelle, scaphocephaly (long and narrow skull) (fig 1), frontal bossing, and two hair whorls. Head circumference was 47.5 cm (above 97%). Previous records of head circumference showed continuous growth on the same percentile. His neurological examination was normal as well as his development. A CT scan with 3D construction (fig 2A and B) revealed early closure of the sagittal suture.

Craniosynostosis is defined as premature closure of the cranial sutures. The incidence of primary craniosynostosis is 1/2000 births. Scaphocephaly is sporadic and more common in males and may cause difficulties during labour. Scaphocephaly does not produce increased intracranial pressure or hydrocephalus, and neurological examination results of affected patients are normal.

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