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BRIEF REPORT

Posaconazole salvage treatment in paediatric patients: a multicentre survey

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Abstract While a paediatric dosage has not been defined, posaconazole is occasionally being used in children. We conducted a multicentre retrospective survey and identified 15 patients (median age 10 years [range 3.6–17.5]) who received posaconazole salvage therapy for proven (9 patients) or probable (6 patients) invasive fungal infections. Posaconazole was administered for a median of 32 days (range 4–262) at a median dosage of 21 mg/kg (range 4.8–33.3). None of the patients discontinued therapy due to adverse events, which were mostly mild and observed in 11 patients. Complete or partial responses were observed in 4/7 patients with zygomycosis, 3/4 patients with invasive mould infection, 1/2 patients with invasive aspergillosis and 1/2 patients with chronic disseminated candidiasis. We conclude from the data that posaconazole displays favourable safety and tolerance and may be useful for management of individual paediatric patients with invasive infections.

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Posaconazole (Noxafil®) is a novel oral second generation antifungal triazole. Due to its extended activity, posaconazole is widely used in adult patients. While a paediatric dosage has not been defined, posaconazole is occasionally being used in children. Here we report the results of a multicentre retrospective survey on safety and efficacy of posaconazole salvage therapy in children.

Patients eligible for inclusion were <18 years of age, had received at least one dosage of posaconazole, and had begun posaconazole therapy prior to the start of the survey. The compound was administered orally at dosages individually determined by the responsible physician until occurrence of intolerance or maximum efficacy on the basis of refractory infection, intolerance of or contraindications to standard therapies, or as best individual therapeutic option. The study was approved by the local ethics committee of Münster, the site of one of the principal investigators (AHG). Invasive fungal infections and response to treatment were classified according to the published EORTC/MSG criteria and a previous clinical trial of antifungal salvage therapy, respectively [1, 2]. Clinical adverse events were recorded and graded according to current Common Toxicity Criteria [3]. For statistical comparisons of continuous data, the Mann-Whitney U test was used. A P value of <0.05 was considered as significant.

The survey identified 15 patients (9 girls, 6 boys; median age 10 years, range 3.6–17.5) who received posaconazole as salvage treatment for proven (n=9) or probable (n=6) invasive fungal infection (7 cases with zygomycosis, 4 cases with invasive mold infection, 2 cases with invasive aspergillosis, and 2 cases with chronic disseminated candidiasis) (Table 1). To the best of our knowledge, this is the largest case series of the use of posaconazole in children with proven and probable invasive fungal infection. Most patients had acute leukaemia (10 cases), one patient each suffered from non-Hodgkin lymphoma, aplastic anaemia, solid tumour, soft tissue trauma, chronic granulomatous disease, and diabetes mellitus. Three patients were allogeneic haematopoietic transplant recipients. Nine patients had been exposed to therapeutic dosages of glucocorticosteroids and nine patients had a period of profound neutropenia (≤500/μl) within the four weeks prior to the start of posaconazole. All patients had received systemic antifungal therapy prior to treatment with posaconazole (median duration 22 days, range 4–319), in most cases with at least two antifungal agents in combination or sequentially. Six patients received posaconazole as single agent, and nine patients in combination with other systemic antifungal compounds (3 cases with amphotericin B, 1 case with caspofungin, and 5 cases with amphotericin B and caspofungin). The median duration of treatment with posaconazole was 32 days (range 4–262); the median daily dosage was 21 mg/kg (95%CI 17–25; range 4.8–33.3). Seven patients received posaconazole at a daily dosage of 600 mg or less (6 patients <13 years of age), 7 patients at a daily dosage of 800 mg (3 patients <13 years of age), and one 10-year old at a daily dosage of 1200 mg. Plasma levels of posaconazole were not determined in the majority of the patients due to the lack of drug monitoring for posaconazole in most centres.

In none of the patients was treatment with posaconazole discontinued due to clinical or laboratory adverse events (AEs). Irrespective of cause, 22 clinical AEs were observed in 11 patients (73%). Most AEs (18/22; 8 patients) were of grade I/II; 4/22 recorded AEs were grade III (3 patients). There was no relationship between incidence of AEs and dosage of posaconazole. The most commonly recorded AEs were fever, nausea and/or vomiting, abdominal pain, diarrhea, headache, and skin eruptions. Increases in laboratory hepatic and renal function parameters during therapy were frequent in this population of severely immunocompromised children usually receiving multiple concomitant drugs. However, the mean of the last available values during treatment of liver transaminases, bilirubin, alkaline phosphatase and creatinine were not significantly different from baseline. Overall, both pattern and extent of adverse events observed in this survey do not appear to be substantially different from those reported in adults [4–6].

When analysing efficacy of posaconazole salvage therapy, complete or partial responses were observed in 60% of the patients: in 4/7 patients with zygomycosis, in 3/4 patients with invasive mold infections, in 1/2 patients with invasive aspergillosis, and in 1/2 patients with CDC (Table 1). Overall survival at 3 months post start of

Table 1 Responses to posaconazole salvage therapy

Infection	Number of patients				
	CR	PR	SD	NR	Survival
Invasive zygomycosis (4/3)	3	1	1	2	5/7
Invasive mold infection (4/0)	2	1	–	1	2/4
Invasive aspergillosis (1/1)	–	1	–	1	2/2
Chronic disseminated candidiasis (0/2)	1	–	1	–	2/2
All (9/6)	6	3	2	4	11/15

The numbers of proven/probable invasive fungal infections are given in parenthesis

CR complete response, *PR* partial response, *SD* stable disease, *NR* non-response

treatment was 73% (11/15). Although we recognise that the assessment of efficacy is curtailed by the retrospective nature of this analysis and different indications, the rate of complete or partial responses in our survey was comparable to adults receiving posaconazole salvage therapy [7–10].

In summary, the results of our analysis indicate that posaconazole may be safe and efficacious in the salvage management of invasive fungal infections in immunocompromised children and adolescents. However, the data of ongoing dose-finding pharmacokinetic studies are urgently needed before posaconazole can be recommended in children as salvage treatment for invasive fungal infections.

Conflict of interest TL has received grants from Gilead; he is a consultant to Gilead, Merck, Sharp & Dohme and Schering-Plough, and served at the speakers' bureau of Astellas, Gilead, Merck, Sharp & Dohme and Schering-Plough. AHG has received grants from Gilead and Merck, Sharp & Dohme; he is a consultant to Astellas, Gilead, Merck, Sharp & Dohme and Schering-Plough, and has served at the speakers' bureau of Astellas, Gilead, Merck, Sharp & Dohme, Pfizer, Schering-Plough and Zeneus/Cephalon. All other authors have nothing to declare.

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