Voriconazole plasma monitoring
A C Pasqualotto,1,2 M Shah,3 R Wynn,4 D W Denning1,2,5

ABSTRACT

Aims: Very little information is available regarding the use of voriconazole drug monitoring in children with invasive fungal infections. The purpose of this study was to report the cases of five paediatric patients treated with voriconazole, in which plasma levels were used to monitor therapy.

Methods: Five children treated with voriconazole were included in this case series. Voriconazole plasma levels were determined using either a bioassay or liquid chromatography–tandem mass spectrometry.

Results: The patients’ ages ranged from 2 to 10 years old (mean 6.2 years). Three patients had acute leukaemia and two had suffered severe burn injuries. Doses administered varied from 3.4 mg/kg every 12 h to 8.1 mg/kg every 8 h. Plasma voriconazole concentrations were unpredictable for these paediatric patients. Subtherapeutic levels were frequently observed, despite progressive increments in dosage. For others, voriconazole levels markedly increased after a small increment in dosage. Phenytoin caused important drug interactions with voriconazole for two of the patients.

Conclusions: The dose administered did not correlate with exposure as measured by plasma levels of voriconazole. While the optimal dosage for voriconazole in children is still unknown, drug monitoring seems warranted to ensure adequate exposure, and after dose increments to prevent excessive exposure. Drug interactions significantly altered exposure.

Voriconazole is a second-generation triazole antifungal agent with enhanced in vitro activity against various fungi. It is considered to be a first line primary therapy for invasive aspergillosis, and is equivalent to a regimen of amphotericin B followed by fluconazole for the treatment of candidaemia. However, since clinical studies with voriconazole have included only adults (>11–18 years old), experience in paediatric patients has been limited to case reports or series of cases. Accordingly, the optimal dose of voriconazole in children has not been fully established, but it is believed to be greater than adult dosing. The purpose of this paper is to report the cases of five

METHODS

Five children treated in different hospitals in the United Kingdom were studied. All patients received voriconazole as a loading dosage (range, 5.2–6.0 mg/kg intravenously in two dosages) and 3.4–6 mg/kg intravenously twice daily thereafter.

Voriconazole plasma levels were determined at the Regional Mycology Laboratory, Salford. Before 2002, samples were processed using a bioassay. In recent years, voriconazole has been measured by liquid chromatography–tandem mass spectrometry. This validated method is sensitive and faster than the bioassay or high-pressure liquid chromatography–UV methods. Targeted trough voriconazole levels were 0.25–6.0 µg/ml. The lower limit of quantification was 0.1 µg/ml. Concentrations below that limit were recorded as zero.

RESULTS

Table 1 summarises the clinical findings from the five paediatric patients studied (three patients with leukaemia and two patients with burns). Voriconazole levels and dose adjustments for these patients are presented in fig 1.

DISCUSSION

Voriconazole is known to have variable pharmacokinetics. In adults, steady-state plasma levels after 3–6 mg/kg twice daily intravenous infusion range from 3–6 µg/ml. Steady-state concentrations are achieved after 5–6 days (shorter if a loading dose is given). After 200 mg twice daily orally in adults, steady-state plasma concentrations generally range from 2–3 µg/ml. However, in a study of voriconazole for the treatment of invasive aspergillosis, patients on standard doses demonstrated levels in plasma ranging from <0.1 µg/ml to as high as 9.7 µg/ml. Studies in adults revealed nonlinear pharmacokinetics, which are thought to be related to saturation of metabolism, resulting in a threefold increase in the area under the curve (AUC) following a 33% increase in dosage. Thus, there is substantial inter-subject variability in the plasma concentrations achieved, especially in patients suffering from drug-drug interactions. CYP2C19, the major isozyme implicated in the metabolism of voriconazole, exhibits greater genetic polymorphism. As a result of a point mutation in the respective gene, some people are poor metabolisers, while some others are rapid metabolisers. Up to 7% of whites and ~20% of non-Indian Asians have a deficiency in the expression of this enzyme. The observed interpatient variability in voriconazole levels is ~100-fold, and we are not aware of any other anti-infective agent with a similarly profile.

Unlike the findings in adults, studies have revealed that voriconazole undergoes linear pharmacokinetics in children. Paediatric patients have a higher capacity for elimination of voriconazole per kg of body weight than do adult healthy volunteers, and dosages of 4 mg/kg may be required in children to achieve exposures consistent with those in adults following dosages of 3 mg/kg. Preliminary evidence suggests that the mean AUCT associated with a dose of 8 mg/kg taken intravenously in children approaches that seen with 4 mg/kg in adults. Export, recommended dosage of intravenous voriconazole in 2–11-year-old...
patients is 7 mg/kg every 12 h, and no loading dose is recommended. Recommended oral maintenance dosage for these paediatric patients is 200 mg every 12 h. Because of the assumed limited gastrointestinal transit time, oral suspension should be preferred to the tablet formulation. There are no formal recommendations so far for the use of voriconazole in children in the United States. Given the relative unpredictability of voriconazole levels, measurement of plasma concentrations to identify extreme levels is warranted. In a previous study, patients with invasive aspergillosis who failed to demonstrate random levels >0.25 μg/ml had a higher probability of treatment failure. These findings were also confirmed in a recent study, which showed a significant relationship between disease progression and drug

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**Table 1** Summary of patients’ characteristics

<table>
<thead>
<tr>
<th>Case</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underlying diseases</td>
<td>ALL</td>
<td>T-cell ALL</td>
<td>Severe burn injuries; multiple</td>
<td>Severe burn injuries; multiple</td>
<td>Acute myelocytic leukaemia</td>
</tr>
<tr>
<td>Schedule</td>
<td>B</td>
<td>C</td>
<td>debridements</td>
<td>debridements</td>
<td>M5</td>
</tr>
<tr>
<td>Disease presentation</td>
<td>Left paraspinal lump while on</td>
<td>Left hemiparesis on day 34</td>
<td>Wound infection, sepsis</td>
<td>Seizures, severe</td>
<td>Sinusitis, orbital cellulitis and</td>
</tr>
<tr>
<td></td>
<td>the maintenance phase</td>
<td>34</td>
<td>after chemotherapy</td>
<td>encephalopathy</td>
<td>proptosis</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Aspergillus fumigatus abscess on</td>
<td>A. fumigatus</td>
<td>Probable</td>
<td>Invasive cutaneous</td>
<td>Invasive sinusits caused by</td>
</tr>
<tr>
<td></td>
<td>the back. Later CNS aspergillosis</td>
<td>back.</td>
<td>Aspergillus</td>
<td>aspergillosis</td>
<td>A. fumigatus</td>
</tr>
<tr>
<td>Concomitant drugs*</td>
<td>Vincristine</td>
<td>Ambisome, Caspofungin</td>
<td>Caspofungin</td>
<td>Phenobarbitone (previous</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>week), Midazolam</td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Voriconazole failed to contain CNS</td>
<td>Died in 6 months. Positive</td>
<td>Died within 1.5 month</td>
<td>Died in 8 days</td>
<td>Clinically stable (followed by</td>
</tr>
<tr>
<td></td>
<td>infection (replaced by caspofungin</td>
<td>PCR test for Aspergillus in</td>
<td></td>
<td></td>
<td>140 months)</td>
</tr>
<tr>
<td></td>
<td>and posaconazole). Clinically stable</td>
<td>the CSF just before death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(followed by 27 months)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

ALL, acute lymphoblastic leukaemia; CNS, central nervous system, PCR, polymerase chain reaction; CSF, cerebrospinal fluid. *Only drugs taken concomitantly with voriconazole were listed here. Apart from systemic antifungal drugs, only medications that could potentially cause drug interaction with voriconazole were listed. Each case is posted at www.aspergillus.org.uk as case histories.
Voriconazole is an antifungal drug with marked inter-patient variation. Higher dosages of voriconazole are required to obtain the same plasma levels in children than in adults.

What this study adds

- Appropriate voriconazole plasma levels are difficult to obtain in children, and marked intra-patient variability in these levels occurs.
- Optimal voriconazole dosage will probably require adjustments on an individual basis.

REFERENCES

5. Walsh TJ, Driscoll TA, Ainetta AC, et al. Pharmacokinetics, safety, and tolerability of voriconazole in hospitalized children. 46th Interscience Conference on Antimicrobial
An adolescent otherwise healthy male presented with acute onset chest pain. Physical examination was remarkable for early diastolic murmur of aortic regurgitation. Transthoracic and subsequently transoesophageal echocardiography revealed aortic dissection extending to the arch. CT angiography revealed a circumferential type of aortic dissection extending from the aortic root to the arch (type A) with extension of the dissection flap into the right brachiocephalic artery (fig 1).

**DISCUSSION**

The typical aortic dissection appears on contrast enhanced CT as an intimal flap that separates the false from the true lumen. Features indicative of a true lumen are outer wall calcification and eccentric flap calcification; beak sign, larger cross sectional area and slow enhancement are indicators of a false lumen. In some instances, an atypical configuration of intimal flap is encountered. These include a calcified false lumen in chronic cases, an aorta with three or multiple channels, an extremely narrow true lumen, or rarely, as in the present case, a circumferential intimal flap. The latter may be further complicated by intimointimal intussusception, although this was not evident in our case.

**Figure 1** Enhanced CT shows an intimal flap in the ascending aorta.

### Images in paediatrics

**Circumferential aortic dissection**

An adolescent otherwise healthy male presented with acute onset chest pain. Physical examination was remarkable for early diastolic murmur of aortic regurgitation. Transthoracic and subsequently transoesophageal echocardiography revealed aortic dissection extending to the arch. CT angiography revealed a circumferential type of aortic dissection extending from the aortic root to the arch (type A) with extension of the dissection flap into the right brachiocephalic artery (fig 1).

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**Competing interests:** None.

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### REFERENCES

ADOS-G total scores and in the proportions regressing were small and entirely non-significant. The study still had power to detect a quite modest difference between cases and controls, of just one tenth of the range of normal variation: “Comparison of the combined case and control groups had 80% power to detect a mean titre difference of 45% (or 0.16 log10(mIU/mL))”.

The method of using peripheral blood mononuclear cells (PBMCs) as a proxy for gut mucosa has been employed in earlier studies and by Dr Wakefield. Measles virus replicates widely in immunologically active cells and if present in the gut mucosa, would be expected to be present in PMBC.

The proportion of children with regression (21%) is expected from other studies and does include children whose parents date the onset of regression and autism to within 2 weeks of the MMR vaccination.

Further research into gastrointestinal symptoms in ASD is certainly needed. We have assessed (as described) a range of gastrointestinal symptoms in cases and controls (report in preparation) and many parents of children reported past vomiting, abdominal pain, diarrhoea and constipation (fewer reported current symptoms). We defined enterocolitis (the term used by Wakefield) as described, a definition familiar to paediatric gastroenterologists and replicable. Only one child in the control group had such a constellation of symptoms. A period of 14 days should be long enough to exclude short term infections.

Dr Wakefield continues to assert a causative relationship between the MMR and autism. While no one study on its own can be considered absolute proof, the accumulated evidence of epidemiological and clinical studies, including our own, shows no plausible causative link between MMR and autism. More than a coincidence in timing is needed. Dr Wakefield’s findings have not been independently confirmed. The d’Souza paper provides evidence of the “vulnerability of PCR technology to support claims of association” with high likelihood of false positives. An alternative question that can be asked of proponents of the view put forward by Wakefield and colleagues is: “What is the scientific evidence of such a link?”.

**REFERENCES**


**BOOK REVIEW**

Ollie


Ollie is a true account of a brave boy with autism who is later diagnosed with leukaemia. Ollie’s father, Stephen Venables, is a fantastic and experienced writer who is able to draw in the reader. The book is an honest portrayal of the difficulties faced by a family when a child is diagnosed with autism and subsequently leukaemia. It gives incredible insight into life with an autistic child, helping the reader imagine how the disorder takes over and dominates family life.

Frequently, trainees feel they have had very limited exposure to autism, their knowledge being based on the film *Rain man*. Reading this, I was able to empathise and see how a diagnosis of autism affects everyday family life. From a paediatric training perspective, it is much easier to understand and remember the key features of autism reading this book than a textbook. For example, it portrays what Ollie was like at nursery school – useful if you are asked to carry out a school visit. The book made me aware of the detail that families remember of encounters with the medical profession. For professionals, a patient may be one of many we see each day, whereas for the family, the encounter and its details are far more memorable. We read of how Ollie’s family set out guidelines for staff regarding the way they would like Ollie to be treated. There are also many pages where hospital medicine is described from a family perspective, so acute paediatric trainees will also benefit. A well thought out index and bibliography provides useful reference material for professionals, making it easy to refresh memories on different therapies.

The book describes in detail the pathway from parental concern to a diagnosis of autism and the various types of treatment. Many alternative therapies are discussed as Ollie’s mother Rosie tries desperately hard to find anything that might help, including dietary supplementation as well as restriction. The education process is covered well, and a description of a battle with the local education authority is included. I learnt many things about alternative therapies and how Ollie’s family felt. Discussions of different therapies are fairly balanced, as the family weigh up the benefits and disadvantages of each, as well as acknowledging the medical profession’s scepticism on occasion. The Lovaas method, which often is non-covered in conventional community paediatric textbooks, is described as part of the narrative. The author has woven explanations of different techniques into Ollie’s story, maintaining a balance of opinions with accounts of why and how Ollie’s parents chose techniques they thought would help him.

However, this book comes with a caution. Many of the controversies surrounding autism are discussed, and although opinions are given equal weight, the book cannot be used as medical fact. For example, Ollie was described as having an “overall pattern of reduced health” immediately following his MMR, and it is stated that “perhaps... the combined vaccine at fifteen months did lasting damage”.

I would not recommend this book to parents of autistic children when the diagnosis is first made as it is almost too raw and tragic, especially in light of Ollie’s subsequent death from leukaemia. However, I would strongly recommend this book to all paediatric trainees and consultants, regardless of whether they are based in the community or not. I hope those that read it will be inspired to reflect upon how their interactions with families are seen by the families themselves.

A Raykundalia

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**CORRECTION**

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The last sentence of the results section of the abstract should read “Phenobarbitone caused important drug interactions with voriconazole for one of the patients.”