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Letters to the Editor

5 June 2003

Dear Editor,

PALIVIZUMAB PROPHYLAXIS OF RESPIRATORY SYNCYTIAL VIRUS INFECTION IN HIGH-RISK INFANTS: A NOTE OF CAUTION

We read with interest the article by Vogel *et al*. regarding respiratory syncytial virus (RSV) monoclonal antibody prophylaxis.[1] We would like to raise a few issues that are relevant to this article. First, the RSV infection rate that is reported in the literature is between 5 and 17%, both from studies in the UK and USA.[2–4] Over the past 2 years (January 2001–April 2003), our unit has cared for 61 infants (gestation range 24–32 weeks, median 26 weeks) with chronic neonatal lung disease/bronchopulmonary dysplasia (BPD) on home oxygen therapy. Over this time period, the RSV infection rate was 14.8% (9/61), with a hospitalization rate of 9.8% (6/61). The infection rate and hospitalization figures[5] for the New Zealand cohort appear significantly different. There are probably multiple reasons for this (geography, weather, housing, general virulence of virus strains). Second, the cost-effective analysis calculated is based on the local infection and readmission rates. The Impact study[6] percentages have been used to derive the number needed to treat (NNT) of 6 for the BPD group. Our experience is different and the equivalent calculations would result in a NNT of 30 to achieve the 39% reduction reported in the Impact study (Table 1).[6]

Finally, the benefit of RSV prophylaxis in an Australian intensive care setting has been reviewed and no significant cost benefits were found.[7] Our south-east Queensland data also suggest that the BPD cohort do not show a cost benefit on the model applied in the Vogel *et al*. article.

In the article by Vogel *et al*., it may be useful to note that in the comparison of international recommendations, the UK guidelines quote from the manufacturer[8] and not from a peer reviewed article.[9]

The recommendations that are put forward by Vogel *et al*. are justified for the New Zealand population but should not be generalized to the Australian population. Currently available evidence concerning the cost-benefit of palivizumab does not support its use in the Australian population of infants with BPD discharged home on supplemental oxygen therapy. Until such evidence becomes available (ideally a well-designed cost-effectiveness trial specifically for the Australian population) the use of palivizumab has to be a clinical decision taken on a patient-to-patient basis.

Table 1 Calculations based on Impact[6] criteria of relative-risk reduction of 39% for BPD infants

Control event rate (%)	Experimental event rate (%)	Absolute risk reduction (%)	NNT	Cost/case prevented from hospitalization
9.8	6.5	3.3	30	$NZ143 000

BPD, Bronchopulmonary dysplasia; NNT, number needed to treat.

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14 June 2003

Dear Editor,

FLUOXETINE INDUCED AUDITORY HALLUCINATIONS IN AN ADOLESCENT

We report a very serious and unexpected side effect with the off-label use (i.e. the use of medications outside the terms of Australian approved product information) of a selective serotonin reuptake inhibitor (SSRI), fluoxetine, for the treatment of depression in an adolescent male.

A 16-year-old boy presented with depression and suicidal ideation. He was assessed and was found to have a major depressive disorder, he was initially managed with individual psychotherapy and parental support. After 8 weeks there was no improvement and he continued to deteriorate in his school and social functioning and so was commenced on fluoxetine 20 mg mane. There were no psychotic symptoms. After 3 days on fluoxetine, he presented acutely with auditory hallucinations telling him to kill his mother, father, sister and himself. He recognized these voices as ego-dystonic and was extremely distressed by them. His medication was ceased and he required a short course of clonazepam to sedate him for his marked agitation. Three days later his hallucinations ceased. There have been no recurrences. After 6 months of individual psychotherapy, he has made a good recovery from his depressive episode.

The use of antidepressants in children has increased.[1] Much of this use in children and adolescents is off label. With this increasing off-label usage, clinicians need to be vigilant for unusual adverse events; this is because it is unlikely that rare side effects, as reported in this letter, would be identified in a clinical trial. With regards to SSRI, there have been reports of mania and agitation, but an extensive literature search has failed to demonstrate previous reports of isolated auditory hallucinations in adolescents. There have, however, been reports of hallucinations with use of fluoxetine in adults. This present case demonstrated a good temporal relationship between the use of the drug and the onset of symptoms; with cessation of the drug there was cessation of his symptoms. Although improvement on de-challenge is an important indicator of causality, it should be noted that without rechallenge it cannot be excluded that the hallucinations occurred independently of the start of fluoxetine. Rechallenge was not possible in this case as the patient was very distressed by his symptoms and was very reluctant to restart fluoxetine or another related drug.

The data on which this increased use of antidepressants in children have been based on have largely been extrapolated from work in adults. There are few randomized controlled trials exploring the efficacy of SSRI in children and adolescents with depression. In only two randomised-controlled trials using fluoxetine for paediatric depression was a response above that of placebo seen.[2,3] Given the limited efficacy data and the potential serious side effects, we would currently advise caution in the use of SSRI for off-label use in children and adolescents.

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Dear Editor,

SEVERE VINCRISTINE NEUROTOXICITY WITH CONCOMITANT USE OF ITRACONAZOLE

We would like to share our experience of severe itraconazole–vincristine interaction which emphasizes the need to use this particular antifungal agent with caution when co-administering vincristine to patients. Itraconazole, with its broad-spectrum of antifungal activity, is often prescribed for childhood cancer patients for both treatment and prophylaxis of fungal infections. However, many of the chemotherapy protocols that these children are treated with, especially for lymphoid malignancies, also include the vinca alkaloid, vincristine.

Our first patient was an 8-year-old boy with T-cell acute lymphoblastic leukemia (ALL) who was receiving induction therapy with oral dexamethasone and weekly intravenous vincristine (1.5 mg/m^2). Concomitantly, he received prophylactic itraconazole (5 mg/kg per day) as there had been a recent rise in the incidence of fungal infections in our unit. This was believed to be related to major building and earth works being carried out in the vicinity of the hospital. Four days after the third dose of vincristine, he presented with bilateral ptosis and paralytic ileus. Twenty-four hours after the onset of the initial symptoms, he developed generalized tonic-clonic seizures with progression to status epilepticus. Examination of the cerebrospinal fluid (CSF) and computerized tomography of the brain were normal. Serum sodium at this time was 120 mmol/L and serum osmolarity was 205 mosm/L, suggesting a syndrome of inappropriate antidiuretic hormone secretion (SIADH) as the cause of severe hyponatremia.

He required assisted ventilation for 72 h and the seizures were controlled with phenytoin. The combination of neurotoxicity and SIADH pointed to vincristine toxicity, which was likely to have been aggravated by co-administration of itraconazole. Following cessation of itraconazole and reduction in the subsequent doses of vincristine, the SIADH resolved after 2 weeks while the bilateral ptosis resolved 3 weeks thereafter.

The second patient was a 2-year-old boy with precursor B-cell ALL who was also started on prophylactic itraconazole with the commencement of induction chemotherapy. After the second weekly dose of vincristine (1.5 mg/m^2), he presented with severe abdominal pain associated with abdominal distension and absent bowel sounds. He was diagnosed as having vincristine-induced ileus. This improved after 8 days with conservative measures. He was then deemed well enough to receive the third dose of vincristine. The itraconazole was not stopped. Unfortunately, 2 days after receiving the vincristine, he returned with inability to walk and to pass urine. Clinical examination revealed bilateral lower limb weakness grade 2/5, areflexia, a palpable bladder and reduced anal tone. An urgent magnetic resonance imaging (MRI) scan ruled out a spinal cord lesion.

However, the MRI scan of the brain showed bilateral symmetrical demyelinating changes in the parietal and occipital areas. This was thought to be consistent with vincristine neurotoxicity and this diagnosis was further supported by the electromyography findings, which showed electrophysiological evidence of sensorimotor peripheral neuropathy. Examination of the CSF was normal. Itraconazole was stopped and the remaining two doses of vincristine were omitted. The paraparesis and bladder control improved over the following 4 weeks.

Although vincristine neurotoxicity is not an unknown entity,[1] such side effects are unusual with the cumulative doses

administered to both these patients (5 mg in patient 1 and 2.7 mg in patient 2).

The most likely explanation is the co-administration of itraconazole, which blocks the CYP3A subfamily of hepatic cytochrome P450 enzymes which then leads to the consequent delay in the metabolism of vincristine. In addition, itraconazole inhibits the P-glycoprotein efflux transport pump of the cells, resulting in high intracellular vincristine levels.[2] Clinicians administering chemotherapy need to be aware of the interaction between vincristine and itraconazole, where even a single dose can lead to severe toxicity.[3–5] Although previous reports of itraconazole interaction have only involved vincristine, it is reasonable to assume that all vinca alkaloids interact in the same manner because they share similar metabolism pathways. We agree with the recommendation that prophylactic itraconazole be interrupted during the time of vincristine administration to minimize the incidence and/or severity of neurotoxicity which in turn leads to the omission of scheduled vincristine doses and deviation from the treatment protocol.

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