ORIGINAL RESEARCH

Nitazoxanide for the treatment of infectious diarrhoea in the Northern Territory, Australia 2007-2012

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A B S T R A C T

Introduction: Australian Indigenous children suffer a high burden of diarrhoeal disease. Nitazoxanide is an antimicrobial that has been shown to be effective against a broad range of enteropathogens. To date, its use has not been reported in the tropical Top End (northernmost part) of the Northern Territory, Australia. The objective was to describe the use of nitazoxanide at the Royal Darwin Hospital, Northern Territory, and to assess any association with the time to resolution of diarrhoea.

Methods: Eligible children (≤13 years) were identified from dispensary records as having been prescribed nitazoxanide during the audit period, 1 July 2007 to 31 March 2012. Patient demographics, symptoms, diarrheal aetiology, treatment details and clinical outcomes were obtained by chart review.

Results: Twenty-eight children were treated with nitazoxanide, mostly for *Cryptosporidium* infection associated with prolonged diarrhoea. Dehydration was evident in 27 (96%) children on admission, and 11 (41%) were underweight. Diarrhoeal duration prior to treatment was 11.5 days (6.5 days pre- and 5 days post-admission). For children ≥12 months, nitazoxanide was prescribed according to guidelines stipulated by the Centers for Disease Control and Prevention (CDC). Resolution of diarrhoea occurred a median of 2.4 days (IQR: 1.4–7.3) after starting treatment. An increase in weight for length at discharge was found for all children.

Conclusions: Prompt resolution of diarrhoea without adverse outcomes suggests nitazoxanide may be an effective treatment for *Cryptosporidium* infection in this setting. Its role in the treatment of other causes of infectious diarrhoea needs further investigation. Randomised trials will further direct its use and determine optimal dosing regimens.

Key words: Cryptosporidium, diarrhoea, gastroenteritis, Indigenous, nitazoxanide, paediatric.

Introduction

Infectious diarrhoea is common in children. Globally, it is the third leading cause of mortality in children less than 5 years, accounting for 800 000 deaths annually[1]. In the Northern Territory, Australia, Indigenous children are disproportionately burdened, with higher rates of hospitalisation and longer duration of illness than non-Indigenous children[2]. Prolonged and recurrent episodes of diarrhoeal illness can result in environmental enteropathy syndrome, and complications including severe dehydration, acidosis and hypokalaemia are more common[3]. Diarrhoeal episodes often compound the problem of co-existing malnutrition, risking sub-optimal growth and poor cognitive outcomes[4]. Rehydration and correction of electrolyte imbalances are the mainstays of treatment, with an occasional role for targeted antimicrobial therapy.

Nitazoxanide is a thiazolide antimicrobial developed in the 1980s with reported activity against a broad spectrum of pathogens. These include protozoa (*Cryptosporidium*, *Giardia*, *Isospora*, *Cyclospora*), helminths (*Ascaris, Trichuris, Ancylostoma duodenale, Enterobius, Strongyloides, Taenia coli and Hymenolepis nana*)[5], some bacteria (bacteroides and clostridium)[6], and viruses (rotavirus, respiratory syncytial virus and possibly hepatitis C)[4]. In vitro studies indicate nitazoxanide acts by inhibiting pyruvate-ferredoxin oxidoreductase (PFOR) enzyme-dependent reactions necessary for anaerobic energy metabolism. Nitazoxanide has also been shown to inhibit viral replication[4].

Nitazoxanide is not currently licensed for use in Australia, but is recognised as an orphan drug (medicine designed to treat a rare disease or one for which treatment is not commercially available) by the Therapeutic Goods Administration and is available for compassionate use[7].

There is only one retrospective study of nitazoxanide use in Australia. This was conducted by Yeung et al[8] in Alice Springs, Northern Territory, between November 2006 and June 2009. The group attempted to retrospectively identify case-control subjects for the 46 Indigenous children admitted with *Cryptosporidium* infection and treated with nitazoxanide over the study period. Nutritional outcomes were compared at discharge and 7 months follow-up. Weight gain occurred in a higher proportion of the nitazoxanide-treated group at discharge (82% of 44 treated children had a positive change in weight for height compared to 75% of 61 untreated children) and 7 months post-discharge (66% compared to 57%). However, the significance of these results was not clear, and confounding factors such as nutritional rehabilitation and comorbidities were not considered.

A number of small, randomised control trials indicate faster recovery among children treated with nitazoxanide compared to placebo for *Giardia*, amoebiasis, *Cryptosporidium*, rotavirus, norovirus, and also for diarrhoea where no enteropathogens were found[4,9-14]. Using Medline, PubMed, Cochrane Library (1960–September 2011; search terms *nitazoxanide*, *diarrhoea*, *Cryptosporidium*, *paediatric*), two systematic reviews, 12 randomised control trials, and one case report were found relating to nitazoxanide use in both immunocompromised and immunocompetent children. Only articles pertaining to immunocompetent children are considered here.

The broad range of enteropathogens where efficacy has been shown raises the prospect of empiric use of nitazoxanide therapy in the treatment of undifferentiated paediatric infectious diarrhoea.

Nitazoxanide has been prescribed intermittently for children at the Royal Darwin Hospital (RDH), Northern Territory, since 2006. However, the frequency and indications for its use are not clear. The objective of this study was to review the compassionate use of nitazoxanide in this setting, and to better define the indications for, and outcomes associated with, nitazoxanide use in this setting.

Methods

The RDH is a 350-bed tertiary facility that serves the Top End (northernmost part) of the Northern Territory. This

includes a population of 230 000 (49 000 ≤13 years) in an area of 516 945 km^2, with 126 000 residing in Darwin. Approximately 30% of the population is Indigenous[15]. Pharmacy records were used to identify children aged ≤13 years prescribed nitazoxanide at the RDH from 1 July 2007 to 31 March 2012. The discharge medical diagnoses for these patients, based on the *International Classification of Diseases*, 10th edition (ICD-10) criteria were also recorded[16]. The total number of admissions to the paediatric infectious ward for the study period, including those with infectious diarrhoea, was identified.

Medical files of patients who received nitazoxanide during the audit period were reviewed by the primary investigator. Information for each participant was recorded on standardised data collection sheets, including demographics, symptoms, investigations and treatment details. Immunisation status was ascertained from the Northern Territory Immunisation Register based on adherence to the recommended Northern Territory schedule at the time of admission[17]. 'Remote residence' was defined as per definitions set by the Australian Bureau of Statistics[18].

Nutritional status was assessed based on pre-morbid 'well weights' from health centre records prior to admission (within the previous 6 months). If a pre-morbid weight was not available, the discharge weight was used instead. World Health Organization (WHO) definitions were used to define those moderately underweight (weight-for-age z score between −3 and −2) or severely underweight (weight-for-age z score less than −3), and moderately (height-for-age z score between −3 and −2) or severely stunted (height-for-age z score less than −3)[19].

Diarrhoea was defined as ≥3 liquid stools per day. Resolution of diarrhoea was defined as ≤2 stools per day, maintained for at least 72 hours or until hospital discharge. Eosinophilia was defined according to the RDH pathology reference ranges for eosinophilia at various ages.

Descriptive statistical analysis was performed using STATA v12.1 (http://www.stata.com) and Microsoft Excel Solver.

Ethics approval

Ethics approval was obtained from the Human Research Ethics Committee of the NT Department of Health and Families and Menzies School of Health Research; reference number HREC-2012-1754.

Results

Patient details and demographics

Of the 7010 admissions to the paediatric infectious ward over the study period, 1275 (18%) were for infectious gastroenteritis, and nearly three-quarters (73%) of infected children were Indigenous, mostly retrieved from remote settings. Twenty-eight children received treatment with nitazoxanide. Of these, 27 were infected with *Cryptosporidium*. A total of 102 children were admitted with *Cryptosporidium* infection during the study period, but treatment only occurred in 26% of cases. All but one of the treated children were Indigenous. The ages of treated children ranged from 4 months to 6 years (Table 1), including nine children less than 12 months old. Fifty-four per cent of the study cohort was male and <8% resided in urban areas. One-third were not fully immunised, and for the majority (86%) infectious contacts were not identified (Table 1).

Co-existing acute medical diagnoses

An overwhelming majority of children (26) had one or more medical comorbidities. Malnutrition was common. At admission, eight children (30%) were moderately underweight, three (11%) were severely underweight, four (14%) were moderately stunted, and another four (14%) children were severely stunted. Other diagnoses included ear infections (*n*=11; 39%); lower respiratory tract infections (*n*=9; 32%); anaemia (*n*=6; 21%) and cutaneous fungal infections (*n*=6; 21%). Seven children (28%) had eosinophilia on full blood examination. Scabies and urinary tract infections were documented in a further 15% of the study cohort.

Table 1: Demographics, signs and symptoms and clinical outcomes of children treated for *Cryptosporidium* infection at Royal Darwin Hospital, 1 July 2007 – 31 March 2012 (*n*=28)

Subject demographic characteristics	No. (%)	Median; IQR
Age (months)		14; 10–17
Male	15 (54)	
Indigenous	27 (96)	
Remote residence	26 (93)	
Fully immunised for age[†]	19 (68)	
Rotavirus fully immunised for age	19 (68)	
Potential infectious source identified	4 (14)	
Signs and symptoms at admission		
Days of diarrhoea (*n*=20)		6.5; 2–21
Vomiting reported (*n*=28)	16 (57)	
Dehydration based on pre-morbid well weight (*n*=28)		
Mild (0–5% of well-weight)	9 (32)	
Moderate (5.1–10% of well weight)	11 (39)	
Severe (>10% of well weight)	8 (29)	
Dehydration based on clinical estimates (*n*=17)		
Mild	11 (65)	
Moderate	4 (24)	
Severe	2 (12)	
Reduced appetite (*n*=24)	18 (75)	
Reduced fluid intake (*n*=26)	18 (69)	
Weight-for-age *z* score	–	−1.7; −2.6 to −1.1
Well weight-for-length *z* scores	–	−1.3; −2.1 to −0.4
Signs and symptoms post-admission prior to nitazoxanide		
Duration of diarrhoea (days) (*n*=28)	–	5; 3–10.5
Signs and symptoms post–nitazoxanide treatment		
Days to resolution of diarrhoea (*n*=17)	–	2.4; 1.4–7.3
Clinical outcomes	–	
Resumption of normal feeds (days) (*n*=22)	–	5; 1–15
Enteral nutrition rehabilitation (days) (*n*=28)	–	14.5; 5.7–21
Intravenous fluids	–	2; 0–5.2
Median time to well weight (days) (*n*=17)]	–	6; 4–13
Length of stay (days) (*n*=28)	–	20; 15–24
Discharge weight-for-length *z* scores (*n*=28)	–	−1; −1.4 to −0.6

[†] Up to date as per the Australian Northern Territory Immunisation Schedule

IQR, interquartile range

Symptoms and signs

Where data were recorded (*n*=20), a median of four episodes of diarrhoea occurred per day at admission, with diarrhoeal illness extending for a median of 11.5 days (6.5 days pre- and 5 days post-admission) before nitazoxanide was commenced. Vomiting, dehydration, reduced appetite and decreased fluid intake were also common among treated children (Table 1).

Diarrhoeal aetiology

Cryptosporidium was identified by microscopy in the stools of 27 (96%) nitazoxanide-treated children. One child was treated empirically despite a negative stool result because of persistent diarrhoea and malabsorption. One child was co-infected with *Salmonella*.

Antimicrobial treatment

The prescribed dose of nitazoxanide varied. Nineteen children (68%) were treated according to the CDC dosing protocol[20]. The remaining nine children were less than 12 months (minimum age 4 months; minimum weight 4.8 kg), and received doses ranging from 50 mg to 100mg BD for 3 days. Twenty-three children received the full course. All children received empiric antihelminthic treatment with albendazole for 3 days, either prior to hospitalisation or at admission. The child co-infected with *Salmonella* did not receive treatment other than nitazoxanide and albendazole. In the 18 (64%) patients whose stools were re-examined post-treatment, none had a positive stool result for *Cryptosporidium*.

Clinical outcomes

Resolution of diarrhoea was achieved a median of 2.4 days after commencement of nitazoxanide (Table 1). Normal feeds were resumed a median of 5 days after commencement of nitazoxanide, and time to recovery of pre-morbid weight was 6 days. All children recorded improved weight-for-age *z* scores at discharge compared to admission (−1 compared to −1.3; see Table 1). Median length of stay was 20 days. No adverse effects were recorded.

Discussion

The primary reason identified by the audit for nitazoxanide use in the Top End of the NT between 2007 and 2012 was cryptosporidiosis. *Cryptosporidium* is a common cause of acute watery or persistent diarrhoea in immunocompetent and immunocompromised children, especially in developing countries[21]. Cryptosporidiosis is a notifiable disease. It is generally self-limiting in immunocompetent patients, although recurrent symptoms develop in 40% of cases following initial resolution, and 45% develop persistent diarrhoea (>14 days)[22]. There are no studies comparing *Cryptosporidium* infection or treatment with nitazoxanide in Indigenous versus non-Indigenous subjects. However, it is clear that infections within Indigenous communities are common, and are likely facilitated by the low infectious dose and prolonged shedding of the *Cryptosporidium* oocytes in the stools of infected patients (up to 5 weeks)[21] .

During the study period, diagnosed *Cryptosporidium* diarrhoea accounted for 1.5% (*n*=105) of all infectious diarrhoea admissions. Only 27% of those with *Cryptosporidium* infection received treatment with nitazoxanide, mostly for persistent diarrhoea. Untreated patients were not assessed in this study; however, it is possible that failure to treat reflects a milder illness and/or a lack of awareness of potential nitazoxanide efficacy by the treating clinician. None of the treated children were found to have *Giardia*, amoebiasis, rotavirus or norovirus, against which nitazoxanide may also have efficacy[23].

Whilst a number of trials of nitazoxanide have described beneficial effects, existing evidence is not sufficiently robust to support the routine use of nitazoxanide for infectious diarrhoea. The drug's manufacturer has sponsored all except one of the published trials[24], and only small numbers have been randomised to the treatment intervention (*n*=176)[4,9,13,24,25]. In addition, all trials have been performed outside of Australia, and therefore the applicability of results to this study population remains uncertain. An effective therapy for infectious diarrhoea in the Northern Territory would clearly have significant community benefits. Improved resolution of diarrhoea could result in cost savings due to reduced number of hospital admissions, reduced length of stay, and decreased aeromedical retrieval costs.

Notably, whilst other antimicrobials for *Cryptosporidium* have been studied, such as macrolides and paramomycin, evidence for their efficacy is poor[21], and they are not routinely used in practice.

Most children treated with nitazoxanide had resolution of diarrhoea in less than 3 days, consistent with the literature[4]. Resolution of diarrhoea is likely to have contributed to the weight gain observed in treated children. However, interpretation of this finding is confounded by both the

enteral and intravenous rehydration and nutritional rehabilitation that was clinically prescribed for most children.

There was a large discrepancy between clinical estimates of dehydration versus those based on 'well weights', which suggested greater degrees of dehydration. The literature suggests that clinicians tend to over-estimate dehydration in children[26]. Persistent diarrhoea was present in the majority of cases in this study, and it is likely that 'well weight' estimates reflected, at least in part, weight loss due to persistent diarrhoea rather than acute dehydration per se.

Three-day dosing regimens recommended by the CDC for immunocompetent persons with *Cryptosporidium* diarrhoea are 100 mg BD (1–3 years), 200 mg BD (4–11 years) and 500 mg BD (adults). In the present study, the CDC dosing regimens for patients greater than 12 months were followed. The CDC does not support nitazoxanide use in children less than 12 months because of inadequate data in this age group. Overall, 24 children less than 12 months have been randomised to the treatment intervention in two studies examining nitazoxanide for rotavirus gastroenteritis[23,24]. The varied dosing schedules prescribed for children in the present cohort of treated infants less than 12 months reflects the paucity of data to direct use in this age category[20].

The absence of adverse effects reported in this cohort is consistent with published randomised trials where few adverse events were identified in either treated or placebo groups[4,13]. Even though the study cohort included nine children <12 months, it was reassuring to note there were no adverse effects reported and a good clinical response was achieved.

Limitations of this study include the lack of control data in infected children not treated with nitazoxanide and the retrospective case series design. Some studies report *Cryptosporidium* infection to be self-limiting in immunocompetent children[20,21], raising the possibility that the observed benefit among treated children may have occurred without treatment. However, time to discharge, weight gain and timely resolution of diarrhoea following

treatment commencement all provide supportive evidence of a treatment effect in this cohort.

Conclusion

Based on current evidence, it is reasonable to consider nitazoxanide for children with persistent diarrhoea, even in cases where no enteropathogen is isolated. The data suggest a role for nitazoxanide in Indigenous children with *Cryptosporidium* infection who also suffer malnutrition. However, further independent, appropriately powered, multi-centre, double-blinded placebo-controlled studies across a range of settings are needed to assess the broader efficacy and safety of nitazoxanide as an empiric treatment for paediatric diarrhoea. In particular, the pharmacokinetics and safety profile of nitazoxanide among infants less than 12 months old need further investigation. The data obtained in this audit have been used to inform the design of a randomised control trial of nitazoxanide for paediatric infectious diarrhoea in the Northern Territory.

Acknowledgements

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