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A REVIEW ON FIDAXOMICIN FOR THE TREATMENT OF CLOSTRIDIUM DIFFICILE INFECTION IN PAEDIATRICS

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Abstract:
Fidaxomicin is a new macrocyclic antibiotic with a narrow spectrum. It inhibits bacterial RNA polymerase and kills C difficile while having little impact on normal intestinal flora. On January 10, 2011, the US FDA granted orphan drug designation to all formulations of Fidaxomicin for the treatment of C difficile infections in paediatric patients. Fidaxomicin is bactericidal against Clostridium difficile and has a long post-antibiotic effect. Despite the fact that this medication has an orphan designation for paediatrics, all available pharmacokinetic and pharmacodynamic data were from subjects over the age of 18.Fidaxomicin is a bactericidal antibiotic with a long post-antibiotic effect against Clostridium difficile. Despite the fact that this medication is designated as orphan for paediatrics, all available pharmacokinetic and pharmacodynamic data were from subjects over the age of 18. Fidaxomicin's MIC90 against Clostridium difficile ranges from 0.0078-0.25 mcg/ml. Fidaxomicin has a poor absorption rate. Patients receiving fidaxomicin had the highest peak plasma concentration of 0.191 mcg/ml. Fidaxomicin faeces are extremely high after oral administration. In the 100, 200, and 400 mg/day groups, the average faecal concentrations in C difficile patients were 255.6 mcg/g, 441.7 mcg/g, and 1443.3 mcg/g, respectively. The average faecal concentration at 400 mg/day was 5700 times greater than the highest MIC90 of fidaxomicin against C difficile. Fidaxomicin 200 mg twice day and vancomycin 125 mg four times daily were contrasted for 10 days in a phase III clinical research. No patients under the age of 18 took part in the study, and only two patients were under 18. Fidaxomicin's clinical cure rates were comparable to those of vancomycin. Patients in the fidaxomicin group saw fewer recurrences than those in the vancomycin group when they had non-North American Pulsed Field type 1 strains of the infection. Both treatments' side effects were comparable. The majority of patients only had minor gastrointestinal problems. Vancomycin and metronidazole are both effective treatment alternatives to fidaxomicin, particularly for individuals who have C difficile infections that keep coming back. Systemic side effects are uncommon in patients, which increases compliance. The dose of fidaxomicin is expected to be 200 mg given orally twice a day for patients 16 years and older. Additional clinical trials in pediatric patients are needed before therapeutic recommendations can be made in this population.

KEYWORDS: *Fidaxomicin; Pediatrics; Clostridium difficile; Phar-macokinetic, pharmacodynamics.*

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INTRODUCTION:

Clostridium difficile is a gram-positive, anaerobic, spore-forming bacillus that causes antibiotic-associated diarrhoea and pseudomembranous colitis. Antibiotic therapy can occasionally disrupt the normal bacterial flora of the colon. This results in C difficile colonisation, which produces powerful toxins that cause mucosal inflammation and damage [1]. C difficile infection typically causes mild-to-moderate diarrhoea and abdominal cramping, but some patients experience acute abdomen and life-threatening fulminant colitis [2]. One of the most common nosocomial infections is C difficile colitis. C difficile infection affects approximately 20% of hospitalised patients [3]. This infection affects over 700,000 people in the United States (US) each year, including paediatric patients[4].Children's diarrhoea is commonly caused by C difficile infections. Between 1997 and 2006, the number of C difficile cases in children over the age of one more than doubled. Paediatric patients with C difficile infection were younger, Caucasian, and had private insurance [5]. Most patients recover without specialised treatment, but in some cases, symptoms can last for months or even years. C difficile colitis is currently treated with vancomycin or metronidazole, as well as the discontinuation of the precipitating antibiotic [6]. While the initial response to these medications has been positive, resistant strains of C difficile are emerging, and the recurrence rate is quite high. Within 60 days, 30% of patients experience a recurrence of illness [2]. Fidaxomicin is the first member of a new class of narrow spectrum macrocyclic antibiotics. Optimer Pharmaceuticals Inc., San Diego, CA, created fidaxomicin. On January 10, 2011, the US Food and Drug Administration (FDA) granted orphan drug designation to all formulations of fidaxomicin for the treatment of C difficile infections in paediatric patients 16 and younger. The FDA is currently considering the drug for standard approval. Approval is expected in May 2011 [7].The purpose of this article is to provide a review of the pharmacokinetic and pharmacodynamic profiles, dosage and tolerability, clinical effectiveness, and clinical application of fidaxomicin in the treatment of C difficile infection, as well as to determine whether this medication is appropriate for use in the paediatric population based on the available literature. A PubMed search was performed using the keywords "fidaxomicin", "paediatrics", "pharmacokinetics", and "pharmacodynamics". There was no article found when the search terms "paediatrics" and "fidaxomicin" were combined.

PHARMACOKINETIC

Fidaxomicin pharmacokinetics were studied in healthy volunteers as well as patients with C difficile infection who were 18 years old (49.3 8.6 years). Systemic absorption of fidaxomicin was low and plasma concentrations were mostly undetectable (5 mcg/ml) after multiple-dose administration of 100, 200, or 400 mg/day of oral fidaxomicin in both patients with C difficile infection and healthy adults. However, the proportion of C difficile patients with measurable fidaxomicin plasma concentrations increased in a dose-dependent manner. In the 100, 200, and 400 mg/day groups, the percentage of patients with measurable plasma fidaxomicin concentrations was 14.3, 56.3, and 81.3%, respectively. The maximum peak plasma concentration measured was 0.191 mcg/ml [9]. Fidaxomicin levels in the faeces are extremely high after oral administration. The average faecal concentrations in C difficile patients in a phase II study were 255.6 mcg/g, 441.7 mcg/g, and 1443.3 mcg/g in the 100, 200, and 400 mg/day groups, respectively. At 400 mg/day, the average faecal concentration was approximately 5700 times higher than the highest MIC90 of fidaxomicin against C difficile (0.25 mcg/ml).Fidaxomicin produces a faecal metabolite that is also highly active against Clostridium difficile. Fidaxomicin levels in urine were below the limit of detection in all specimens obtained. Fidaxomicin has a half-life of 0.94 to 2.77 hours. Patients with renal and hepatic impairment require no adjustment due to low systemic absorption. There were no reported drug interactions [10].

PHARMACODYNAMICS

Fidaxomicin works by preventing bacterial RNA polymerase's sigma-dependent transcription and selectively eradicating C difficile with little impact on the normal gut flora. Fidaxomicin has a prolonged (> 24 hours) post-antibiotic impact and shows bactericidal activity against C difficile. In compared to vancomycin, it exhibits quicker killing and a prolonged antibacterial action following drug removal. Despite the fact that this medication is designated as an orphan drug for paediatric use, complete pharmacokinetic and pharmacodynamic data on participants under the age of 18 were available. Depending on the in vitro circumstances,

the fidaxomicin MIC90 value for C. difficile ranges from 0.0078 to 0.25 mcg/ml. At more alkaline pHs, the MIC90 value climbed 2 to 8 fold. Rarely did resistance arise on its own. Azithromycin, ampicillin, telithromycin, ciprofloxacin, metronidazole, vancomycin, rifampin, and rifaximin have not been associated with any cross-resistance. Fidaxomicin had no effect on facultative aerobes and Gram-negative anaerobes (MIC > 16 mcg/ml) (i.e., Bacteroides species, enterobacteriaceae, Haemophilus species, and Pseudomonas aeruginosa). It exhibits activity (MIC 2 mcg/ml) against a small number of other Gram-positive anaerobes besides Clostridium difficile, such as Peptostreptococcus species, some lactobacilli, and Staphylococcus aureus (both methicillin-susceptible and resistant), but poor activity (MIC > 4 mcg/ml) against a large number of other Gram-positive bacterial species, including (both vancomycin susceptible and resistant)

DOSAGE/TOLERABILITY

Adult patients in a phase II trial were given 50 mg BID, 100 mg BID, or 200 mg BID of oral fidaxomicin. The subjects in the 200 mg BID group had the highest rates of clinical cure. Fidaxomicin at this dose was extremely well tolerated. Nine out of forty-five subjects reported adverse events (four patients in each of the lower dosage groups and one patient in the 400 mg/day group). All adverse events (fall, shortness of breath, leg pain, renal colic, bronchitis, pneumonia, urinary tract infection, hypotension, fluid overload, pancreatitis, diarrhoea, cardiac failure, angina, cerebro-vascular damage, gastro-intestinal bleeding, and Staphylococcus aureus bacteremia) did not appear to be related to the study medication [11, 12].

PHASE III CLINICAL TRIAL

Fidaxomicin and vancomycin were compared for efficacy and safety in a phase III prospective, multicentre, double-blind, randomized, parallel-group, non-inferiority clinical trial for the treatment of C difficile infection. In the US and Canada, 629 adult patients with a mean age of 61 were enrolled. Participants in the trial were to be at least 16 years old, but only two patients who were 18 at the time of enrolment and none who were younger than 18 took part in the study. All patients had a positive stool toxin test result within 48 hours of randomization and acute symptoms of C difficile infection (greater than three incomplete bowel movements in the previous 24 hours). The subjects might have obtained Fidaxomicin 200 mg twice day or vancomycin 125 mg four times daily were given to the patients at random for 10 days. Every 12 hours, patients in the fidaxomicin group received an antibiotic with matching doses of placebo in between. Every six hours, the vancomycin group's participants took medicine. The placebo and the trial drugs were both packaged to seem the same. The primary end point was clinical cure, which was determined as the symptoms disappearing and the infection of C difficile not requiring any additional treatment as of the second day following the conclusion of the course of therapy. Recurrence of C difficile infection (diarrhoea and a positive stool toxin test within 4 weeks of treatment) and worldwide cure (cure with no recurrence of C difficile infection) were the secondary end goals.

For the per-protocol analysis, 538 patients (87.1%) underwent evaluation. Both the modified intention-to-treat analysis (88.2% with fidaxomicin and 85.8% with vancomycin) and the per protocol analysis (92.1% with fidaxomicin and 89.8% with vancomycin) found that the rates of clinical cure with fidaxomicin were noninferior to those with vancomycin. Patients in the fidaxomicin group had a greater overall cure rate than those in the vancomycin group because they experienced fewer infection recurrences. Both the per-protocol analysis (13.3% with fidaxomicin and 24% with vancomycin, P = 0.004) and the intention-to-treat analysis (15.4% with fidaxomicin and 25.3% with vancomycin, P = 0.005) showed this to be true. Patients with non-North American Pulsed Field type 1 strains had a decreased recurrence rate.

CLINICAL APPLICATION

Fidaxomicin is a potential new medication that offers several benefits over metronidazole and vancomycin for the treatment of C difficile colitis. Normal gut flora is unaffected due to its limited antibacterial spectrum. Contrary to metronidazole, fidaxomicin has a poor absorption rate. This enables significant amounts of the medication to enter the colon. Systemic side effects are relatively uncommon in patients, which may help with compliance. One of the main benefits of fidaxomicin over vancomycin is the significant decrease in C difficile recurrences.

The presence of specific sigma-factors in the bacteria is required for fidaxomicin to have bactericidal activity. A bactericidal antibiotic with a protracted post-antibiotic action is fidaxomicin. Vancomycin, a bacteriostatic antibiotic lacking post-antibiotic activity, is disadvantaged by these characteristics [8]. Vancomycin and metronidazole are effective therapeutic substitutes for fidaxomicin, particularly in

individuals with recurrent C difficile infection. Patients who have previously had faecal cultures that were positive for non-North American Pulsed field type 1 C difficile strains may benefit from receiving fidaxomicin as their first line of treatment. Despite the fact that all of these pharmacokinetic and pharmacodynamic data are now only available for adults, researchers may eventually use this knowledge to undertake safety clinical trials in children. Optimer Pharmaceutical Inc. is actually working on.

CONCLUSION:

C difficile colitis can be a major issue in children who are being treated with broad spectrum antibiotics. Optimer pharmaceutical inc. has only conducted clinical trials in adults so far. The phase III study has no paediatric patients and only 2 patients over the age of 18. Before therapeutic recommendations can be made in this population, additional pharmacokinetic/pharmacodynamic clinical trials in paediatric patients are required. Metronidazole and oral vancomycin should remain the main stay of treatment for C difficile infection in paediatric patients for the time being.

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