Nifuroxazide in Diarrhea

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Abstract

Thirty four diarrheal children with mild degree of dehydration who were attended at the out-patient Department of Pediatrics, Siriraj Hospital were treated with oral nifuroxazide for 5 to 7 days in conjunction with oral rehydration solution. Eighteen out of twenty one children whose stool culture revealed no pathogenic bacteria recovered satisfactorily. Eight children with salmonella or shigella in their stool still passed diarrheal stool and needed nalidixic acid to get rid of the pathogens. There were five cases who lost to follow up and two of them had shigellosis.

เรื่องย่อ

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Diarrhea is one of the major health problems of developing countries in terms of incidence, mortality and morbidity. Children under five have approximately 500 to 750 million episodes of diarrhea every year. Nearly five million children die every year.1 Those who survive are in malnourished condition. The result is repeated episodes of diarrhea, impaired growth and poor quality of life.

Acute diarrhea is a self-limiting illness lasting two to five days irrespective to the cause. The basic principles of the management is to maintain hydration and electrolyte balance. However, physicians still prescribe various antibiotics in addition to the management of acute diarrhea. Reports have shown that the use of antibiotics is not only a waste of time and money, but also harmful to the patients and may prolong the diarrhea or cause toxic side-effects.2 In special circumstance,
for example: Cholera, Shigellosis, the administration of antimicrobial agents will abbreviate the clinical course and/or decrease excretion of the causative organism.

Nifuroxazide is an intestinal anti-infectious agent which inhibits the bacterial synthesis by acting on the nucleic acids and energy metabolism of pathogens. It does not destroy the normal intestinal flora and does not upset the intestinal bacterial equilibrium. It has never been found to induce transferable bacterial resistance. It seems deally benefit for acute infectious diarrhea.

**MATERIALS AND METHODS**

The study has been done since August 1989. Children who came to the out-patient department of Pediatrics, Siriraj Hospital, with the complaint of diarrhea and seen by the investigator were considered to be eligible.

**Excluded were:**

1. Children with clinical signs of dehydration severe enough to be admitted and managed as in patient,
2. Children with history of being improvement but needed reassurance,
3. Institutional handicapped children who were expected to have parasitic infestation,
4. Children with history suggested food poisoning,
5. Children with abrupt onset of watery diarrhea and were expected to be cholera diarrhea.

Either stool or rectal swab culture (RSC) was routinely done in every case and immediately sent to indentify at department of microbiology. The result was reported to be negative for salmonella, shigella or positive with sensitivity pattern but not with nifuroxazide. Other bacteria or viruses were not attempted to be identified since special request and transport media were not available.

Stool examination was done in only those who passed more adequate amount of stool content to be examined during RSC. Ten or more white blood cells per high power field microscope was set as positive suggested bacterial cause.

The dosage of nifuroxazide suspension was administered according to the manufactural recommendations. Children under 6 months of age should have one teaspoonful thrice a day. The duration of medication was up to 5-7 days. The dosage of nifuroxazide suspension was administered according to the manufactural recommendations. Children under 6 months of age should have one teaspoonful thrice a day. The duration of medication was up to 5-7 days.

Oral rehydration solution, antipyretics and other supportive treatment were also given.

Outcome assessment was the parental satisfaction on their child. If it is possible they should express the exact day their child was well after nifuroxazide. According to the manufactural guideline, the clinical results were classified into 3 categories as

**Excellent** – if the diarrhea stopped in less than 3 days and test stool culture became negative.

**Good** – if the diarrhea stopped within 4-5 days

**Poor** – if the diarrhea persisted more than 6 days.

In this study if parents did not satisfy on their child’s condition and seek another medication regardless of the amount of drug that has been taken, we also classified as poor. Drug compliance was assessed by asking whether the child refused and was not able to complete the full course of nifuroxazide.

**RESULTS**

There were 34 patients enrolled in the study. Twenty of them were males. The ages varied from 1 to 108 months old. Thirty patients were under 24 months of age. Duration of diarrheal symptoms varied from 1 to 14 days. Twenty five patients had less than 5 days of diarrhea. Stool frequency could be assessed in 24 of patients. Sixteen had more and eight had less than 10 times a day.

Stool culture results were 8 shigella B, 1 shigella D, 1 salmonella C and 24 negative for salmonella and shigella. Seven stool examinations were all negative except one positive suggested bacterial cause. Three of 6 negative were related to the positive stool culture results (2 shigella B and 1 salmonella C).

Outcome could not be assessed in 5 patients (2 were positive stool culture). Among 29 cases, 9 were excellent, 3 were good, 6 reports of satisfaction but could not express the exact day of response and 11 were poor.

Eight of the eleven poor were positive stool culture. Those who returned for follow up were all good in compliance and reported no side-effects during nifuroxazide treatment.

**DISCUSSION**

The antibacterial activity of nifuroxazide has been shown in terms of low minimal inhibitory concentration determination with various enteric bacteria. Thabaut and Durosair of France had demonstrated the high activity with 738 bacterial strains, but only 7 strains of shigella were included in the study. Buisson showed that 50 per cent of 142 shigella strains from Senegal had less than 2 mg/l. Comier reported 86 per cent (45 in 52 cases) of good results with nifuroxazide (capsule form) in New calidonean children (2 months to 2 years of age). All children were hospitalized and received intravenous fluid. Thirty two out of 39 stool cultures were negative for organisms. The rests were positive for *Escherichia coli*, not shigella.

Comparative randomized double blinded placebo-controlled trial has been conducted by Auzerie and colleagues. All 40 hospitalized of 3 ± 2 days of diarrheal children (1-18 months of age) have been equally randomized to nifuroxazide suspension and placebo. Resolution of diarrhea occurred
more rapid (mean ± SD = 66 ± 20 hours) in nifuroxazide group than placebo (84 ± 32 hours).

The proportion of patients with identifiable microorganisms was relatively high in their group. No details of bacterial strains were reported. Those bacterial diarrhea in placebo group may be cured without antibiotics. Another comparative randomization study was done in 40 Philippine children by Santiago and colleagues. All had abrupt onset and were admitted. Those under 9 months of age were excluded. While 7 cases of shigella, 2 cases of salmonella and 10 cases of other bacteria in nifuroxazide group were cured within 4 days, 8 cases of shigella, 3 cases of salmonella and 9 cases of other bacteria in placebo group were cured within 6 days. Our good results agree with the previous studies in only those who were not shigella or salmonella diarrhea. This could not be the difference in patient selection (in patient VS outpatient) or in outcome assessment (investigator VS parental observations or in compliance).

1. It is possible that our strains of shigella and salmonella resist nifuroxazide.
2. Or cases are so severe that might not be cured by only placebo as previous studies. Unfortunately, we had neither done the sensitivity pattern nor conducted the placebo group.
3. Another point to be mentioned is the theoretical possibility. Shigella and Salmonella invade intestinal mucosa and stay in submucosa. Drugs that cannot diffuse through intestinal mucosal epithelium are expected to have no beneficial effects in the treatment. Only small quantity of nifuroxazide were found in blood stream and urine because it does not cross the intestinal barrier.

Our study is a descriptive study to point out the trend for future study with nifuroxazide in diarrheal Thai infants. The efficacy study has to be done by randomized clinical trial.

CONCLUSION

Nifuroxazide seems to be beneficial in other various etiologic diarrhea except Shigella–Salmonella diarrhea of the Thai infants.

REFERENCES
7. Santiago LT, Ranoa CP, Chan EG, Tejada E. Nifuroxazide (Ercefuryl) plus oral rehydration solution versus oral rehydration alone in hospitalized pediatric gastroenteritis.