Lactulose Therapy in Shigella Carrier State and Acute Dysentery

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Antibiotic-resistant shigella are increasingly prevalent. Lactulose, a non-absorbable disaccharide, was investigated as an alternative therapy for shigella infection on the hypothesis that the short-chain fatty acids (inhibitory to shigella) resulting from metabolism of lactulose by normal colonic flora would diminish shigella excretion. A long-term antibiotic-refractory carrier (large bowel) excreting $10^9$ to $10^8$ Shigella sonneii (e.g. feces was given two courses of lactulose (of 24 and 16 days duration). During lactulose therapy, excretion of shigella was greatly diminished (24-day course) or suppressed below detectable levels (16-day course), but returned to pretreatment levels upon discontinuation of lactulose. The volunteers who developed induced shigellosis during an efficacy test of oral Shigella flexneri 2a vaccine were randomly given oral ampicillin, lactulose, or placebo in double-blind fashion. Daily rectal cultures were taken. After 4 days of therapy, cultures were still positive in four out of four men on lactulose, three of three on placebo and none of three on ampicillin. Mean stool pH of men receiving lactulose (6.1) was significantly lower than those getting ampicillin (7.4), $P < 0.01$, or placebo (7.0), $P < 0.05$. Only in the lactulose group was mean stool pH during therapy significantly decreased compared with the level off therapy (6.1 versus 7.1), $P < 0.02$. Lactulose shows promise for the treatment of shigella carriers but appears ineffective in treatment of acute shigellosis.

The increasing prevalence of multiple antibiotic resistance among shigella has prompted us to seek alternative non-antibiotic therapy for shigella infections (11, 18, 25–27). The normal gut flora are inhibitory for shigella and salmonella enteropathogens (5, 10, 13–16, 21–23). Several investigators have provided evidence that the antagonism is mediated by volatilizable, short-chain fatty acids, which are end products of metabolism of normal gut flora (2, 4, 5, 12–14, 16, 21, 22). The inhibition is pH related (2, 5, 12–14, 16), increasing with lower pH, and apparently involves undissociated acid molecules (12, 13, 16, 22).

Lactulose (Phillips Roxanne, Inc., Columbus, Ohio; 4-0-β-D-galactopyranosyl-β-D-fructose) is a synthetic derivative of lactose containing one molecule of galactose and one of fructose (1). It is formulated as a 50% (wt/wt) syrup and is widely used in Europe and elsewhere as a laxative (1, 6) and in treatment or portal systemic encephalopathy (1, 3, 9). Lactulose is neither absorbed nor hydrolyzed by the human intestine (1, 7) but passes intact into the large bowel where it is actively metabolized by normal gut flora including lactobacilli, Bacteroides, Streptococcus faecalis, and Escherichia coli, resulting in an increased production of short-chain fatty acids, fall in stool pH, and softening of stool consistency (1). Because these effects of lactulose occur in the large bowel, the ecological habitat of shigella, we decided to evaluate lactulose in treatment of asymptomatic carrier and acute dysentery shigella infections.

MATERIALS AND METHODS

Chronic carrier. Lactulose was first used in a 17-year-old institutionalized boy who was a long-term asymptomatic carrier of Shigella sonnei and who has been reported in detail (20). After clinical dysentery in February 1971, this patient continually excreted S. sonnei until June 1972 despite antibiotic therapy to which the shigella was susceptible in vitro. Quantitative cultures, begun after 5 months of continuous shedding, revealed that he was excreting $10^9$ to $10^8$ S. sonnei organisms per g of stool. The patient also had a trichuris infection. Negative jejunal and ileal fluid and bile cultures in the face of heavy stool excretion identified the large bowel as the site of colonization.

Oral lactulose was given in two courses of therapy in December 1971 (24 days) and again in March 1972 (16 days). Lactulose was begun in a dosage of 25 ml every 8 h and was increased to 35 to 45 ml every 6 h in step-wise fashion.

Daily fresh stools were obtained for culture. Quantitations were made by serial dilution of 1 g of homogenized stool in Trypticase soy broth which was...
then plated onto MacConkey, salmonella-shigella, and desoxycholate agars; suspicious colonies were subcultured onto triple sugar iron and identified with specific antisera. Stool pH was not systematically measured.

Acute dysentery. Subjects were healthy adult males who developed acute dysentery due to Shigella flexneri 2a while serving as volunteers in an efficacy test of an oral shigella vaccine. Informed consent was obtained in every instance, no coercion was used, and the men were free to leave the study at any time. Indications for initiation of therapy were one or more of the following: (i) oral temperature ≥ 101 F (38.3 C); (ii) five or more loose stools per 24 h; or (iii) blood and mucus in stools. Ampicillin (500 mg/20 ml every 6 h), lactulose (35 ml every 6 h), or cherry syrup glycerol placebo (30 ml every 6 h) were allocated randomly to nine men in double-blind fashion for 5 days. All three preparations were formulated to resemble one another in color and consistency. One additional volunteer with a known allergy to penicillin received a discrete unlabeled lactulose preparation. In total, three men received ampicillin, four lactulose, and three placebo. Daily rectal swabs were obtained, transported in chilled buffered glycerol saline, and cultured onto salmonella-shigella, MacConkey, and tergitol-7 agars; suspicious colonies were handled as above. Stool pH as measured with pHdrion paper.

RESULTS

Chronic carrier. Daily quantitative cultures in the week prior to lactulose therapy established that the patient was excreting 10⁶ to 10⁷ S. sonnei per g of stool. Lactulose was begun on 13 December in a dosage of 25 ml every 8 h (75 ml/day) and was increased step-wise to 30 ml every 6 h (120 ml/day) in 2 days (Fig. 1). Within 24 h after commencing lactulose therapy, excretion of shigella decreased 3 logs to 10⁵ organisms per g of stool. By 72 h, shigella could no longer be recovered in stool cultures. After 8 days of therapy (21 December), the drug was increased to 35 ml every 6 h, (140 ml/day); on this dosage frank diarrhea developed. Six days later (27 December) there was a bacteriologic breakthrough and 10⁴ S. sonnei per g of stool was recovered. Four days subsequently, the dosage was decreased to 25 ml every 8 h (75 ml/day) and stools again became consistently positive. On 6 January, after 24 days of therapy, lactulose was discontinued; quantitative cultures taken shortly thereafter revealed pre-lactulose levels of 10⁴ to 10⁵ S. sonnei/g of stool.

The temporary suppression of shigella excretion that initially followed lactulose therapy was encouraging. On the other hand, the bacteriologic breakthrough after onset of diarrhea and the resumption of excretion when the dosage was decreased was disappointing. The concomitant trichuris infection was eliminated with a 3-week course of thiabendazole in February, prior to attempting another course of lactulose.

On the morning of 13 March, after 3 weeks during which the patient consistently excreted 10⁴ to 10⁵ S. sonnei per g of stool, lactulose therapy was again begun at a dosage of 25 ml every 8 h (75 ml/day; Fig. 2). Stool cultures became negative on that evening. The dosage was increased to 30 ml every 6 h (120 ml/day) within 2 days and then increased step-wise to 45 ml every 6 h (180 ml/day) without diarrhea. All cultures remained negative throughout the duration of lactulose administration (16 days). Lactulose was discontinued on the morning of 29 March. A quantitative culture 1 day later yielded 10⁵ shigella per g of feces and excretion continued thereafter at pre-lactulose levels.

Acute dysentery. In the acute dysentery treatment groups, the severity of illness prior to treatment was similar and all men had positive cultures when therapy was begun. The mean duration of illness prior to therapy was 1.2 days (range of 1 to 3 days). After 4 days of therapy all three men in the ampicillin group had negative cultures (Table 1). In contrast, none of the men receiving either lactulose or
placebo had negative cultures. Thus there was no difference between the effect of lactulose and placebo, whereas ampicillin, in comparison, stopped excretion of *S. flexneri* 2a.

The mean stool pH of men receiving lactulose was significantly decreased during therapy (6.1) compared with pH off therapy (7.1), *P* < 0.02 (Table 2). In contrast neither ampicillin (pH 7.5 versus 7.4) nor placebo (pH 7.0 versus 6.7) significantly suppressed stool pH. The mean stool pH during therapy was lower in the lactulose group (6.1) than the ampicillin (7.4, *P* < 0.01) or placebo (7.0, *P* < 0.05) groups.

**DISCUSSION**

Shigellosis is often a mild, or nuisance, disease for which antibiotics may be unnecessary (28). However, secondary spread of shigellosis within a family, day care center, center, or custodial institution can transform the nuisance into a disruptive public health problem (29). Use of antibiotics as a control measure has resulted in widespread resistance among shigellae. Any agent that can shorten excretion of shigella without inducing resistance would be a welcome measure for control of secondary transmission. Lactulose had theoretical implications by virtue of its ability to cause increased production of short-chain fatty acids in the human colon with a fall in fecal pH, thus creating conditions inhibitory to shigella. The striking, albeit temporary, effect of lactulose therapy on excretion of *S. sonnei* by an asymptomatic carrier was demonstrated although concomitant stool pH and levels of fatty acids were not monitored. In contrast, lactulose did not curtail excretion of shigella in patients with acute *S. flexneri* 2a dysentery. There are several possible explanations for this difference. (i) In the asymptomatic carrier shigella is apparently confined to the bowel lumen and crypts (20). In acute dysentery shigella are actively proliferating within colonic epithelial cells (17, 19) perhaps removed from the effects of luminal fatty acids. (ii) Patients with acute dysentery have a rapid gut transit and frequent stools (8, 19). It is conceivable that the lactulose was either not completely metabolized by normal gut flora or that the fatty acids produced were rapidly expelled. (iii) Lastly, there may be species differences in susceptibility to fatty acids between *S. sonnei* and *S. flexneri* 2a (6, 24).

At pH 6.0, in vitro, short-chain fatty acids are extremely deleterious for shigella (12, 22); in vivo in mouse cecum at normal pH (6.2 to 6.3), short-chain fatty acids are highly inhibitory against salmonella (4, 5). The mean pH of stools of men receiving lactulose was significantly depressed compared with stool pH off therapy, and it reached a level (pH 6.1) where short-chain fatty acids should have been sufficiently associated to exert deleterious effects; stool fatty acid concentrations were not measured, however.

Long-term asymptomatic carriers of shigella are uncommon. Nevertheless, when they do occur in an institutionalized setting and the strain is antibiotic-resistant, such carriers create a public health problem.

Observations made in this paper suggest that lactulose holds some promise in the treatment of asymptomatic shigella carriers if the drug can be tolerated without occurrence of diarrhea as a side effect. Lactulose seems to offer little in treatment of acute shigellosis.

<table>
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<tr>
<th>Treatment group*</th>
<th>No. of men</th>
<th>No. of men with positive cultures</th>
<th>0*</th>
<th>3</th>
<th>4</th>
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<tr>
<td>Ampicillin</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Lactulose</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Ampicillin versus placebo, *p* = 0.05; ampicillin versus lactulose, *p* = 0.03; lactulose versus placebo, no significant difference (Fisher exact test on culture results after 4 days of therapy).

* Days after commencement of therapy.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>No. of men</th>
<th>Mean stool pH</th>
<th>P value* (on versus off drug)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>3</td>
<td>7.4</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
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<td><em>P</em> &lt; 0.01 (<em>t</em> = 2.59, 39 d.f.)</td>
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<tr>
<td>Lactulose</td>
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<td>6.1</td>
<td>7.1</td>
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<tr>
<td></td>
<td></td>
<td><em>P</em> &lt; 0.05 (<em>t</em> = 1.74, 32 d.f.)</td>
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<tr>
<td>Placebo</td>
<td>3</td>
<td>7.0</td>
<td>6.7</td>
</tr>
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</table>

* *t*, Student's *t* test; d.f., degrees of freedom.
ACKNOWLEDGMENTS

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LITERATURE CITED