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MOUTH-TO-ANUS TRANSIT-TIME PREDICTS THE SEVERITY OF FECAL WATER LOSS IN ACUTE DEHYDRATING DIARRHEA

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Abstract. The mouth-to-anus transit time was estimated in 24 young children admitted to an outpatient rehydration unit with acute dehydrating diarrheal disease by adding an oral fecal marker (brilliant blue) to the first draught of oral rehydration solution. Transit times ranged from 30 to 242 min. There was a highly significant (logarithmic) relationship between rate of fecal output and transit time ($r = 0.74$; $p < 0.001$). Three of 24 subjects could not be rehydrated orally, were declared treatment failures, and were hospitalized for intravenous therapy. All of them had had an initial transit time of less than 50 min, and constituted three of the four subjects with this rapid rate of transit. Thus, a rapid mouth-to-anus transit time had a 100% sensitivity to predict treatment failures and a 75% predictive accuracy for a "positive" test. Although our series is small, the findings suggest that fecal markers may be useful in remote areas to assist in the early detection of diarrheal episodes that cannot be managed by oral rehydration therapy.

Key words: Dehydration; acute infectious diarrhea; oral rehydration therapy; intestinal transit time; Guatemala

Introduction

Acute infectious diarrheal disease is a major public health problem in children throughout the developing world, especially in tropical nations [1, 2], taking new importance with the emergence of a cholera epidemic in Latin America. The major cause of mortality is the severe dehydration which can lead to acidosis and hypovolemic shock. While the infectious process runs its course, the goal of therapy is to maintain a normal state of hydration and electrolyte balance. This was formerly accomplished by intravenous fluid replacement, but the advent of oral rehydration therapy (ORT) [3, 4], based on the enhancement of water and electrolyte absorption coupled to the active intestinal absorption of glucose [5], has provided a simpler and lower-cost alternative. The oral rehydration solution recommended by the World Health Organization contains 111 mmol/L of glucose. ORT has been proven to be equal to intravenous (i.v.) therapy in mild and moderate degrees of dehydration [6, 7]. However, severe fluid losses can rapidly lead to a degree of dehydration which cannot be reversed by the oral-enteral route.

ORT was designed to be used in the rural community setting. Since severe diarrhea is an indication for i.v. rehydration, an early prediction of the efficacy of oral solutions in a given episode of diarrhea could mean the difference between timely referral to a hospital center or an ultimately fatal outcome. We present here the results from a small - but carefully studied - group of dehydrated Guatemalan children derived during the conduct of a clinical investigation into the diarrheal-induced losses of trace elements and the potential differential effects of standard or glycine-containing oral rehydration solutions [8, 9] in which we observed a potentially useful predictive relation between mouth-to-anus transit time early in the course of therapy and the ultimate response to ORT.

Subjects and Methods

We enrolled 24 male children, ranging in age from 8 to 19 months, who were admitted to the Rehydration Unit of the Guatemala Social Security Institute (IGSS) Pediatric Hospital with a history of uncomplicated diarrheal disease of no greater than 4 days duration (*table*). We studied male children exclusively because of our need to separate the collection of feces from the stream of urine. We included only those children whom the medical staff assigned to oral rehydration therapy (ORT) as the first therapeutic modality. Exclusion criteria included a degree of vomiting that precluded the retention of oral solutions or bloody, dysenteric stools.

The protocol had been approved by the Committee on Investigations of the IGSS and the Human Subjects Committee of Institute of Nutrition of Central America and Panama (INCAP). The procedures conformed to the Declaration of Helsinki. Informed written consent was obtained from the mothers or accompanying family member after the nature, purpose and risks of the study had been fully explained.

Twelve of the subjects were assigned to receive the oral rehydration solution (ORS) that was suggested by the World Health Organization [5], while the others received the same base composition plus 111 mmol/L of glycine (Glycine USP, Mallinkrodt Chem. Co., Paris. KY, USA), an addition proposed to enhance fluid and electrolyte absorption [10, 11]. For purposes of this report, all 24 have been considered together as a whole.

Children were weighed initially and serially on a SECA pediatric scale (SECA Co, Germany). Their length was measured in the recumbent position on a metric stadiometer. Children were placed in metabolic beds over plastic basins for complete quantitative collection of stools, care being taken to avoid contamination of feces with urine.

The first dose of ORS contained 20 mg of brilliant blue (Mallinkrodt) as a fecal marker. The time-interval from administration of brilliant blue until its first appearance in stool was considered to be the "mouth-to-anus" transit time. Time of observation was defined as the period in which children were drinking oral rehydration solutions exclusively, and during which fecal collections were made.

Results

Initial weight-deficit (*i.e.* weight-loss due to dehydration) ranged from 0.8 to 9.9%, with both mean and median approximating 4% (*table*). Fifteen (71%) of 21 children presented with degrees of weight loss ≤ 5%, which indicated "mild" states of dehydration; the

Table General characteristics of children studied

	n	*mean*	*S.D.*	*median*	*range*
Age (mo)	24	12.9	3.5	11.0	8.9- 19.0
Initial weight (kg)	24	7.9	1.5	7.4	6.3- 12.9
Weight-deficit (%)[1,2]	21	4.4	2.6	3.9	0.8- 9.9
Weight-for-height (%)[1]	21	86.9	7.2	87.4	75.7-107.4
Weight-for-age (%)[1]	21	79.7	12.7	79.4	62.4-119.3
Height-for-age (%)	24	95.7	5.0	95.9	82.8-108.3

[1] To calculate these indicators the weight value used was the one obtained when child was considered fully rehydrated and discharged from hospital. This was named "rehydrated weight".

[2] $$\text{Weight-deficit} = \frac{\text{Rehydrated weight-initial weight}}{\text{Rehydrated weight}} \times 100$$

remaining six children showed values between 5 and 10% considered as "moderate" dehydration.

The time of observation ranged from 240 to 535 min (mean 383 ± 77 min; median 380 min). During this time, the children were either considered on the road to recovery, and hence started on nutrient-bearing beverages along with their ORS (21 of 24 children), or were declared treatment-failures to ORT and admitted to the hospital for intravenous therapy (3 of 24 subjects). A treatment failure was defined as the clinical decision that oral therapy was not progressing and the child needed i.v. fluids; this was made by the out-patient pediatric resident without knowledge about the appearance time of brilliant blue in the feces.

Figure 1 shows the distribution of mouth-to-anus transit time for the therapeutic failures and for the therapeutic successes. In those children in whom ORT failed, the median value for transit time was 40 min (range 33 to 45 min); three of the 4 subjects who had a mouth-to-anus transit time of less than 50 min turned out to be therapeutic failures with ORT. On the other hand, in those in whom ORT was successful, median transit time was 125 min (range 30 to 242 min).

We also examined the relationship between transit time and the rate of fecal output expressed in ml/kg/h. *Figure 2* shows a scatterplot of these date. The four children with the briefest transit times were also the children who eventually showed the highest rate of sustained fecal output over their respective periods of observation. There was, overall, an obvious curvilinear relationship. Several models were tested to identify the best fit. This proved to be a logarithmic transformation - fecal volume vs 1/transit time - yielding a "r" value of 0.74 with a standard error of estimation of 33.3%.

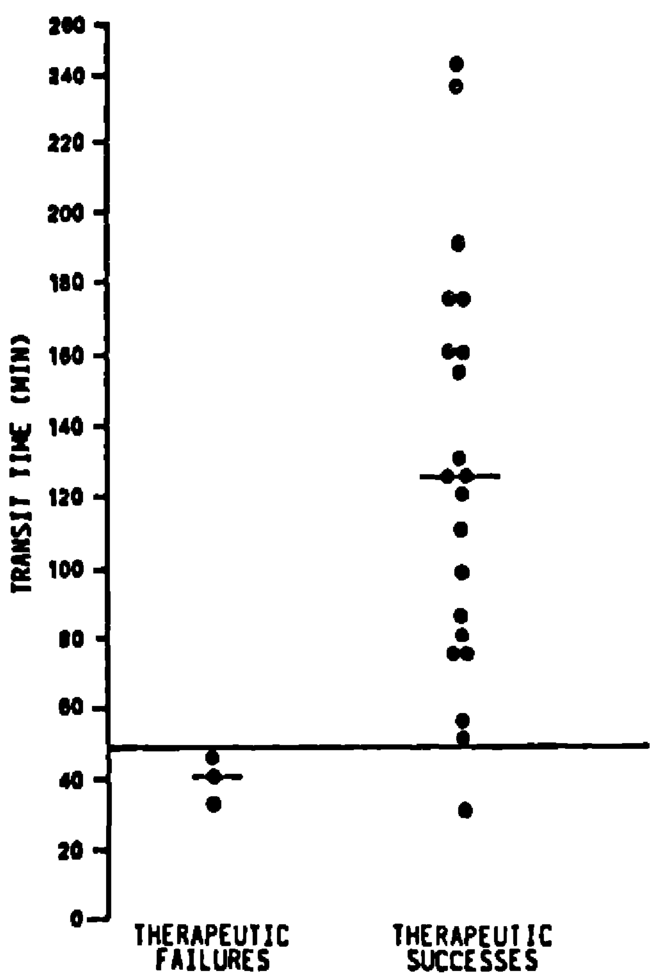

Figure 1. Distribution of mouth-to-anus transit time for the therapeutic failures and the therapeutic successes in the children treated with ORT.

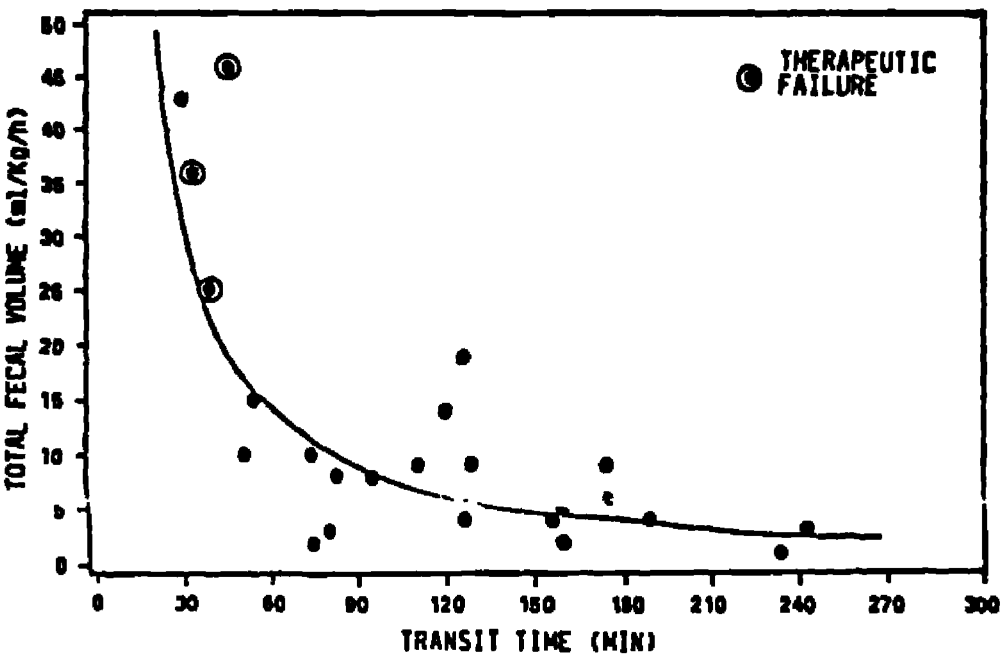

Figure 2. Association between mouth-to-anus transit time and fecal volume output during ORT.

Discussion

Quite distinct to the situation in healthy individuals, in which the total intestinal transit time of a meal may take from many hours to several days [12], most of that delay due to the residence of undigested residue in the colon [13-16], the secretory and osmotic stimuli in acute, infectious diarrhea hasten transit dramatically [16, 17]. For instance, Molla *et al.* [17] reported mean mouth-to-anus transit times from 4.9 to 7.3 h during the acute phase of diarrhea.

Transit time findings in the present study were a fortuitous and serendipitous result of observations in a comparative study of ORS with and without glycine [8, 9]. As part of the protocol, the non-absorbable marker, Brilliant blue, was administered in the first ORS dosing, and this served as the transit indicator. Observations from the metabolic component of the study provided us with data on rates of fecal losses and total fecal volumes. Since no differences in fecal volumes were found between the two treatment groups [9], we have combined the series into a single group for regression analyes.

Comparing our findings to those reported in the literature, we find our mean transit time (115 min) is shorter than the minimum reported in Bangladeshi children (294 min). A relationship between net fecal volume and transit time is well recognized [13, 18], and we confirm the *curvilinear* nature of the relation demonstrated in healthy volunteers fed lactulose by Read *et al.* [13].

The advent of ORT has been a major advance in the promotion of child survival and the reduction of mortality in tropical countries of the Third World [3, 4]. It provides a manageable approach to the maintenance of acceptable hydration while an episode of acute infectious diarrhea runs its course. However, among our 24 patients, if only oral therapy had been available, three children (12%) might have succumbed to their dehydration.

In terms of power of observed mouth-to-anus transit time to predict the outcome of oral therapy, if we use 50 min as the cutoff criterion, we would have a 100% sensitivity for detecting ORT failures. The predictive accuracy of a positive test (brief transit time) would be 75%, the predictive accuracy of a negative test being 100%. With our same 24-patient series, use of the more conventional time reference - "one hour" (60 min) - as a cutoff point, would have still identified all of those who were to need specialized medical therapy, this time with a predictive accuracy of a positive test of 50%; the predictive accuracy of a negative test remains at 100%.

The potentially *practical* aspect of these findings relates to a scenario of incipient diarrhea and dehydration in which ORT is begun in a remote, rural community. Whether the fluid and electrolyte absorption will compensate secretory losses cannot be *known* for certain until therapy has run its course. An early predictor of the probabilities of success or failure by the oral route would allow the village health officers to make the decision to persist with oral therapy in the locality, or refer the patient to the nearest facility with capabilites of intravenous fluid administration.

Our sample size of only 24 subjects, casually studied in a metabolic setting, is far too small to provide rigorous and durable predictive nomograms. More observations of this nature are needed. The advent of *Vibrio cholerae* transmission has enhancèd the value of such a predictor, as fecal losses in cholera can be voluminous [19]. The relationship of fecal volume to intestinal transit is well established, and we would hope that this report will stimulate other investigators working in tropical nations to add a non-absorbable marker to the initial dose of ORS to extend the experience and possibly refine the power of mouth-to-anus transit time as a guide to overall rehydration therapy.

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