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INTERNATIONAL CENTRE FOR DIARRHOEAL DISEASE RESEARCH, BANGLADESH

Memorandum

TO : Dr W.B. Greenough

FROM : Drs Bonita Stanton & John Clemens

DATE : 10.10.83

SUBJECT : A PROPOSAL "ACCEPTABILITY OF ALKALINIZING SOLUTIONS IN CHILDREN"

PROTOCOL OUTLINE

Purpose:

To evaluate the acceptability of several alkalinizing solutions available for use in administering the B subunit/whole cell oral cholera vaccine.

Rationale:

Laboratory work has demonstrated the necessity of maintaining gastric pH above 5 to preserve the antigenic integrity and membrane-binding properties of the vaccine. Because tablets are not suitable for young children, alkalinization of gastric contents must be accomplished with a liquid solution to be given with the vaccine. This work will test acceptability in children of three practical alternative solutions: 1% sodium bicarbonate, 1% sodium citrate (orange flavoured), and milk. We will also evaluate whether an incentive (allowing the subject to keep the cup used for ingesting the solution) has any positive effect on acceptability of the solutions.

Methods:

Sampling Frame

The sampling frame will consist of the urban Dhaka population currently served by the urban volunteers population.

Eligibility:

Children aged ≤ 6 years and ≥ 1 year will be eligible.

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Selection of Subjects

One week before testing the solutions, 25 urban volunteers will be told about the project by their field supervisor during a routine weekly visit. Each volunteer will be asked to recruit 8 mothers in their area, each of whom will bring one child in the above noted age range. Since vitamin A will be included in each solution (vide infra), it will be emphasized that each will benefit by participation. To ensure compliance on the part of the volunteers and field supervisors, their children will also be given the option of taking a vitamin A solution.

Solutions to be tested

Each participating child will be randomly assigned to one of four solutions, administered by the child's mother:

1. .1% $NaHCO_3$ + 50,000 U. Vitamin A (1 dose)
2. .1% Na Citrate + orange flavour + 50,000 U. Vitamin A (1 dose)
3. Reconstituted dry skim milk + 50,000 U. Vitamin A (1 dose)
4. .1% $NaHCO_3$ + 50,000 U. Vitamin A (1 dose) followed 5 minutes later by .1% $NaHCO_3$ alone.

For solutions 1-3, 300 cc. will be offered. For solution #4, 100 cc will be offered in the first dose, followed by 300 cc for the second dose.

Testing Schedule

The homes of 5 volunteers corresponding to a total of 40 study subjects, will be visited each morning. Since the project will be conducted for four consecutive mornings, a total of 200 subjects (50 allocated to each solution) will be tested. It is anticipated the study can be conducted and analyzed within 3-4 weeks.

Administration of the Solutions

All participating mothers and children will meet at the home of their urban volunteer at a prearranged time, corresponding with the usual time of the field supervisor's weekly visit. The 8 mother-child dyads at each session will be randomly (using a random number scheme) assigned to one of the four solutions. Each of four central staff women will monitor the ingestion by 2 children, after the solutions prepared by the investigaor, are allocated to the children. Assignment of children to the central staff women will precede randomization. The central staff women will explain to the two mother-child dyads under their supervision that the liquid contains a health promoting vitamin and that the child should be encouraged to drink all of it. During every other session the central staff women will also explain that the mother may keep the cup if the child succeeds in ingesting

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all of the prescribed solution. The group as a whole will also be told at the outset that 2[illegible] of the children will be asked to drink two cupfuls rather than one cupful of solution.

Just prior to the ingestion, a simple questionnaire will be administered to each mother, asking about the child's age, time of a last meal and last drink, usual diet, and major recent health problems. Any overt signs of malnutrition will also be noted. The child will also be weighed.

After obtaining this baseline information, the solution will be given to each mother, and the time of distribution will be noted. The central staff woman will then make observations about problems during the ingestion (i.e. regurgitation) and will record the time that it takes to ingest the entire volume. If the entire volume is not ingested after 15 minutes, the volume remaining in the cup will be measured and the ingestion will be terminated.

In no instance will the central staff women be told of the identity of the solutions prior to their observation. In addition, the solutions will be randomly assigned in such a way that no 2 children observed by the same central staff woman will receive the same solution. These two methodologic features should greatly augment the objectivity of observations and reduce bias.

Although a cup will be offered as an inducement in only half the sessions, the cups will be given to all participating mothers at the end of <u>every</u> session, regardless the performance of the child.

<u>Data Analysis</u>

The total amount of solutions ingested and the average rate of ingestion (cc/minute) will be compared for the four different "treatment" groups using analysis of variance. The overall success rates (complete ingestion) will be compared using the standard chi-square test. Analogous analyses of this sort will also be performed to compare the performance of clinically distinct age groups ($\leq$18 months, 18-24 months, 24 months - 36 months, 36-48 months, 48+ months) of children. Finally, analysis of co-variance will be used to assess the impact of offering a cup, timing of last feeding, and usual mode of feeding upon dimensional outcomes (volume consumed, rate of volume consumption), and logistic regression will examine the impact of these variables when ingestion is defined as "successful" (nearly complete), or "unsuccessful".

JDC:sc

BUDGET

SALARIES	% TIME DURING STUDY	AMOUNT
Bonita F. Stanton	50%	-
John D. Clemens	50%	-
Urban Volunteer Staff	50%	-

Materials	
300 cups x 300 @4 taka/cup	1200 Taka
5 liter jugs x 3 @ 250 Taka/jug	750 Taka
Watches x 4 @375 Taka/watch	1500 Taka

Solutions and Powders	
$NaHCO_3$	500 Taka
Na Citrate	500 Taka
Powdered milk	1250 Taka
Vitamin A	6250 Taka

Transportation	
Driver, Van, Gasoline x 5 days @ 750/day	3750 Taka
Total:	15, 400 Taka
	(=$641)

Precoded Data Form

Patient name _____ Code *

1 2 3

Date of visit

4 5 6 7

Time of visit: Hour

8 9

Total number of minutes

10 11

Group Number

12 13

Cup Incentive: 0 no
1 yes

14

Age of patient in months

15 16

Hours since last food ingested by child

17 18

Hours since last drink by child

19 20

Usual Drinking Pattern:
0 Breast only
1 Bottle only
2 Cup only
3 Breast and bottle
4 Breast and cup
5 Breast and bottle and cup
6 Bottle and cup

21

Weight of patient in pounds

22 23

Child grossly malnourished appearing:
0 No
1 Yes

24

Other siblings accompanying mother:
0 No
1 Yes

25

Exact time first dose of solution handed to mother

Hour

26 27

Minute

28 29

Was all solution taken from cup : 0 No
1 Yes

30

Exact time that test terminated

Hour

31 32

Minute

33 34

c.c. remaining in cup

35 36 37

Was there any spilling:
0 No
1 Yes

38

If yes, how many c.c. spilled(approximately) 39 40 41

Was there any vomiting or regurgitation
0 No
1 Yes 42

If yes approximately how many c.c. 42 43 44 45

Was second dose of solution given:
0 No
1 Yes 46

If no, why not:
0 Not scheduled
1 child refused,mother cooperated
2 mother refused 47

Time second dose of solution handed to mother
Hour 48 49
Minute 50 51

Time second test terminated
Hour 52 53
Minute 54 55

Was all fluid taken:
0 No
1 Yes 56

c.c. remaining in cup 57 58 59

Was there any spilling
0 No
1 Yes 60

If yes, approximately how many c.c. spilled 61 62 63

Was there any vomiting/regurgitation
0 No
1 Yes 64

If so, approximately how many c.c.'s 65 66 67

Identity of solution:
1 single dose $NaHCO_3$
2 double " " "
3 Na Citrate
4 Milk 68

Total number of c.c. actually ingested and maintained by child:

First Dose 69 70 71

(code999 if not applic.) Second Dose 72 73 74

ABSTRACT SUMMARY:

The choice of an acid neutralizing agent that is palatable to children is an important consideration in the formation of the current B-subunit/whole cell cholera vaccine. We will evaluate the acceptability of four different acid neutralizing requirements in 200 children aged 1-6 years: a) 1% $NaHCO_3$ (1 dose); b) Orange flavoured 1% Na Citrate; c) reconstituted dry skim milk; and d) 1% $NaHCO_3$ (2 doses separated by 5 minutes).

To stimulate the condition of the planned vaccine trial and to counter benefit to each of the participant, 50,000 U. Vitamin A will be added to each of the requirement.

The requirements will be randomly assigned and will be administered by mothers of the children. The amount of each solution taken as well as the rate of ingesting will be monitored to assess acceptability.

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