Attachment 1. 6

Date

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator Dr. Omar Rahman Trainee Investigator (if any) _____

Application No. 85-036P Supporting Agency (if Non-ICDDR,B) _____

Title of Study Prevalence and mechanisms of hypoglycemia in association with diarrhea

Project status:
- (X) New Study
- ( ) Continuation with change
- ( ) No change (do not fill out rest of form)

Circle the appropriate answer to each of the following (If Not Applicable write NA).

1. Source of Population:
   - (a) Ill subjects — (Yes) No
   - (b) Non-ill subjects — Yes (No)
   - (c) Minors or persons under guardianship — (Yes) No
2. Does the study involve:
   - (a) Physical risks to the subjects — Yes (No)
   - (b) Social Risks — Yes (No)
   - (c) Psychological risks to subjects — Yes (No)
   - (d) Discomfort to subjects — Yes (No)
   - (e) Invasion of privacy — Yes (No)
   - (f) Disclosure of information damaging to subject or others — Yes (No)
3. Does the study involve:
   - (a) Use of records, (hospital, medical, death, birth or other) — (Yes) No
   - (b) Use of fetal tissue or abortus — Yes (No)
   - (c) Use of organs or body fluids — Yes (No)
4. Are subjects clearly informed about:
   - (a) Nature and purposes of study — (Yes) No
   - (b) Procedures to be followed including alternatives used — (Yes) No
   - (c) Physical risks — (Yes) No
   - (d) Sensitive questions — (Yes) No
   - (e) Benefits to be derived — (Yes) No
   - (f) Right to refuse to participate or to withdraw from study — (Yes) No
   - (g) Confidential handling of data — (Yes) No
   - (h) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure — (Yes) No
5. Will signed consent form be required:
   - (a) From subjects — (Yes) No
   - (b) From parent or guardian (if subjects are minors) — (Yes) No
6. Will precautions be taken to protect anonymity of subjects — (Yes) No
7. Check documents being submitted herewith to Committee:
   - ___ Umbrella proposal - Initially submit an overview (all other requirements will be submitted with individual studies).
   - ✓ Protocol (Required)
   - ✓ Abstract Summary (Required)
   - ✓ Statement given or read to subjects on nature of study, risks, types of questions to be asked, and right to refuse to participate or withdraw (Required)
   - ✓ Informed consent form for subjects
   - ✓ Informed consent form for parent or guardian
   - ✓ Procedure for maintaining confidentiality
   - ___ Questionnaire or interview schedule *

* If the final instrument is not completed prior to review, the following information should be included in the abstract summary
1. A description of the areas to be covered in the questionnaire or interview which could be considered either sensitive or which would constitute an invasion of privacy.
2. Examples of the type of specific questions to be asked in the sensitive areas.
3. An indication as to when the questionnaire will be presented to the Cttee. for review.

e agree to obtain approval of the Ethical Review Committee for any changes nvolving the rights and welfare of subjects before making such change.

Omar Rahman 23-11-85
for Principal Investigator

Trainee

85-036
25.11.85

SECTION 1-RESEARCH PROTOCOL

PILOT PROTOCOL

1. TITLE: PREVALENCE AND MECHANISMS OF HYPOGLYCEMIA IN ASSOCIATION WITH DIARRHEA

2. PRINCIPAL INVESTIGATOR: Dr. Omar Rahman

CO-INVESTIGATORS: Dr. M.Bennish
Dr. A.N.Alam
Mr. Wahed

COLLABORATORS: Dr. R. Phillips
Dr. D. Warrell
Dr. Akbar

3. STARTING DATE: As soon as possible

4. COMPLETION DATE: 6 ~~12~~ months after approval

5. TOTAL INCREMENTAL COST: US $ 4531.00

6. SCIENTIFIC PROGRAM: This protocol has been approved by the Pathogenesis and Therapy Working Group

Signature of Acting Associate Director, PTWG: Mmmus.

Date: 20 NOV. 1985.

ABSTRACT

Hypoglycemia in association with diarrhea is a known and frequently lethal combination amongst people in Bangladesh. Thus we propose a study to investigate the prevalence and mechanisms of this disorder.

Prevalence will be established by screening for one week all patients admitted with acute diarrhea to the Dhaka station hospital of the International Centre for Diarrheal Disease Research, Bangladesh.

During the course of the study all patients admitted to the general ward and the intensive care unit and selected patients (those with severe dehydration and or characteristic signs and symptoms of hypoglycemia) admitted to the treatment centre will be screened on admission for blood glucose by finger-prick using dextrostix reagent strips read by a glucometer. Appropriate patients [i.e. whose blood sugar on admission is less than 2.2 mmol/litre (40mg/dl)] will be entered into the study and further investigated. Various mechanisms of hypoglycemia will then be evaluated by measuring levels of plasma glucose and the concomitant levels of various hormones,circulating fuels and substrates involved in glucose homeostasis during an episode of hypoglycemia and the changes in these levels with time in response to glucagon and or glucose infusions.

Each hypoglycemic patient's data will then be compared to two sets of controls: i) an age and sex matched patient with acute diarrhea who is normoglycemic on admission [blood sugar greater than 3.3 mmol/litre (60 mg/dl) and less than 5.8 mmol/litre (105 mg/dl) and ii)an age and sex matched patient with acute diarrhea who is hyperglycemic on admission [blood sugar greater than 10 mmol/litre (180 mg/dl)].

For the controls, blood levels for plasma glucose and the concomitant levels of various hormones,cirulating fuels and substrates involved in glucose homeostasis will be measured on admission (during their episode of normoglycemia or hyperglycemia) and at twenty four hours post admission.

The hypoglycemic and the control groups in addition to comparisons of the above blood levels will also be compared to see if there are any differences on the basis of nutritional status, etiological agent of diarrhea,etiological agents of other concomitant infections, duration of fasting, duration of diarrhea and presence or absence of septicemia.

OBJECTIVE

To gain a better understanding of the mechanism and prevalence of hypoglycemia in association with diarrhea amongst people in Bangladesh and thereby learn to manage this frequently lethal combination more effectively.

BACKGROUND

Hypoglycemia in association with diarrhea as alluded to above, is a known and frequently lethal combination amongst people in Bangladesh. The prevalence of this disorder is at least 1% [Molla et al (63)] and may in actuality be much higher. Analysis of data from the biochemistry laboratory in the month of January 1985 alone showed that out of approximately 250 admissions to the general ward and the intensive care unit during that period there were twenty two separate patients with hypoglycemia --blood sugars less than 2 mmol/litre. This works out to be a prevalence rate of approximately 9%.

Perhaps the most striking fact about this "association" is that the case fatality rate for hypoglycemia and diarrhea is significantly higher than the overall case fatality rate for that type of diarrhea, irrespective of the etiological nature of the diarrhea. For example [in the "Molla" study (63)] overall case fatality in shigella was 8.3% compared to 46.2% in shigella associated with hypoglycemia. Similarly in cholera overall case fatality was 0.7% compared to 14.3% in cholera associated with hypoglycemia.

In view of the high mortality of diarrhea in association with hypoglycemia it becomes imperative that a) we learn to better identify the particular subset of diarrhea patients who are prone to hypoglycemia and b)learn to manage this frequently lethal combination more effectively.

Before we explore hypoglycemia in association with diarrhea we feel it is necessary for us to briefly review hypoglycemia in general, and especially in children as they seem to be more prone to developing it in the setting of diarrheal diseases (63,64).

Hypoglycemia can be viewed as a disruption of normal glucose homeostatic mechanisms. In contrast to adults hypoglycemia in children is most commonly associated with fasting (1). While in adults there is no appreciable change in blood glucose levels even with prolonged fasting, in children and neonates there is a significant drop in blood glucose levels within 24 hours of fasting (2).

In order to have a clearer understanding of the phenomenon of hypoglycemia we must briefly review glucose homeostatic processes in the transition from the fed to the fasted state (1a,1b,2)

Under normal circumstances, in the immediate post prandial state part of the glucose derived from intestinal absorbtion under the action of insulin is oxidized completely to carbon dioxide (via pyruvate and Acetyl CoA in the Kreb cycle),part is stored as glycogen (from Glucose 6 Phosphate) and the rest is stored as fat (from Acetyl CoA). Subsequently plasma glucose and insulin levels decline and hepatic glycogenolysis is activated. As glycogen reserves start being depleted plasma glucose and insulin levels continue to drop. The drop in insulin levels activates lipolysis releasing circulating glycerol and free fatty acids . These free fatty acids are then partially oxidized in the liver to produce B hydroxy-butyrate and acetoacetate (the so called plasma ketones) which then constitute alternatives to glucose as major sources of energy entering the Krebs cycle via AcetylCoA. Thus oxidation of fats reduces the need for glucose as an energy source.

However glucose continues to be needed due to the obligate requirement of red blood cells and certain parts of the central nervous system for a steady supply of glucose as fuel. Thus gluconeógenesis (the denovo production of glucose) becomes essential in the fasting state despite the use of ketones as alternative sources of energy. The available substrates for gluconeogenesis include 1)gluconeogenic amino acids 2)unoxidized pyruvate and 3)glycerol (1). Of the three precursors gluconeogenic amino acids are by far the most important -providing approximately 50% of denovo net glucose production,followed by unoxidized pyruvate which provids 30% of net glucose production and lastly glycerol which provides only 10% of net new glucose production (2).

The unique combination of enzymes required for gluconeogenesis is found in the liver and the energy source for this process is provided by the partial oxidation of free fatty acids to ketones.

In order for the above transition (from fed to fasting) to function smoothly and for the blood glucose level to be maintained as far as possible what is needed is : 1) an adequate supply of endogenous gluconeogenic substrates (i.e. amino acids , glycerol and pyruvate), 2) functionally intact hepatic glycogenolytic and gluconeogenic enzyme systems and 3) a normal endocrine system for integrating and modulating the above processes (2).

We have already alluded to the role of insulin in the transition from the fed to the fasted state. It remains the predominant hormone regulating blood glucose levels as it is the only hormone whose direct action decreases the influx of glucose and accelerates the efflux of glucose from the vascular bed. It stimulates muscle glycogen synthesis, the incorporation of amino acids into protein and the conversion of glucose into triglycerides. In addition it stimulates hepatic glycogen synthesis, impairs glycogenolysis and markedly depresses gluconeogenesis. Thus in the fasting state a drop in insulin

levels is crucial to maintaining plasma glucose levels. In all species thus far examined, plasma insulin falls to very low levels during caloric restriction: values below 5-10 micro units per milliliter are routinely noted in the human being under these circumstances (3). Consequently insulin levels greater than 5 to 10 micro units per milliliter in association with blood glucose levels below 50 mg/dl (2.77 mmol/litre) are distinctly abnormal (2).

Opposed to the hypoglycemic effects of insulin are the actions of adrenocorticotropic hormone (ACTH), cortisol, glucagon, epinephrine, and growth hormone. The net effect of these hormones is to increase the ambient blood glucose level by (1) inhibiting glucose uptake by muscle (i.e., epinephrine, cortisol, and growth hormone), (2) increasing endogenous gluconeogenic amino acid supply by mobilization from muscle (i.e., cortisone), (3) activating lipolysis and providing increased fatty acids as a source of energy and glycerol for gluconeogenesis (i.e., epinephrine, glucagon, growth hormone, ACTH, and cortisol), (4) inhibiting insulin secretion from the pancreas (i.e. epinephrine) (5) acute activation of glycogenolytic and gluconeogenic enzymes (i.e., epinephrine and glucagon), and (6) chronic induction of gluconeogenic enzyme synthesis (e.g., glucagon and cortisol (2).

A number of recent studies on fasting non-hypoglycemic infants and children have illustrated the follwing time course of changes of circulating fuels, substrates, and hormones (4,5,6,7);

(1)plasma glucose declines more rapidly and to lower levels than in adults, reaching an average concentration between 40-50 mg/dl (2.2-2.77 mmol/litre) within 24 hours;

2)plasma free fatty acids and B-hydroxy-butyrate increase rapidly, replacing glucose on an equivalent basis (i.e. ketosis is to be expected in fasting children);

3)insulin declines to extremely low levels;

4) significant increases of glucagon, epinephrine, and cortisol, but not growth hormone, occur as fasting progresses.

Recent data suggest that of all the counterregulatory hormones epinephrine and glucagon have cardinal roles in acute glucose counterregulation (1b,8,9,10,11,12,13,14,) whereas growth hormone and cortisol are of minor importance and have only permissive roles if any (1b,10,13.14,15,16). The relative importance of the various counter-regulatory hormones however remains controversial especially in the case of epinephrine. In contrast to the data cited above (about the cardinal role of epinephrine in countering an acute decline in plasma glucose) other studies (17,18,19) seem to indicate that in adults epinephrine is not needed for toleration of fasting or recovery from insulin-induced coma. Despite the controversy about the role of epinephrine in adult hypoglycemia, there seems to be agreement

that epinephrine plays a more important role during fasting in children (5).

The changes in circulating fuels, substrates and hormones described above are all quantitatively greater and more rapid in children than in adults due to earlier depletion of glycogen reserves and greater decline in plasma glucose (1). This relatively more rapid decline in plasma glucose level in children is probably secondary to the much higher rate of energy utilization relative to surface area and or to the smaller size of the protein mass of a child relative to the total body mass compared to adults (2).

Having briefly reviewed glucose homeostasis in normal non-hypoglycemic children let us now address the issues of 1) recognizing the signs and symptoms and 2)diagnosing and investigating the mechanisms of hypoglycemia in infants and children.

Recognition of Hypoglycemia:

The signs and symptoms of hypoglycemia in infants and children are notoriously non specific. The following is a list of signs and symptoms commonly associated with hypoglycemia (1) :

Table I

Newborn:

Tremors, irritability
Lethargy,poor feeding
Hypothermia
Apnea, Seizures

Older Child

Shakiness,nervousness(early insulin reaction)
Acute hunger (early insulin reaction)
Sweating,pallor (late insulin reaction)
Nausea,vomiting
Lethargy,drowsiness
Acute unexplained irritability
Confusion, unresponsiveness
Seizures

Note: Suspicion of hypoglycemia should be increased if above occur while fasting and improve with eating.

The sine qua non of hypoglycemia is evidence of a blood glucose level that is abnormally low. As alluded to above interpretation of a particular blood glucose level has to be done in context of the duration of fasting of the child and the appropriate blood glucose level for that duration of fasting for that reference population.

There is little disagreement that blood glucose values less than 20 mg/dl (1.1 mmol/litre) in the newborn, less than 30 mg/dl (1.66 mmol/litre) in the older infants and children, and less than 40 mg/dl (2.2 mmol/litre) in the adolescent or adult are indicative of the need for immediate intervention (1).Whether these values represent disrupted homeostatic mechanisms (as opposed to well documented decreases in blood glucose with fasting in normal children) once again depends on the duration of fasting.

There does not seem to be a perfect correlation between the absolute blood glucose level and the manifestion of symptoms.Some children exhibit symptoms at levels of blood glucose not commonly associated with symptomology while others are relatively asymptomatic even in the face of distinctly low blood glucose values (1). Symptoms seem to be associated with the level of B-hydroxy butyrate in the blood. If B-hydroxybutyrate is high lower glucose appears to be tolerated while if both are low , symptoms are more likely to occur(5).

Hypoglycemic symptoms depend also on the rate at which blood glucose falls (20). In acute hypoglycemia (typically the result of excess insulin administration or secretion) the initial symptoms are due to excessive adrenergic activity-the patient is tremulous, anxious, sweats profusely, and has palpitations. Cerebral dysfunction follows, with alteations in behaviour, especially slowness and irritability, preceeding clouding of consciousness and coma. Seizures occur in 10=20% of adults and are more common in children (21). There may be features of decortication or decerebration (22) and not infrequently, focal abnormalities, particularly hemiplegia (23).

Classification of Neonatal, Infant and Childhood Hypoglycemia:

There have been many attemps to classify neonatal, infant and childhood hypoglycemia. The following is a composite of several schemes (1,2).

Table II

Neonatal hypoglycemia

I) Small for gestational age infant
[defective oxidation of F.F.A. and inability to utilize gluconeogenic substrates (24)]
II) Transient Hyperinsulinism of the newborn infant
1) Infant of the Diabetic Mother (24)
2) Infant with Erythroblastosis

Infant and Childhood Hypoglycemia

I. Functional Hypoglycemia of Fasting (25)

II. Hormonal Abnormalities
A) Hyperinsulinemia (1,2)
1) B-Cell hyperplasia
2) B-cell tumors
3) Nesidioblastosis
4) Functional B cell secretory defects

B) Counter-regulatory hormone deficiency: (1,2,17)
1) Epinephrine
2) Cortisol
3) Growth Hormone
4) Glucagon

III. Inherited Metabolic Defects: (1,2,17)
1) Glycogenolysis
2) Gluconeogenesis
3) Lipolysis
4) Metabolism of other sugars and amino acids.

Table II (cont.)

IV. Reaction to Drugs of Toxins
1) Ethanol (inhibits gluconeogenesis)
2) Propranolol (blocks catecholamine responses and inhibits lipolysis)
3) Oral hypoglycemic agents (increases insulin secretion)
4) Natural toxins: hypoglycins [e.g. unripe ackee fruit causes hypoglycemia by inhibiting fatty acid oxidation (26)]
5) Quinine [increases insulin secretion (27)]

V. Secondary to Other Systemic Disease.
1) Cyanotic heart disease [depletion of glycogen stores (28)]
2) Tumors [production of insulin like substances (29]
3) Liver dysfunction [probably due to disrupted gluconeogenesis and/glycogenolysis (30,31)]
4) CNS disorders [disruption of neuro endocrine pathways (8)]
5) Sepsis [inhibition of gluconeogenesis, accelerated depletion of glycogen reserves,increased peripheral utilization of glucose,endotoxin mediated increased insulin secretion----(32,33 34)]
6)Reyes Syndrome [defects in hepatic gluconeogenesis (35)]
7) Malnutrition [probably a subset of fasting functional hypoglycemia due to decreased protein mass --(36)]

-VI Undetermined causes.

It is beyond the scope of this protocol to discuss in depth all the causes of hypoglycemia listed above. I shall deal with certain selected issues. The reader is referred to the above references for a more extensive discussion of the various causes listed above.

Fasting functional hypoglycemia

This is perhaps the most common form of hypoglycemia in children.Other synonyms are "Ketotic Hypoglycemia", "Substrate limited hypoglycemia" and "Hypoalaninenemia". The typical patient usually a male between the ages of 2 and 7 years is underweight and hyperactive,has a decreased intake of food, becomes drowsy ,

has disconjugate eye movements, vomits and may have a seizure. Often there is a preceeding minor infection or a period of intense physical activity. Characteristically ketonemia and ketonuria accompany a low blood sugar (37). Previously this condition was considered to be a distinct entity and was thought to be related to a lack of gluconeogenic amino-acid substrate, specifically alanine (i.e. hypoalaninemia) (2). The debate hinged around the issue of whether the carbon skeleton used to synthesize alanine was derived from the oxidative deamination of other amino acids in muscle (thereby implying that alanine was indeed a major element in the synthesis of glucose from protein) or if it was derived from glucose itself (implying that rather than being a substrate for gluconeogenesis alanine would be one conponent of a recycling process, glucose--pyruvate--alanine---glucose.) The bulk of evidence now seems to favor the latter hypothesis (25). Thus hypoalaninenemia is not a specific cause of hypoglycemia rather it is a consequence of it. Ketotic hypoglycemia is now viewed not as a pathological entity but merely represents one tail of the distribution curve of the normal response of young children to fasting (25,38).

Hyperinsulinemia:(1,2)

1)Characteristically seen in newborn infants with prolonged intractable hypoglycemia requiring continued intravenous glucose or an older infant under a year of age with recurrent hypoglycemia.

2) Sine qua non is demonstrating inappropriately elevated insulin levels during hypoglycemia . As fasting insulin levels tend to be very low in normal children and absolute levels of insulin may not be very much higher in children with hyperinsulinism one needs a very sensitive assay to detect all children with this abnormality.

3)Indirect evidence of this abnormality may be obtained by demonstrating inappropriately low B-hydroxybutyrate and F.F.A in relation to decreased glucose levels. Fasting B-hydroxybutyrate levels less than 1.1 mmol per litre are considered by some authors to be diagnostic of inappropriate insulin secretion, even if the measured insulin concentration is low (27,39). However other authors feel that the low level of B-hydroxybutyrate in the face of low plasma glucose is not totally specific for hyperinsulinism (17).

4) As insulin suppresses glycogenolysis there should be aprompt glycemic response to glucagon (40).This is in contrast to other fasting hypoglycemias where glycogen reserves are already depleted by the time blood glucose levels fall significantly.

5) It is important to measure simultaneous C-peptide levels in order to demonstrate the pancreatic origin of the increased insulin secretion. If insulin is high and C-peptide is low ,it suggests an extra pancreatic source for the inrease in insulin [e.g. a tumor (29)]

Epinephrine Deficiency (1)

1)The importance of this disorder in producing hypoglycemia (as mentioned above) remains controversial in adults but seems to be fairly well established in children (5).

2)A frequent abnormality found among children ages 2-8 with recurrent hypoglycemia.

3)Affected children characteristically have a history of being small for gestational age or having had asphyxia or other perinatal problems.

4)These children form part of a broader non-specific syndrome of what used to be called "ketotic hypoglycemia or hypoalaninenimia" and is now referred as fasting functional hypoglycemia with many of the same historical and physical characteristics.

5)The definitive test is the demonstration of inappropriately low epinephrine levels in the face of low blood glucose.Normal epinephrine responses for plasma glucose levels of 2.2 mmol/litre (40mg/dl) range from 350 to over 2000pg per milliliter (8).

6)The cause of epinephrine deficiency while not definitively established is probably a result of irreversible injury to the developing adrenal medulla with usually intact adrenal cortical responses.

7)The condition is generally mild in childhood and in most cases can be managed simply by providing a substantial snack at bedtime and extra sugar containing fluids during times of acute illness. Children usually tend to grow out of their symptoms before 10 years of age.

Cortisol Deficiency (1)

1)Relatively rare but important as severe hypoglycemia may be first manifestation of adrenal cortical insufficiency.

2)Suggestive evidence includes a history of recent therapeutic use of steroid, hyperpigmentation or other signs of Addison's disease and associated hypotension of hyponatremia.

3) Definitive test is low cortisol in the face of hypoglycemia.

4)Not important for rapid counter regulation as glycemic effects take hours to be activated.

Growth Hormone Deficiency (1)

1)Mechanisms leading to hypoglycemia are not clear and it is not known why only a small proportion of growth hormone deficient children become hypoglycemic. Other evidence cited above (8) seems to suggest that growth hormone is not needed for acute glucose counter regulation.

2)Diagnosis should be suggested by patients exhibiting decreased rate of growth.

3)Not important for rapid counterregulation as glycemic effects take hours to be activated.

Glucagon Deficiency (1)

1)While theoretically an important consideration (it is the most important hormone in rapid glucose counterregulation), glucagon deficiency as a cause of hypoglycemia is quite rare (41).

Inherited Metabolic Defects (1,2)

1)Most common is Glucose 6-phospatase deficiency (Von Gierke's disease). This is a defect of both gluconeogenesis and glycogen lysis resulting is severe hypoglycemia after very brief periods of fasting.

2)Characteristic findings include enlargement of the liver and kidneys which are engorged with glycogen and fat, lactic acidosis growth failure, hyperlipidemia, hyperuricemia and a bleeding tendency (42).

3)Frequent daytime feedings and nocturnal intragastric glucose infusions seem to prevent recurrent hypoglycemia [as quoted in (1)].

4) I will not discuss in depth any other of the gluconeogenic and glycogenolytic enzyme defects. However I would like to point out that measurement of blood lactate during hypoglycemia is very

important because elevation of lactate in the face of a low blood glucose is indiciative of problems in gluconeogenesis.

5)Carnitine deficiency is the only well described fatty acid oxidation defect. It seems to be associated with fasting hypoglycemia without ketosis (43). Usually in these cases one can show elevated free fatty acids,but very low ketones in the presence of low blood glucose.

6)The definitive diagnosis of the various hepatic enzyme deficiencies is made by determining specific enzyme activities, glycogen content, and structure in liver biopsy specimens. Open liver biopsies are preferable to needle biopsies, in order to obtain adequate tissue for the appropriate biochemical studies.(2)

Reaction to drugs and Toxins:(1)

rrr1)I will not discuss this category in depth except to note that certain medications, mouthwashes, or teething remedies contain significant amounts of alcohol and can be very potent hypoglycemic stimuli in infant. The mechanism as mentioned above is due to an inhibition of gluconeogenesis.

Hypoglycemia secondary to other systemic disease:

1)I will only discuss the role of sepsis in depth. The reader is referred to the references cited above for a more detailed discussion of the other items in this category.

2)Hypoglycemia has occasionally been observed in septic patients.Most commonly it has been observed in the setting of fulminating pneumocccal infection in hyposplenic patients (32). In this subset of patients the mostprobable mechanism is : adrenocortical insufficiency due to the Water-house-Friderichsen syndrome (44).

3)It has been shown that injection of gram negative bacteria or endotoxin regularly results in hypoglycemia (45-52). The mechanisms that have been implicated to explain hypoglycemia in animals with sepsis are inhibition of gluconeogenesis (47,49,52) and or direct depletion of hepatic glycogen by endotoxin (53,54).

(4)Endotoxin has also been shown to stimulate insulin secretion from the pancreas(33) and activated macrophages appear to release insulin like substances after stimulation by salmonella endotoxin (34a)

(5)There is well documented evidence that Gastrointestinal Peptide (G.I.P.) and other intestinal hormones stimulate insulin release (34b) and it would not be unreasonable to postulate that patients suffering from diarrhea may have altered insulin output in response to increased release of enteric hormones from damaged bowel mucosa. Morishita and colleagues (34c) have shown increased blood levels of gastrin, secretin, V.I.P. and glucagon in patients with cholera.

5)Gram positive infections seem to inhibit gluconeogenesis from alanine and lactate but not pyruvate (55,56,57).

(6)Other factors may also contribute to the hypoglycemia seen in association with sepsis.Hypotension and decreased tissue perfusion cause a shift to anaerobic glycolysis which requires 18 times more glucose toprovide the same energy (58) Thus peripheral utilization of glucose is sharply increased. This seems to be the primary mechanism for hypoglycemia in neonates with bacteremia (59.60).

(7)Metabolic acidosis has been shown to impair gluconeogenesis (61) and clinical hypoglycemia has been observed in three patients with proved lactic acidosis, two of whom had sepsis (62).

Generalized Hepatic Dysfunction:

(1)The issue of hypoglycemia resulting from an impairment of general hepatic function is still unclear. Hypoglycemia has been described in patients with hepatocellular carcinoma and in alcoholics (30). It is an uncommon complication in cirrhosis probably due to the fact that the amount of functioning liver required to produce sufficient glucose appears to be relatively small (1) . For cirrhotics who are not alcoholics or do not have hepatocellular carcinoma it seems to be almost always associated with sepsis and particularly in patients with circulatory failure (30).

Now that we have reviewed glucose homeostasis and the various mechanisms of hypoglycemia let us direct our attention back to the issue of hypoglycemia in association with diarrhea amongst people in Bangladesh.

As mentioned above a certain number of Bangladeshi patients with diarrhea develop hypoglycemia and appear to have a significantly higher mortality than those diarrhea patients without hypoglycemia (63). Molla et al examined the case records of 26,521 patients less than 10 years of age who presented to the Dhaka hospital of the International Centre for Diarrheal Disease Research,Bangladesh, over a period of four years with acute diarrhea of various etiologies. The important conclusions derived from this study are as follows:

1) The authors noted that on admission (according to a retrospective chart review) approximately 1% (231/26,521)of the children admitted to the Dhaka hospital were hypoglycemic (blood sugar less than 2.2mmol/litre). This figure of 1% has to be viewed in the context of the way it was arrived at. All admissions were not screened. Only children who exhibited certain characteristic signs and symptoms of hypoglycemia (lethargy,vomiting,convulsions etc) were tested. Given the fact

that signs and symptoms of hypoglycemia are fairly non-specific (1) it is quite possible that a certain proportion of children who were relatively asymptomatic were missed. Thus the actual prevalence of hypoglycemia in association with diarrhea may well be higher.

2) The hypoglycemia seemed limited to children below the age of ten and was evenly distributed among that group.Once again given the selection process it is possible that some older children and adults were missed.

3) The authors graded the severity of the hypoglycemia into three categories: mild=2.0-2.2 mmol/litre, moderate=1-2.2 mmol/litre and severe=less than 1 mmol/litre. The severity of the hypoglycemia seeemed unrelated to the duration of diarrhea. Unfortunately however no data on the duration of fasting was recorded in the clinical charts.

4) The authors found no relation between the etiological agent of diarrhea and the incidence of hypoglycemia. Shigella , Vibrio cholerae and mixed infections were all implicated. However there is.no quantitative data of the relative proportions.

5)Perhaps the most significant finding of the "Molla" study (as outlined above) was that the case fatality rate for children with hypoglycemia and diarrhea was significantly higher than the overall case fatality rate for that particular type of diarrhea irrespective of etiology of diarrhea or age of the patients (all patients however were below the age of ten). Thus in Shigella overall case fatality was 8.3% against 46.2% in shigella associated with hypoglycemia. Similarly in cholera overall case fatality was 0.7% compared to 14.3% in cholera with hypoglycemia, and in mixed infections overall case fatality was 4.8% compare to 40% in diarrhea with hypoglycemia. In addition it is important to note that the overall case fatality figures included the high mortality of children with hypoglycemia . Thus it is reasonable to assume that the contrast between the mortality of diarrhea patients with hypoglycemia and those without hypoglycemia would be much more stark.

The only study which has looked into the mechanisms of profound hypoglycemia in patients with acute diarrhea was done by Hirschorn et al (64). They were also the first to report such cases. Their study was conducted in the period 1963-1966 on children with acute diarrhea presenting to the Cholera Research Laboratory (now known as the International Centre for Diarrheal Disease ,Research, Bangladesh) treatment centre at Dhaka Bangladesh. The major conclusions of this study were as follows:

1) The authors documented thirteen non kwashiokor,non marasmic children with diarrhea who had profound hypoglycemia out of a total number of 693 admissions over a period of two years. Thus a low figure for the prevalence of hypoglycemia in asssociation with diarrhea is 13/693 (app. 2%).

In certain special sub-populations (e.g. children with marasmus

or kwashiokor) it may actually be much more common. Wharton reporting from Uganda in 1970 (36) noted that moderate hypoglycemia [blood sugar between 20-40 mg/dl (1.1-2.2 mmol/litre)] was a common feature 25/76 in kwashiorkor but seemed to be of little clinical significance (prognostically) if the blood glucose level remained above 20 mg/dl (1.1 mmol/litre). Profound hypoglycemia [blood sugar less than 20 mg/dl (1.1 mmol/litre)] on the other hand with symptoms was rare (2/76), was uniformly fatal and seemed to occur as part of a clinical tetrad of hypoglycemia, hypothermia,coma,and severe bacterial and parasitic infection.

2)Cases were documented in association with cholera, shigellosis, typhoid, non-choleravibrios and acute diarrhea of unknown origin. Thus no specific etiological predominance could be demonstrated.

3)In this non marasmic,non kwashiorkor group there appeared to be no consistent relationship between degree of malnutrition-(as measured by convalescent blood protein,weight/age) and incidence of hypoglycemia.

4) The authors considered a number of different mechanisms of hypoglycemia as possible explanations and we will briefly review their findings in terms of these mechanisms:

i)Circulatory failure/shock leading to hypoxia: Hypoglycemia has been reported in association with shock (48). Although several of the children in the study were in circulatory collapse at the time of their hypoglycemia others developed hypoglycemia in the absence of hypotension or many hours after acute dehydration had been corrected.

ii)Hyperinsulinism: Levels of circulating insulin were low both during hypoglycemia and after the administration of glucose and glucagon,adrenaline. As mentioned above insulin assays need to be very sensitive to detect the small rise in insulin concentration felt to be diagnostic of this disorder. Thus methodological constraints (in 1966) may have prevented detection of hyper insulinism. Increased insulin secretion is however unlikely given that B-hydrxy butyrate levels measured in the blood during hypoglycemia were considerably higher than those consistent with hyperinsulinism.

iii)Fasting functional hypoglycemia: The authors carried out a number of mini studies to establish baseline norms for glucose values in Bangladeshi children. They found that : i)the mean fasting blood glucose after an overnight fast of 31convalescent or well children was 63.3 mg/dl (s.d.+- 11.8) [3.51 mmol/litre (s.d.+- 0.66)] with a range of 36-81 mg/dl (2-4.5 mmol/litre). ii)when 17 children with acute diarrhea who were initially normoglycemic were fasted 8 developed hypoglycemia (2 with only mild symptoms) after a mean fast of 30 hours during which time they received lactate infusions but no glucose.

Thus it is possible that fasting contributed to the hypoglycemia in some of the children but it cannot be implicated in 6/13 who were without food for only a short time,equivalent to an overnight fast. The crucial factor here is the validity of the historical data. It is difficult to get a very accurate feeding history from most patients.

4) Hepatic dysfunction was considered as a possible mechanism of hypoglycemia as there was a notable elevation of serum-glutamic-pyruyic-transaminase ,suggesting hepatic necrosis in one case and there were scattered areas of hepatic necrosis in 3 of the patients. This is however an unlikely possibility as very little functioning liver is required to support gluconeogenesis.

5)The major category of mechanisms which was not fully examined (probably due to methodological constraints) was the status of counter regulatory hormones.There is some indirect evidence that inadequate counter-regulatory mechanisms may have played a role in some of the cases. In one patient on autopsy hemorrhage into the adrenal cortex and medulla were noted. In another patient the increae in blood glucose after exogenous adrenaline and glucogon (in the face of low insulin levels) raises the issue of inadequate endogenous hormone secretion. This again may be due to inadequate production of endogenous hormone or as has been shown in some cases due to an inability of low blood glucose to stimulate counter-regulatory hormone release as a result of dysfunctional neuro-endocrine pathways (8).

6)Enzymatic defects in the metabolic pathways are also another possibility which were not fully examined. The lack of hepatomegaly in 9/13 cases make glycogen storage diseases an unlikely etiology. However in 4/13 cases there was clinical hepatomegaly and acidosis (measured by decreased levels of Hco3-- (no lactate levels were measured)) and Glycogen 6 phosphatase deficiency cannot be totally ruled out.

7)The common finding of acidosis among these children seems to point towards problems in gluconeogenesis. The acidosis could be result of impaired gluconeogenesis (inherited enzymatic defects,endotoxin inhibition,?insufficient adrenal hormones) or could be secondary to increased anaerobic glycolysis due to decreased tissue perfusion from circulatory collapse as a result of septicemia and may have caused impaired gluconeogenesis (32).

8)Another possibility is hypoglycemia secondary to some natural toxin or hypoglycin, as the use of herbal or homeopathic medicines is very common. No such history was elicited in most cases. Here once again the validity of historucal data is debatable.

In summary while the authors of the above study investigated a number of mechanisms they were not able to come up with any definitive mechanistic explanation for the hypoglycemia associated with diarrhea. There infact may not be one unifying mechanism to explain the hypoglycemia of all the patients with diarrhea. They may well be a heterogenous group from the point of view of their disruptions in glucose homeostasis.

Given that hypoglycemia is a frequently fatal complication in a certain number of diarrhea patients in Bangladesh we propose a study to investigate the prevalence and the mechanisms of this disorder . While at this point it would be premature to postulate any of the above mentioned mechanisms of hypoglycemia to be more or less likely as an explanation, we hope to particularly focus on the role of sepsis in hypoglycemia and hormonal dysfunctions as these are the two major categories not well investigated in previous studies.

An understanding of the mechanism of hypoglycemia may have important implications for management.For example if hyperinsulinism is an important cause then glucose infusions may not only be inadequate but may infact promote a rebound increase in insulin secretion further worsening the hypoglycemia (27). This is particularly important in view of the common practice of giving a child with "suspicious" signs of potential hypoglycemia (i.e.lethargy) a one time bolus of 25% dextrose with no follow up continuous infusion of intravenous dextrose.In this case adequate treatment may require in the short term the use of a continuous intravenous drip of dextrose at a rate and concentration enough to flood the system and compensate for any rebound increase of insulin. In the long term management of hyperinsulinism diazoxide (an inhibitor of insulin release) or even sub-total pancreactomy may be necessary if medical treatment is unsuccessful (1,2). If counter regulatory hormone deficiencies are important in this disorder then one might consider supplementation with these agents. Even in the case where glucose infusions remain the modality of choice prospective studies are needed to document the appropriate rate and concentration of glucose infusions to maintain adequate plasma glucose levels. Although there exist theoretical calculations of glucose metabolic rates in children and infants, and by inference optimal glucose infusion rates to maintain adequate plasma glucose levels (65) they have for the most part been derived from data on well nourished western children and and the dynamics of glucose metabolism may be significantly different in a Bangladeshi population with a much higher rate of malnutrition and a consequently lower protein mass relative to body weight.

SPECIFIC AIMS

To document the prevalence and investigate the mechanisms of hypoglycemia in association with diarrhea in patients in Bangladesh.

Prevalence will be documented by measuring for the period of one week the admission blood glucose values of all patients admitted to the Dhaka hospital of ICDDR'B by means of finger prick using dextrostix reagent strips. By screening all admissions (including the treatment centre, the general ward and the intensive care unit) we hope to get a representative population of people with diarrhea in Bangladesh. We realize however that due to possible seasonal variations in disease prevalence our statistics will not be totally representative of the true prevalence of this condition. As a follow up to this present study we hope to institute fingerprick dextrose measurements in the year round hospital surveillance system which currently follows up a random 4% sample of all hospital admissions.

The mechanisms of hypoglycemia will be investigated by measuring in appropriately selected subjects the levels of plasma glucose and the concomitant levels of various hormones , circulating fuels and substrates involved in gluconeogenesis (insulin, C-Peptide,growth hormone, cortisol, glucagon, epinephrine, alanine, lactate, B-hydroxybutyrate, Free Fatty Acids) during the episode of hypoglycemia and their changes over time in response to glucagon and or glucose infusions.

Each hypoglycemic patient will then be compared to two sets of controls: a) an age matched normoglycemic(on admission) patient with acute diarrhea and b) an age matched hyperglycemic (on admission) patient with acute diarrhea. For the controls plasma glucose and the concomitant levels of various hormones, circulating fuels and substrates involved in glucose homeostasis will be measured on admisssion (during their episode of normoglycemia or hyperglycemia) and at twenty four hours post admission

Apart from comparing the levels of plasma glucose and the concomitant levels of various hormones,circulating fuels and substrates on admission and at 24 hours post admission the three groups will also be compared on the basis of i)nutritional status -(arm circumference,weight/age,weight/height,convalescent blood protein), ii)duration of fasting, iii)duration of diarrhea, iv)etiology of diarrhea, v)etiology of any concomitant infection apart from diarrhea and vi)presence or absence of septicemia.

PATIENTS AND METHODS

Statistical Analysis:

Prevalence of hypoglycemia in association with diarrhea in Bangladeshi children will be established by measuring for the period of one week the admission blood glucose values (by means of a finger prick using dextrostix reagent strips read by a glucometer (65) of all patients admitted either to the treatment centre, the general ward or the intensive care unit of the Dhaka station hospital of the International Centre for Diarrheal Disease Research, Bangladesh. By screening all the admissions for a week we hope to get a representative population of people with diarrhea in Bangladesh. This is of course not taking into account the seasonal variation in disease prevalence and the fact that the patients coming to the hospital are somewhat self selected. The ideal methodology would be to do a year round survey in the community and the hospital settings.

In addition to screening blood glucose values we will also assess the nutritional status of each admission for that one week by measuring arm circumference, weight for age and weight for height. By collecting this data we hope to be able to establish baseline norms for blood glucose values according to nutritional status for patients with acute diarrhea in Bangladesh. In particular we would like to document the norms for children suffering from marasmus and kwashiorkor as there seems to be some controversy (36) about the prevalence of hypoglycemia in this group.

In order to validate the accuracy of the dextrostix/glucometer we will compare simultaneous plasma glucose measurements (done at the laboratory by the glutoxe oxidase method) on all patiemts in the study.

In investigating the mechanisms of hypoglycemia we have decided to study twenty hypoglycemic patients divided into the following age categories: i)0-0.99, ii)1-5.99, iii)6-14.99 and iv)15 and above. For each hypoglycemic patient we have decided to study two controls ,i) an age and sex matched patient with acute diarrhea who is normoglycemic on admission ---[blood sugar greater than 3.3 mmol/litre (60 mg/dl) and less than 5.8 mmol/litre (105 mg/dl)] and ii) an age and sex matched patient with acute diarrhea who is hyperglycemic on admission---[blood sugar greater than 10 mmol/litre (180 mg/dl)]. Thus in total we will be studying sixty children.

We plan to compare the three groups on the basis of the following: i) mean plasma glucose level (by the nature of the selection process of the three groups they will be significantly different) ii)mean plasma levels of insulin, C-peptide, cortisol, growth hormone, glucagon, alanine, lactate, B-hydroxybutyrate, free fatty acids, SGOT,SGPT, serum electrolytes, urea nitrogen, creatinine, and total white cell count iii) nutritional status iv)etiology of diarrhea v) etiology of any concomitant infection

vi) presence or absence of septicemia vi)duration of diarrhea and vii)duration of fasting.

STUDY DESIGN

Inclusion Criteria

Hypoglycemic Criteria:

Any patient whose screening admission blood glucose by dextrostix is less than 2.2 mmol/litre (40 mg/dl) will be classified as hypoglycemic and will be entered into the study if legal consent is obtained from the legal guardian.

Normoglycemic Control Group:

The first age and sex matched patient with acute diarrhea whose admission blood glucose level by dextrostix is greater than 3.3 mmol/litre (60g/dl) and less than 5.8 (105 mg/dl) will be entered into the study as a normoglycemic control if consent is obtained from the legal guardian.

Hyperglycemic Control Group:

The first age and sex matched patient with acute diarrhea whose admission blood glucose level by dextrostix is greater than 10.0 mmol/litre (180 mg/dl) will be entered into the study as a hyperglycemic control if legal consent is obtained from the legal guardian.

Exclusion Criteria:

The only exclusion criteria is one that applies to the controls: Any patient having a history of diabetes or diagnosed as having diabetes will be excluded from the control groups.

SCHEDULE OF STUDY PROCEDURES

The methods for establishing the prevalence of hypoglycemia in association with acute diarrhea in Bangladeshi children have already been described in the previous section.

The mechanism of hypoglycemia will be investigated as follows:

(1) During the course of the study all admissions to the general ward and the intensive care unit will have their admission blood glucose levels screened by finger prick using dextrostix reagent strips read by a glucometer (65).

(2) If the glucometer reading is less than 2.2mmol/litre (40 mg/dl) the patient will be classified as hypoglycemic and will immediately be transferred to the intensive care unit.Once legal consent is obtained from the legal guardian the patient will be entered into the study.

(3)Immediately an angio-catheter will be inserted into one of the ante-cubital veins by the investigator and blood will be collected for:

Routinie Blood Tests
Complete Blood Count and Differential
Hematocrit
Blood culture-including Shiga toxin detection.
Plasma glucose (blood to be collected in fluoride oxalate tubes and to be separated immediately and frozen. Measurements to be done by the hexokinase method)
Serum urea,creatinine,electrolytes,total protein.

Blood Tests for Research purposes:
Plasma Insulin (66)
Plasma C-peptide (67)
Glucagon (68)
Catecholamines -(Epinephrine,Norepinephrine) (69)
Cortisol (1)
Growth Hormone (70)
Plasma Ketones (71)
Plasma free fatty acids (72)
Plasma Alanine (73)
Plasma Lactate (74)
SGPT
Endotoxin -limulus lysate test
Detection of macrophage insulin like activity

4) In the case of all hypoglycemic children [with dextrostix values less than 2.2 mmol/litre (40mg/dl)] once the initial bloods are drawn a bolus of 2mls/kg of a 250gms/litre (25%) dextrose solution will be immediately infused by rapid intravenous injection in the arm not containing the angio-catheter. Immediately thereafter a solution of half strength acetate and 50gms/litre (5%) dextrose will be infused. Initially the infusion will be wide open ,then subsequently the rate will be readjusted according to repeat dextrostix measurements at 15min, 30min, 60min, 120min, 240min and 24hrs.

7) If at any time a dextrose stix reading shows blood glucose to be less than 2.2 mmol/litre (40mg/dl) an immediate bolus of 250gms/litre (25%) dextrose solution will be given and a repeat dextrostix will be checked fifteen minutes later.

8) After the initial blood draw at 0hrs, blood will be collected for dextrostix measurements and plasma glucose at 15min, 30,min, 60min, 120min, 240min and 24 hours. Blood will also be collected for plasma insulin, Cpeptide, epinephrine and glucagon at 30min, 60min, 240min and 24 hrs. Cortisol,Growth Hormone, G.I.P., Plasma alanine, lactate and plasma ketone levels will be checked at 240min and 24 hrs. In addition to blood collected for routine hospital management of the patient a total of 8 ml in six different collections over a period of 24 hours will be drawn for research purposes.

9)A full history and physical examination will be recorded using the standard hospital forms. In addition specific data of interest will be coded on the data sheets enclosed.

10)Other admission investigations will include stool culture (for salmonellae, shigellae, vibrio cholerae, E-Coli LT/ST and Rota Virus), stool microscopy and urine analysis.

11)All the patients will remain in the study until discharged from the hospital. Their clinical course will be closely followed and all treatments including timing and dose of drug therapy and fluids will be recorded for the first twentyfour hours.

12)Patients who die (if consent is obtained) will have a fine needle percutaneous biopsy of the liver immediately post mortem. When possible during full autopsy, samples of liver will be taken for PAS staining before and after diastase digestion for detection of glycogen depletion.

13)Controls:

For each hypoglycemic patient there will be two sets of controls:

i)an age and sex matched patient with acute diarrhea who is normoglycemic on admission --[blood sugar greater than 3.3 mmol/litre (60 mg/dl) and less than 5.8 mmol/litre (105 mg/dl)]

ii) an age and sex matched patient with acute diarrhea who is hyperglycemic on admission --- [blood sugar greater than 10 mmol/litre (180 mg/dl].

The process of selection of controls will be as follows: Once a hypoglycemic patient has been identified, starting the next day all admissions (to the general ward and the intensive care unit) in the same age and sex category will be screened by dextrostix for their admission blood glucose values. The first age matched patient with acute diarrhea having a normal screening admission blood glucose value will be entered into the study as a normoglycemic control provided consent is gotten from the legal guardian. Similarly the first age matched patient with acute diarrhea having an elevated screening admission glucose value by dextrostix will be entered as the hyperglycemic control. The screening for controls will continue until a normo and hyper glycemic pair are found. As regards age categories of hypoglycemic patients, they will be classified into the following categories: i)0-0.99, ii)1-5.99, iii)6-14.99 and iv)15 and above..

14) In the case of controls the initial blood collection will be exactly the same as the hypoglycemic patients. Subsequently however they will not have any 15min, 30min, 60min,. 120min, 240min blood drawings but will have a 24 hr blood drawing ,once again the same as the hypoglycemic patients.

15) The controls will continue to receive the standard hospital treatment for their condition. They too will continue to be in the study until discharged from the hospital and their clinical course will be closely followed with all treatment including timing and dose of drug therapy and fluids for the first 24 hrs duly recorded.

We have decided to provide some type of positive incentive to the participants in the study. Thus all patients enrolled in the study will be screened 24hrs post admission for anemia by means of a "spun hematocrit" and any patient found to be significantly anemic will be appropritely treated with iron supplements.

SUMMARY OF DATA COLLECTION

[Hypoglycemic Group only (**); all other tests will be done on all three groups.]

Ohrs:

i)history and physical exam.

ii)Routine Blood Tests: Serum electrolytes, urea nitrogen, creatinine, total protein, complete blood count and differential, blood culture (including shiga toxin), dextrostix, and plasma glucose.

iii)Research Blood Tests: plasma insulin, C-peptide, cortisol, glucagon, catecholamines, growth hormone, G.I.P.,plasma ketones, free fatty acids, alanine, lactate, albumin, SGPT and endotoxin and macrophage stimulaion assay

**15min--- Routine tests: dextrostix, plasmas glucose.

**30min---Routine tests: dextrostix, plasma glucose.
Research tests:
plasma insulin, C peptide, catecholamines and glucagon

**60min--Routine tests: dextrostix, plasma glucose.
Research tests: plasma insulin, C peptide, catecholamines and glucagon

**120min-Routine tests: dextrostix,plasma glucose
Research tests: Glucagon, catecholamines, insulin and Cpeptide.

**240min-Routine tests: dextrostix, plasma glucose.
Research tests: plasma insulin, C peptide, catecholamines, cortisol, growth hormone, glucagon, alanine, lactate, plasma ketones and free fatty acids and G.I.P..

24hrs-----Routine tests : dextrostix, plasma glucose.
Research tests: plasma insulin, Cpeptide, catecholamines, cortisol, glucagon, alanine, lactate, plasma ketones, free fatty acids, total protein and G.I.P..

Misc.---Routine tests :i)stool(one sample) for bacteriological cultures/Elisa test and microscopy.
Research tests : urine analysis.

Positive incentive--- Blood for "spun hematocrit" 24 hrs post admission

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ABSTRACT SUMMARY

1)As mentioned above we have decided to study twenty hypoglycemic patients and forty controls (half of whom will be normoglycemic and the other half hyperglycemic). As each of the groups will be preselected according to an admission blood glucose value ,their mean plasma glucose values will be significantly different by virtue of the selection process --[hypoglycemia being defined as blood glucose<2.2mmol/litre (40mg/dl), normoglycemia being defined as blood glucose greater than 3.3 mmol/litre (60mg/dl) and less than 5.8 mmol/litre (105 mg/dl) and hyperglycemia being defined as blood glucose greater than 10 mmol/litre (180 mg/dl).]

All the studies cited in the literature have had twenty hypoglycemic patients or less so we should not have any problem with statistical significance of our results. In any case a lot of our analysis will deal with interpreting the levels of various hormone, circulating fuels and substrates involved in gluconeogenesis concomitant to a particular glucose value. As the glucose values will not be similar in the three groups we will for the most part be comparing our results in the hypoglycemic patients with controls in the literature derived from provocative testing. For example if we need to interpret the measured level of plasma insulin concomitant with a blood glucose value of 1.1 mmol/litre in our hypoglycemic group we need to compare it to data derived from normal (non hypoglycemic) children who have undergone provocative testing to reduce their blood glucose levels to 1.1 mmol/litre.

2)Our prevalence statistics will (as mentioned previously) not be totally representative due to the possible effect of seasonal variation in disease prevalence on the prevalence of hypoglycemia. We hope that follow up data collected via the surveillance system (which currently samples a randomized systematic 4% sample of all hospital admissions throughout the year) may be more helpful in this regard. In addition we recognize the fact that patients coming to the hospital are a self selected group and do not completely represent the community at large.

3)We would like to emphasize that adequate attention will be given to ensuring that glucagon assays reflect pancreatic glucogon and not enteric glucagon which has no documented counter regulatory role.

4) We have no explicit exclusion criteria for our hypoglycemic patients and we have very broad inclusion criteria. The only absolute requirement is that these children have an associated episode of diarrhea on admission. The diarrhea does not have to be their only disorder or even their primary disorder. The presence or absence of other concomitant infections (e.g. pneumonia) is not a reason for exclusion. In fact we will be specifically comparing the frequency of concomitant infections in the three

groups.

3)The only invasive procedure that we will do during the study is blood drawing. The amount of blood drawn for research purposes (a total of 9mls in six different collections over a period of 24hr) will pose no risk to the patients.

4)In order to safeguard confidentiality and protect anonymity all patients enrolled in the study will be assigned a study number and that number will be used throughout when analysing information collected from such patients.

5)Informed consent will be obtained from the legal guardian of the patient in each case. Patients will receive the same level of care (the best available for their condition) regardless of whether they agree to participate in the study or not.

6)In addition to the data forms enclose a complete standard medical history and physical examination will be recorded at the time of entry into the study.

7)The study will also require the use of hospital records (which we will record ourselves), blood, stool and urine.

8)Each individual patient will receive the best care available for their condition. The major disadvantage is that some blood will be drawn for research purposes which otherwise would not have been done.

This relatively minor and transient inconvenience (at no time will any patient face any significant adverse consequence as a result of being in the study) needs to be weighed against the potential benefits accruing from the information gained in this study. Future patients will benefit because a better understanding of the mechanism of hypoglycemia in association with diarrhea and a more accurate knowledge of its prevalence will help doctors to treat/prevent its adverse consequences.

In addition as a positive incentive, all participants in the study will be screened for anemia on the basis of a 24hrs post admission hematocrit. Anyone found to be significantly anemic will be appropriately treated with iron supplements.

DETAILED BUDGET

(1) Personnel Services

Name	Cost
Dr. Omar Rahman Dr. M. Bennish Dr. A. Alam Dr. D. Warrell Dr. R. Phillips Dr. Akbar	Pilot protocol: NO CHARGE

(2) Supplies and Materials

Item	Cost
Needles, syringes, vials for blood collection	$1000.00
5 Glucocheck monitors Dextrostixs (3000)	$1500.00
Total costs for supplies and materials	$2500.00

(3) Laboratory Tests For Research Purposes

(For one hypoglycemic patient who completes the study)

Test	Cost/Test ($)	No. of Tests	Cost ($)
Serum electrolytes	02.77	1	02.77
BUN	01.34	1	01.34
creatinine	02.58	1	02.58
Plasma glucose	01.58	2	03.16
Plasma insulin Plasma C peptide Plasma cortisol Plasma growth hormone Plasma catecholamines Plasma glucagon Plasma alanine Plasma lactate Plasma ketones Plasma G.I.P.			NO COST
Serum SGPT	01.95	1	01.95
Serum albumin protein	02.00	1	02.00
Blood endotoxin assay	10.00	1	10.00

(3) Laboratory Tests (cont)

Test	Cost/Test	No. of Tests	Cost
Urine analysis	01.72	1	01.72

Total Lab. costs for one hypoglycemic patient	25.52
Total Lab. costs for twenty hypoglycemic patients	0510.40
Similarly Total Lab. costs for forty controls	1020.80
Total Lab. costs for all sixty patients	1531.20

BUDGET SUMMARY

(1)Personnel Services	0000.00
(2)Total costs of supplies and materials	2500.00
(3)Total Lab. costs for sixty patients	1531.20
(4)Equipment	0000.00
(5)Patient hospitalization costs	0000.00
(6)Outpatient care	0000.00
(7)ICCDDR'B Transport	0000.00
(8)Travel and Transportation of Persons	0000.00
(9)Transportation of Things	0500.00
(10)Rent,Communication & Utilities	0000.00
(11)Information services	0000.00
(12)Printing and Reproduction	0000.00
(13)Other contractual services	0000.00
(14)Construction,renovation,alteration	0000.00
Total cost for sixty patients	4531.20

ENGLISH CONSENT FORM

Your patient is suffering from diarrhea. Sometimes in patients suffering from this disease the blood sugar can fall to a very low level and this can be very dangerous for the patient. We are trying to determine the cause of this problem and thus help prevent/treat it.

If you agree we will enter your patient in our study . The patient will receive the best possible care for his/her disease.In addition to the routine tests (blood,stool,urine,Xrays), we will need to take a small amount of extra blood (a total of 9 ml in six different collections over 24 hrs) for research purposes. This small amount of blood will not cause any harm to the patient.

The patient will remain in the study until he/she is discharged from the hospital. All appropriate measures will be taken to treat the patient. During the study the patient will not undergo any physical injury apart from the little pain at the time of drawing blood

Your consent to include your patient in this study will help us determine the most effective treatment for this condition. In addition as an extra benefit for participating in the study the patient will be screened for anemia and if found to anemic will be treated appropriately.

You are free to withdraw your patient from the study at any time you wish. Even if you do not give consent for the study, the patient will get the appropriate treatment for this condition.

We will let you know the reports of the investigations done if and when you so desire.

Signature of Investigator:----------
Date----------

Signature / Thumbprint of
Legal Guardian----------

Date----------

আন্তর্জাতিক উদরাময় গবেষণা কেন্দ্র Hypoglycemia Protocol
বাংলাদেশ

সম্মতি পত্র

আপনার শিশু ডায়রিয়ায় ভুগছে। কখনো কখনো এ অবস্থায় শর্করার পরিমান অতিরিক্ত কমে যেয়ে রোগীর অবস্থা মারাত্মক হতে পারে।
আমরা এ পরিস্থিতির কারন জানার জন্য এবং উপযুক্ত চিকিৎসা পদ্ধতিতে এ রোগ নিরাময়ের জন্য গবেষণা চালাচ্ছি।

আপনার সম্মতিক্রমে আপনার রোগীকে নিয়ে গবেষনার জন্য তাকে হাসপাতালে ভর্তি করবো। এখানে রোগীর সর্বোত্কৃষ্ট চিকিৎসার ব্যবস্থা করা হবে। সাধারন পরীক্ষার জন্য রোগীর মলমূত্র ইত্যাদি ছাড়াও ৬টি বিভিন্ন রকম পরীক্ষার জন্য আমরা রোগীর শরীর হতে ৯ মি: লিটার রক্ত নেবো। এই সামান্য পরিমান রক্তের জন্য রোগীর কোন ক্ষতি হবেনা।

রোগী সুস্থ হয়ে না ওঠা পর্যন্ত তাকে হাসপাতালে থাকতে হবে। এইখানে তার উপযুক্ত চিকিৎসা করা হবে। কেবলমাত্র একবার রক্ত নেওয়া ছাড়া আর কোন কারিরিক কষ্ট দেওয়া হবেনা।

গবেষনা কাজে আপনার সম্মতি আমাদেরকে সর্বোত্কৃষ্ট চিকিৎসা পদ্ধতি নির্নয়ে খুবই সাহায্য করবে। রক্ত পরীক্ষা দ্বারা আপনার রোগী রক্ত স্বল্পতায় ভুগছে জানতে পারলে তারজন্য চিকিৎসা করা হবে এবং রক্তবৃদ্ধির ব্যবস্থা করা হবে।

আপনি যে কোন সময়ে আপনার সম্মতি প্রত্যাহার করে নিতে পারেন। আর আপনি যদি এ গবেষনায় যোগদান করতে নাও চান তা'হলেও আপনার রোগীকে আমরা উপযুক্ত চিকিৎসা করবো।

আপনি এ গবেষনার বিভিন্ন রকম ফলাফল জানতে চাইলে আমরা জানাবো।

গবেষকের স্বাক্ষর

তারিখ

অভিভাবকের স্বাক্ষর

তারিখ

Form # 1 Hypoglycemia Study Budget No:

History:

Date & time:---------- Glucose status on admission----------
Patient's name---------- Adm: #---------- Study #------- Age-------

PRESENTING COMPLAINTS

DIARRHEA:

Duration:---------- hrs

Frequency in last 24 hrs:----------

Character: 1 = yellow liquid
2 = mucoid
3 = bloody mucoid

VOMITING:

Duration:----------hrs
Frequency in last 24 hrs

LAST FEEDING:----------hrs prior to Ohr blood

Quantity and type of food eaten at last feeding:

FEVER PRIOR TO ADMISSION :---------- 0=No, 1=Yes

OUTSIDE MEDICATIONS---------- 0=None; 1=homeopathic;
2=allopathic

Dose------

# of Doses-----

HX. OF ALTERED MENTAL STATUS 0=No hx; 1=lethargy;
2=irritability
3=seizures/convulsions

Duration:----hrs prior to admission

BIRTH HX: 0=premature; 1=normal; 2=post mature;

GESTATIONAL STATUS: 0=Normal size for gestational age
1=Small for gestational age

MATERNAL HX: Hx of Diabetes-- Yes; No;

Form # 2 pg 1 Hypoglycemia Study Budget #
Physical Exam

Date & time:---------- Patient's name:-----

Admission #:--------- Study #:---------- Age------
Glucose status-------+

Radial Pulse------ Rythym 0=regular; 1=irregular
Volume 0=good; 1=low

Rectal Temp.------- F Resp: -----/min

Weight: on admission-----kg Height-------cm
24 hr.---------- kg
Discharge-------- kg

Discharge wt/age:----- % of 50th percentile------
Discharge wt/ht:--- % of 50th percentile------

Arm circum:-------- % of 50th percentile------

Triceps skin fold
thickness: % of 50th percentile------

Dehydration status : 0=none-mild 1=moderate 2=severe

Abdomen: Bowel sounds: 0=normal; 1=sluggish; 2=absent;
Tenderness on palpation : 0=none; 1=localized;
2=generalized
Liver: 0 =not palp.; 1=palp. non tender, -----cm
2=palp. tender,------cm

Lungs: clear; rhonchi/rales;

Heart: Rhythm 0=regular 1= irregular
Murmurs 0=none 1= systolic 2=diastolic

Skin: 0=not cyanotic 1=cyanotic

Genitalia: Hypogonadism--- yes; no;

Form # 2 pg 2. Hypoglycemia Study
Physical Exam Study #----

Name:---------- Admission #------- Age:---------

Mental Status: 0=alert and oriented;
1=lethargic but resp. to verb stimuli
2=unconscious but localized resp. to pain
3=unconscious with non localized resp. to pain
4=unconscious with no resp. to pain but reflexes intact
5=decorticate
6=decerebrate

Convulsions/Seizures: 0=absent; 1=focal seizures
2=generalized seizures

Muscle strength: 0=normal; 1=focal paresis but not plegia
2=hemiplegia;

Muscle tone: 0=normal; 1=flaccid; 2=spastic

Deep Tendon Reflexes: 0= normal bilaterally
1= hyporeflexive unilat.
2= hyporeflexive bilat.
3= hyperreflexive unilat.
4= hyperreflexive bilat.

Dorsiflexion of Great Toes: 0=normal bilat.
1=unilat. abnormal
2=bilat. abnormal

Form # 3 Hypoglycemia Study Budget Code #

Investigations

Date & time :---------- Glucose Status------ Study #-----

Patient's name:---------- Admission #-------- Age------

Blood Tests:

Name of Test	0hr	15min	30min	60min	120min	240min	24hr
Plasma Glucose							
Dextrostix							
Insulin							
Cpeptide							
Glucagon							
Catecholamine:							
Epineph							
Norepineph							
Cortisol							
G.Hormone							
G.I.P.							
Alanine							
Lactate							
Ketones							
F.F.A.							
Na							
K							
Cl							
HCO3							
BUN							
Creatinine							
Albumin							
T.Protein							
SGPT							
Hct							
WBC							
polys							
bands							
lymps							
monos							
eosin							
baso							
(Endotoxin assay)							

Form # 3 pg 2

Hypoglycemia Study

Investigations

Date & time:----------

Glucose Status:----------

Patient's Name:----------

Admission #---------- Age----
Study #----------

Blood culture ----------

Stool microscopy:
PH
Puscells/hpf
R.B.C. /hpf
Veg. Giardia
Veg. Emoeba H.
Other Worms

Stool culture:

Salmonellae
Shigellae
Vibrio Cholerae
ETEC
Rotavirus/Elisa
Other