E SHEET) ETHICAL REVIEW COMMITTEE, ICDDR,B.

ncipal Investigator Dr. Ali Miraj Khan Trainee Investigator (if any) _____

lication No. 97-017 Supporting Agency (if Non-ICDDR,B) USAID/N

e of Study Evaluation of efficacy Project status:
rentral gentamicin in a (✓) New Study
e daily dose..... ( ) Continuation with change
( ) No change (do not fill out rest of form)

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

Source of Population:
(a) Ill subjects (Yes) No
(b) Non-ill subjects Yes (No)
(c) Minors or persons under guardianship (Yes) No

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)

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

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) NA
(d) Sensitive questions Yes (No) NA
(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 NA

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.

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

Ali Miraj Khan
Principal Investigator

Trainee

27 NOV 2004

RESEARCH PROPOSAL

SECTION 1 : TITLE PAGE

a) **Title: Evaluation of efficacy of parenteral gentamicin in a single daily dose versus conventional three divided doses in malnourished children.**

b) Principal Investigator(PI): Ali Miraj Khan, MBBS
Assistant Scientist, CSD

Co-Investigators: N.H.Alam, MBBS, MD
Senior Medical officer, CSD
T. Ahmed, MBBS.,PhD
Senior Medical Officer, CSD

Consultant: George J. Fuchs, MD
Director, CSD

c) Source of funding : USAID/W

d) Budget: US $ 96,128

e) Duration of the project: 1½ years from the date of starting

f) Starting date : As soon as possible

Date 31 Aug, 97.

Signature
Divisional Director
Clinical Sciences Division

ABSTRACT SUMMARY:

A prospective, open and randomized clinical study has been designed to evaluate and compare efficacy of once daily administration of parenteral gentamicin with same amount of drug administered conventionally in three divided doses in malnourished children. This study also aims to determine the effects of malnutrition on the pharmacokinetics of once daily dosing of gentamicin. The study protocol aims to enroll 156 malnourished children (weight for height below 70%) aged 1 to 5 years of either sex with infection where gentamicin will be indicated. These patients will be randomly assigned into one of the two treatment schedules : gentamicin once (G1) or thrice (G-3) daily. Another twenty children with normal weight for height will be enrolled to compare the effects of malnutrition on the pharmacokinetics of once daily dosing of gentamicin. Pharmacokinetics will be measured according to the standard method from 20 patients of each group. On 2nd day of treatment, blood samples will be collected for assay of serum concentrations of gentamicin immediately before (trough value) and 1 (peak value) 3,5,8 and 24 (if in once arm daily) hours after administration of the drug. Serum gentamicin will be measured by fluorescence polarization assay (Abbott Laboratories) or EMIT homogeneous enzyme immunoassay (SYVA). In twenty patients from each group of once daily regimen of gentamicin, plasma elimination half lives($t_{½}$, h), first order elimination-phase rate constants (k, h^{-1}), volume distribution (Vd, l/kg)and clearance (CL, l/kg/h) will be estimated.Evaluation of efficacy of gentamicin in all groups will be performed by clinical and laboratory parameters. Attempts will be taken to detect gentamicin related toxicity by renal, auditory and vestibular function test. For comparison of major two groups by means of discrete variables the Chi-square or Fisher's exact test will be used. For continuous variables Student's t or the Mann-Whitney test will be applied. Test for two-tailed, $p < 0.05$ will be considered significant. Exact confidence intervals for differences in efficacy and nephrotoxicity will be calculated.The study will be conducted in the Clinical Research & Service Centre of ICDDR,B. and duration of study will be one and half years.

REVIEWS :

Ethical Review Committee.....

Research Review Committee.....

Signature of the Director of ICDDR,B & remark if any.....

SECTION II: RESEARCH PLAN

Introduction

1. **Hypothesis :** Daily, single-large dosing of parenteral gentamicin may be equally or more efficacious with potential for diminished toxicity compared to conventional divided dosing.

2. **Objectives:** i)A prospective, open and randomized clinical study will be conducted to compare efficacy of once daily administration of parenteral gentamicin with same amount of drug administered conventionally in three divided doses in malnourished children.

ii) The study will also examine the effects of malnutrition on the pharmacokinetics of once daily dosing of gentamicin.

3. **Background:** Aminoglycosides are usually used in the treatment of severe gram negative infections. The ability of aminoglycosides to bacteriologically cure gram negative bacillary infection is strongly associated with a high peak serum concentration (1). The major drawback of aminoglycosides is their potential for nephrotoxicity and ototoxicity. With the use of gentamicin, the most extensively used aminoglycoside, nephrotoxicity has been reported to occur in up to 17% of patients while impairment of hearing is 8% or so and vestibulotoxicity was observed in approximately 3% of patients (2,9,18). Whereas nephrotoxicity is usually reversible (3,4). The ototoxicity is often not (5,9,18). Alteration of dosing strategy has recently been advocated to reduce the side effects. Specifically, once daily administration of aminoglycosides has been advocated in certain situations (6-8). In experimental animal infections, a large once daily dose of aminoglycosides produced more efficient bacterial killing (7,8). In man, the renal accumulation of gentamicin, netilmicin and amikacin was less with once daily dosing compared with divided doses or continuous infusion (10,11). A recent study demonstrated a significant reduction in nephrotoxicity when gentamicin was given once daily instead of in divided doses (12). The conventional multiple doses have generally been administered to patients in three or occasionally two divided doses. Such regimens were originally devised depending mainly on theoretical grounds to avoid excessively high serum concentrations that were feared to be toxic as well as to maintain therapeutic serum concentration (i.e. above the MIC for the infecting organism) through the course of a day. However, it has recently been observed that once daily administration reduces the risk of ototoxicity in a lower through concentration (13,14). Further, a large dose and higher peak concentration would be expected to result in superior penetration into infected tissues and optimize efficacy (8). Although the total daily dose of parenteral gentamicin has universally been administered in two or three divided doses, optimal efficacy and safety of this dose regimens is currently controversial.

Aminoglycosides show concentration-dependent bactericidal activity. They also have a "post-antibiotic effect" (i.e. a period of suppression of bacterial growth after cessation of exposure to aminoglycoside concentrations above the minimal inhibitory concentration). The duration of this effect is dependent on the aminoglycoside serum concentration achieved and the

duration of exposure and in part on the presence of granulocytes (15,16). There is also evidence *in vitro* that bacteria exposed to aminoglycosides are temporarily less susceptible to these drugs for a period after antibiotic effect (19). For these microbiological reasons, it was considered that less frequent dosing of aminoglycosides might be possible and even advantageous. It has therefore been suggested that the administration of a large dose once daily could maximize the rate of bacterial killing through the post-antibiotic effect preventing regrowth of bacteria during the period of low antibiotic concentration in serum. A retrospective analysis of cases included in various clinical studies conducted at the John Hopkins University Hospital revealed that the ratio of maximal peak serum concentration of an aminoglycoside in a patient to the aminoglycoside MIC of the infecting organism was the most important determinant of good clinical response (20). This perhaps reflects the concentration dependent bacterial killing by aminoglycosides. In laboratory animals, the single daily dose results in less nephrotoxicity (7,8). Moreover, uptake in the inner ear tissues in rats was greater with continuous infusion, though it is not known whether this results in more ototoxicity (5). In one study with healthy volunteers, tobramycin given once or thrice daily for 9 days, no significant difference in vestibulotoxicity was observed (18). In clinical studies, once-daily netilmicin or amikacin has been compared with conventional thrice or twice daily regimens, usually in combination with one or more other antibiotics. These studies found equal efficacy for both dosing regimens and a tendency towards less toxicity in the once-daily groups(13,14). After review of recent literatures, it is assumed that other than one single study, no further well-performed clinical trials have been conducted for evaluation of once daily dosing of gentamicin, the most extensively used aminoglycoside.

Protein energy malnutrition is a global problem. Malnourished children are very vulnerable to infections, particularly those caused by Gram negative organisms (22). Protein energy malnutrition imposes biological alteration on various organs. Alteration of body compositions, particularly presence of nutritional oedema can influence plasma disappearance of drugs by changing their volume distribution. Compromised cardiac and renal functions with decreased glomerular functions can seriously affect elimination of the drugs. Also, there is an increase in total body water with marked increase of extra cellular water. So pharmacokinetics are likely to be different in PEM subjects. Therefore, it is necessary to know about pharmacokinetics of gentamicin which is largely unknown (23).

4. Rationale/ singificance of the study:

If once daily dosing of gentamicin is efficacious in the treatment of gram negative infections without additional toxicity compared to conventional divided dosing, then once daily dosing would be definitely advantageous, time saving and less costly.

5. Specific aims of the study :

i) To assess the efficacy and potential for diminished toxicity of daily single large dosing of gentamicin compared to conventional divided dosing.

ii) To determine the effects of malnutrition on the pharmacokinetics of once daily dosing

of gentamicin.

6. Sample size calculation :

In a recent study of aminoglycoside in children with once versus multiple doses(microorgisms were klebsiella and pseudomonas aeruginosa, sensitivity being 92% and 100% respectively), clinical efficacy was 87% vs 63% respectively (21). Therefore, following the formula of

$$\frac{P1(100-P1)+ P2(100-P2)}{(P1-P2)^2} \cdot f\ \alpha\ ß$$

we consider power to be 90% and level of significance 0.05 and if we expect similar success, then number of patients will be 64 in each group. Again considering nephrotoxicity up to 17% (in adults) with multiple dose regimen (2), if we expect less nephrotoxicity up to 2% in children with single dose regimen (26), then using same formula and same power with similar level of significance, we need 71 patients in each group. We shall pick up the greater number. Considering 10% dropouts, we shall recruit a total of 176 patients, 78 in either group with additional 20 children of normal weight for height for comparing the effects of malnutrition on pharmacokinetics of once daily dosing of gentamicin.

7. Methods:

7.1 Patient Selection:

The study protocol aims to enroll 156 malnourished children (weight for height below 70%) aged 1 to 5 years of either sex with confirmed infection where gentamicin will be indicated. Similarly another twenty children with normal weight for height will be enrolled to compare the effects of malnutrition on the pharmacokinetics of once daily dosing of gentamicin. They will be admitted into inpatient department of Clinical Services and Research Centre of ICDDR,B. The following infections are expected to be available for entry into study: intra-abdominal infection with septicaemia, intrabdominal infection with pneumonia, septicaemia etc . Exclusion criteria will be allergy to aminoglycoside, renal impairment, vestibular and hearing disturbance, neutropenia and hypokalaemia. After fulfillment of inclusion criteria malnourished patients will be assigned into one of the two treatment groups according to the random number table using permuted block of block length 4 and 6. One group will receive gentamicin once daily and other group will receive gentamicin in three divided doses. Number will be in sequential order and will be kept in sealed envelop. Randomization list and sealed envelop will be prepared by a trained and responsible person who is not involved in the study. 20 children with normal weight for height will receive single dose therapy of gentamicin. Before enrolment into the study, patients' history will be reviewed for previous treatment with potentially ototoxic drugs (aminoglycosides, furosemide or ethacrynic acid, vancomycin, cisplatinum etc.) renal disease and diminished hearing or vertigo.

7.2 Therapy :

Gentamicin dose (intravenous): 5 mg kg/day (24) either the whole dose once a day or divided into three doses.Before therapy and during therapy patient will remain in perfectly well hydrated state.

Duration of treatment : Usually 7 - 10 days, but it may be prolonged depending on the time taken for complete resolution of clinical signs and symptoms and return of laboratory parameters to normal.

7.3 Pharmacokinetics and serum assay:

Pharmacokinetics will be measured in 20 patients from each group according to standard method (25). On 2nd day of treatment, blood samples will be collected for assay of serum concentrations of gentamicin immediately before (trough value) and 1 hour (peak value), 3,5,8 and 24 (if in once arm daily) hours after administration of the drug. Serum gentamicin will be measured by fluorescence polarisation assay (Abbott Laboratories) or EMIT homogeneous enzyme immunoassay (SYVA). In twenty patients from each group of once daily dose regimen, plasma elimination half lives($t_{½}$, h), first order elimination-phase rate constants(k, h^{-1}), volume distribution (Vd, l/kg)and clearance (CL, l/kg/h) will be estimated.

7.4 Laboratory investigations:

Before starting gentamicin, blood will be drawn for culture and CBC including platelet, will be done simultaneously and these will be repeated on 3rd day and last day of therapy. Antibiotic sensitivity will be tested by conventional disk diffusion assay on agar plates. Reporting will be graded as sensitive (equivalent to MIC <4 mg/l), intermediate (equivalent to MIC 4-16 mg/l) or resistant(MIC >16 mg/l).

7.5 Assessment for auditory and vestibular function:

Regular clinical monitoring will be performed meticulously.Audiometric assessment will be performed in doubtful cases by pure tone and bone conduction audiometry in sound proof chamber during and after treatment. (The referral facility is very close to ICDDR,B.).

7.6 Renal function test :

The renal function in each patient will be monitored before, during therapy, thrice weekly and immediately after therapy and one week after discontinuation of therapy. The parameter for evaluation will include rise of serum creatinine concentration. (Nephrotoxicity will be defined as an increase in the baseline serum creatinine of greater than 35 micro mol/l). During therapy, 24 hours" urine will be collected daily for assessment of creatinine clearance.

Maximal efforts will be given to detect any side effect discussed and prompt measurements will be taken to stop the trial immediately on detection and appropriate steps will be taken to reverse the side effect.

7.7 Evaluation of efficacy :

i) Clinical :

It will be determined on the last day of therapy and defined as favourable if there is clinical improvement with resolution of clinical symptoms of infection, return to normal body temperature for at least 48 hours and normalisation of white cell count. Failure will be defined as persistence or worsening of clinical manifestation of infection or death due to uncontrolled infection after 72 hours of therapy. Indeterminate will be labeled when evaluation is not possible.

ii) Bacteriological :

Bacteriological efficacy will be evaluable if gentamicin is the only effective antibiotic with regard to the cultured microorganism and will be defined as favourable if culture becomes negative. Unfavourable response will be classified if culture for same microorganism is positive even after adequate period of therapy.

iii) Dropout from evaluation :

Patients will not be included in the evaluation of efficacy when gentamicin will be stopped for any reason within 72 hours of it's commencement.

7.8 Statistical analysis: The primary analysis will be based on clinical success rate of all groups and pharmacokinetics parameters. And secondary analysis will be based on incidence of nephrotoxicity and ototoxicity.

For comparison of major two groups by means of discrete variables the Chi-square or Fisher's exact test will be used. For continuous variables Student's t or the Mann-Whitney test will be applied. Test for two-tailed, $p < 0.05$ will be considered significant. Exact confidence intervals for differences in efficacy, nephrotoxicity and ototoxicity will be calculated.

7.9 Ethical issue: Recent studies show that incidence of nephrotoxicity and ototoxicity due to gentamicin even with single dose regimen is very low (26). Maximal efforts will be given to detect any side effect discussed and prompt measurements will be taken to stop the trial immediately on detection and appropriate measures will be taken to reverse the side effect.Parents of the patient will be informed in details regarding the nature of the study and due consent from them will be taken before entry into study. They can refuse participation in the study or can withdraw from the study at any time.And for these reasons, usual standard treatment for the child will not be affected.

7.10 Relevance and policy implication : In the developing countries, the vast majority of children are usually malnourished. They are usually susceptible to gram negative infection and gentamicin is extensively used if they suffer from gram negative infection. Most common example is lower respiratory tract infection.So if single dose gentamicin is equally effective as multiple doses, then timing , logistic and financial benefit will be of immense benefit in the context of the third world. Again if toxicity of single dose is found to be less than conventional doses, then single dose will be preferred everywhere and will fit properly in policy implication of gentamicin therapy as standard dose.

References

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CONSENT FORM

(This form will be read and explained clearly in local language before consent is obtained)

Your chid is suffering from serious infection for which administration of injectable gentamicin is one of the major parts of management.

International Center for Diarrhoeal Diseases Research, Bangladesh (ICDDR, B) is planning to conduct a study in the Clinical Research Center, Dhaka to examine the effect of once daily dosing of gentamicin. We expect that this single dose will work better than the conventional three divided doses of gentamicin.

If you agree, the following procedures will be followed.

1. Your child will get standard clinical care and management as practiced by physicians of this hospital.

2. After confirming infection, your child may get either single dose or three divided doses of gentamicin.

3. Necessary investigations including blood test will be done for standard care of the patient.

4. If your child is included in special drug study (pharmacokinetics) then one of the three following procedures will be followed.

a) 1.5 milliliter of blood will be taken twice if your child gets gentamicin in three divided doses .

b) 1.5 milliliter of blood will be taken six times if your child gets gentamicin for once daily dose.

c) 1.5 milliliter of blood will be taken four times for if your child gets gentamicin for once daily dose.

5. The study involves no major risk. We will maintain the confidentiality of the medical records.

6. At any time of the study, you may withdraw your child from the study, but his routine care by us will not be hampered. If you have any question to ask, we will be happy to answer them.

7. If you agree to participate in this study, please sign below.

Signature of the Investigator	Signature of witness	Signature or thumb impression of the Guardian

'DGET				
le: Clinical trial of single dose gentamicin ...				
Dr Ali M. Khan				
			Amount in	US Dollar
ne item	**% effort**	**1st year**	**2nd year**	**Total**
rsonnel Cost				
A.M. Khan, PI	50	6,509	3,255	9,764
Ashish K. Chowdhury	5	260	130	390
esearch Physician (CSA) x 2	100	2,345	1,173	3,518
cretarial service (Mrs S. Ali)	25	1,572	786	2,358
atistician	10	500	250	750
Sub-total:		11,186	5,594	16,780
cal Travel (Gen transport & conveyance)		200	100	300
pplies & Materials				
ationeries		200	100	300
n-stock supplies		300	200	500
spital supplies		100	100	200
Sub-total:		600	400	1,000
her contractuals				
stage, fax, DHL, email etc.		500	200	700
nting & publication		200	100	300
Sub-total:		700	300	1,000
erdepartmental services				
ansport (Dhaka)		200	200	400
edical illustration		50	50	100
rox, mimeograph		100	100	200
rary servi ce charge		50	50	100
boratory tests & drug assay		25,000	25,000	50,000
Sub-total:		25,400	25,400	50,800
pital expenditure		3,500	0	3,500
ne personal computer with accessories for data analysis				
tal Direct Cost		41,586	31,794	73,380
erhead (31%)		12,892	9,856	22,748
TAL PROJECT COST		54,478	41,650	96,128

02/Apr/97

INTERNATIONAL CENTRE FOR DIARRHOEAL DISEASE RESEARCH, BANGLADESH
Mail : ICDDR,B, GPO Box 128, Dhaka-1000, Bangladesh
Phone : 871751-60, Telex : 675612 ICDD BJ
Fax : 880-2-883116, 886050, 871568, 871686, Cable : Cholera Dhaka

CENTRE
FOR HEALTH AND
POPULATION RESEARCH

MEMORANDUM

Date : 23 January 1997

From : Acting Director

To : Dr. Ali Miraj Khan, CSD

Ref : Protocol Funding

You are aware that your protocol entitled "Evaluation of efficacy of parentral gentamicin in a single daily dose versus conventional three divided doses in malnourished children" was sent to USAID/W sometime ago for funding. USAID, in turn, sent your protocol to resource persons for external review.

Enclosed please find the comments of the external reviewers. Please respond to the reviewers' comments and submit your responses to Dr. Ishtiaque Zaman as soon as possible so that your responses may be forwarded to USAID for their consideration.

Thank you.

Enclo: As stated.

GUIDE FOR EVALUATING USAID/CHR PROPOSALS

Reviewer 1

Name of proposal: Evaluation of efficacy of parenteral gentamicin in a single daily dose versus conventional three divided doses in malnourished children.

Name of proposed Investigator: Ali Miraj Khan, MBBS
Assistant Scientist, CSD

1) Goals: The goal of the project, well stated in the title, is reasonable and important.

2) Design: The design of the study is basically appropriate. As appropriate, the investigators obviously read and modeled the design of the proposed project on key paper on this subject (Prins et al, 1993) -- the proposed statistical analysis in the proposal is word for word from the Prins et al. article.

The one important area that is of concern to this reviewer is the investigators definition of "malnutrition" as weight-for-age <60%. The investigators propose to include children 1-5 years of age. At the older end of this age range, children are likely to very low weight-for-age, not because they are acutely malnourished, but because they are stunted (low height-for-age). Will children who are low height-for-age, but acceptable weight-for-height be "acceptable to infections" as suggested on page 4. The investigators should clarify the definition of malnutrition and explain why they have chosen not to use weight-for-height or a combination of height-for-age and weight-for-height for their inclusion criteria. This point is important because, otherwise, age may be an important confounder and/or effect modifier in the trial and with relatively small sample sizes, slightly unbalanced cells on age may bias results.

Otherwise, definitions, sample size, clarity of analysis, feasibility, and adequacy of lab methods are acceptable.

3) Appropriateness: The literature does not strongly suggest that once daily dose of gentamicin will be more effective than multiple dosing, but there are two potential benefits from positive results from this study: cost-savings and reduced nephrotoxicity.

4) Timing and budget: Timing okay. Budget: N/A.

5) Ethics: Acceptable.

6) Background: The investigators appear to have a good understanding of the field and have reviewed the literature well.

7) Other: None

R2

2. EVALUATION OF THE EFFICACY OF PARENTERAL GENTAMICIN IN A SINGLE DAILY DOSE VERSUS CONVENTIONAL THREE DIVIDED DOSES IN MALNOURISHED CHILDREN

Proposed investigators: Khan & Fuchs

Reviewer - 2

1. Goals

The research has a clear primary goal.

2. Design

The research is well-designed, with appropriate methods. The investigators have omitted to mention whether the pharmacokinetics of gentamycin in eutrophic children are already well known - if not, their second objective can only be achieved by included a group of eutrophic children.

The precise form of randomization to be used should be specified (i.e. block randomization or otherwise). The exact criteria to be used to determine whether treatment needs to be prolonged should be specified.

At least a 25% margin for dropouts should be included in the sample size calculations. It is not clearly whether the nephrotoxicity calculations are based on 17% vs. 15% or 17% vs. 2%. No justification is given for expecting a reduction of this (latter) magnitude. Sample size calculations are also required for the pharmacokinetics component of the study. If it is really the case that only 20 individuals per group are required for this component, then it would not be necessary (or desirable) to carry out the frequent bleeding of all study participants to assess serum concentrations of the drug.

The analysis plans should precisely identify the primary and secondary analyses rather than describing the analysis strategy in general terms.

The study appears to be feasible.

No interview forms or record abstracts included.

3. Appropriateness

There are major cost and compliance advantages to simplified antibiotic dosing schedules. Improved efficacy and reduced toxicity would of course be highly advantageous.

Testing the new dose regimen in a group of malnourished children would appear to be an important contribution to existing knowledge.

R2

4. Timing and budget

Insufficient information provided to evaluate.

5. Ethics

The investigators should clarify how serious the toxic side-effects could be. If they could cause serious discomfort or illness, then the study should incorporate sequential monitoring of side-effects by an independent investigator with access to the codes, and clearly defined stopping rules for the trial. It is not clear why the proposed regime has not been first tried with volunteers, with intensive monitoring for side-effects. The investigators might like to refer to NIH (or other similar) ethics guidelines for drugs trials.

6. Background

Adequate background information presented.

R3

Name of proposal: Evaluation of efficacy of parenteral gentamicin in a single daily dose versus conventional three divided doses in malnourished children (2)

Name of investigator: Khan et al.

Reviewer-3

Date of review: December 1996

Comments

The proposal should specify in the title as well as in the objectives, the purpose of giving parenteral gentamicin. The title for example states that it will evaluate the efficacy of gentamicin, but it does not say for what outcome.

It is not clear how the second 'aim of the study' (see p. 4) will be approached. How are the authors planning to 'determine the effects of malnutrition on the pharmacokinetics of once daily dosing of gentamicin' if all the children included in the study are malnourished (as planned). What will be the comparison group used to conclude that malnutrition has an effect on pharmacokinetics? Please explain.

Sample size calculations: The study is designed to show **no difference** in outcomes between two different treatments. For this purpose, the study has to have a high statistical power so that if no differences are found, it cannot be attributed to the fact that the study lacked statistical power. The usual power used for this type of studies is 90% or more. The authors used the usual 80% level, which is inadequate for the type of study proposed.

Patient selection: What do you mean by 'suspected' infection (p. 5). How can the efficacy of the treatment be tested if the infection is not confirmed at baseline?

The sections on *Ethical issues* and *Relevance and Policy* Implications are missing.

GUIDE FOR EVALUATING USAID/CHR PROPOSALS

Name of proposal : Evaluation of efficacy of parenteral gentamicin in a single daily dose versus conventional three divided doses in malnourished children.

Responses to comments of 1st Reviewer :

1) Goals :

We appreciate the comment.

2) Design :

We appreciate the comments. We have also revised the statistical analysis description.

We agree with the reviewer's suggestion that weight for height is a more refined criteria to define the degree of malnutrition in the clinical context of our study . Therefore, the inclusion criteria has been revised to use weight for height less than 70% instead of weight for age $<60\%$.

3) Appropriateness :

We appreciate the comment.

4) Timing and budget:

Further details of the budget are now provided.

5) Ethics :

We appreciate the comment.

6) Background :

We appreciate the comment.

7) Other: None

GUIDE FOR EVALUATING UNSAID/CAR PROPOSALS

Title of Research: EVALUATION OF THE EFFICACY OF PARENTERAL GENTAMICIN IN A SINGLE DAILY DOSE VERSUS CONVENTIONAL THREE DIVIDED DOSES IN MALNOURISHED CHILDREN.

Responses to the comments of 2nd Reviewer :

1. Goals

We appreciate the comment.

2. Design

We appreciate the comments and accept the reviewer's suggestion to include a group of eutrophic (non-malnourished) children to achieve the second objective.

As per reviewer's suggestion, we have modified the randomization schedule. All patients will be randomly assigned to one of the treatment groups according to the random number table using permuted block of block lengths of 4 and 6.

The criteria to prolong the treatment will depend on the time needed for complete resolution of infection. This will depend on bed side clinical assessment and laboratory parameters.

We anticipate a 10% dropout rate based on the dropout rate of other similar drug trials conducted in our Centre.

Nephrotoxicity calculations are based on 17% vs 2%. We expect a reduction of this magnitude because recent studies in children experienced an incidence of nephrotoxicity varied between 0 and 5% .

It will be a baseline study to determine the pharmacokinetics component. So we think that 20 individuals per group is adequate number. Additional sample size calculations for this purpose are not required .We agree with reviewer that it would not be necessary to carry out frequent bleeding of all study participants to assess serum concentrations of the drug. And all these have been modified in the proper section of the proposal.

The primary analysis will be based on the outcome of clinical cure rate of all groups as well as pharmacokinetics parameters. Secondary analysis will focus on the incidence of nephrotoxicity and ototoxicity. The proposal has been revised accordingly.

An abstract is now included .

3. Appropriateness

We appreciate the comments.

4. Timing and budget

Further details of the budget are now provided.

5. Ethics

We have mentioned the serious side effects of gentamicin that may result in nephrotoxicity and ototoxicity. In recent studies, it has been assumed that side effects are fewer in children than adults and varies between 0 and 5% and between 0 and 8% respectively. We plan to sequentially monitor potential toxicity by clinical and laboratory parameters. In the event of

development of any toxicity, we shall immediately stop the drug and change to alternative arrangement. The literature review reveals one trial of single dose gentamicin in children. No nephrotoxicity was observed in this trial but two cases of mild ototoxicity detected.

6. Background

We appreciate the comment.

GUIDE FOR EVALUATING USAID/CHR PROPOSALS

Name of proposal : Evaluation of efficacy of parenteral gentamicin in a single daily dose versus conventional three divided doses in malnourished children.

Responses to the comments of 3rd Reviewer:

1. We have emphasized the principal objective of the study to make the title short and simple.We feel including all the outcomes in the title would make it too lengthy .

2. We have revised our study design to include a group of non-malnourished children in order to determine the effects of malnutrition on the pharmacokinetics of once daily dosing of gentamicin.

3. As per suggestion of reviewer, we accept the power of 90% for sample size calculation and we have modified sample size accordingly.

4. In place of suspected infection, we will specify infection at baseline. Accordingly we have modified patient selection criteria and this has been mentioned in the relevant place of the proposal.

5. In recent studies, it has been seen that the incidence of nephrotoxicity and ototoxicity is much less in children (0 to 5% and 0 to 8% respectively) compared to adults. Many pharmacokinetics studies have been previously conducted in malnourished children receiving conventional aminoglycosides regimens. Moreover, we shall monitor toxicity

sequentially on the basis of clinical assessment and laboratory feedback and if there is any development of toxicity, we shall immediately stop the trial and take the appropriate measures . The proposal has been revised to describe this in details.

6. In the developing world, most of the children are malnourished and they frequently suffer from gram negative infection where gentamicin is usually used. If single dose of parenteral gentamicin proves to be equally effective and to have the same or fewer side effects as compared to conventional three divided doses, then cost and time savings will have obvious policy implications. All above have been incorporated in the research proposal.