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A randomised double blind placebo controlled trial of oral Ephedrine and Etilefrine in the prevention of recurrent (stuttering) attacks of priapism in sickle cell disease: A multicentre International study in older children and adults.

Study Protocol

Priapism In Sickle CELL Study (PISCES)

CONFIDENTIAL

DISCLAIMER: This protocol is not intended as an *aide memoir* and is only to be used for individuals registered within the context of this clinical trial. This version of the protocol has been written solely for the purpose of the ethical approval in the UK.

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1. SUMMARY STATEMENT

This randomised (phase IV) double blinded placebo controlled trial aims to compare the efficacy and side effects of standard dose Etilefrine with two doses of Ephedrine in patients with sickle cell disease and stuttering intermittent attacks of priapism.

2. INTRODUCTION

Sickle cell disease (SCD) is the commonest inherited disorder of the haemoglobin molecule worldwide with a varying frequency of affected population per country. Carrier rates range from 0.1% in Europe to 40% in sub-Saharan African. It is estimated that there are approximately 12,000 affected individuals resident in the United Kingdom (Streetly *et al* 2001). Priapism, defined as painful, persistent penile erection in the absence of sexual stimulus, is a poorly documented but recognised complication of the disease. The precise incidence is unclear and earlier reports in the literature suggested that the prevalence of this complication in SCD was of the order of 2-6% (Miller *et al* 1995). Another report from the United States reported a higher incidence of 28% on direct questioning (Mantadakis *et al* 1999). We recently conducted a multicentre international semiquantitative study (Adeyoku *et al* 2002), which showed a much higher prevalence of 35%. Both these latter studies highlight a poor knowledge of this complication in patients and families with sickle cell disease. Some of the variability in the reported incidence may arise from the reluctance of patients to volunteer this information at clinic attendances and also a lack of awareness on patients' part that priapism is a complication of SCD. Mantadakis *et al* reported that only 7% of male patients attending a clinic in Texas, USA were aware of such an association.

The acute complications of priapism include pain, dysuria and psychological distress. Priapism can also precede or follow an acute painful bone pain crisis.

The long-term sequelae of priapism are also psychologically and physically damaging. These include varying degrees of erectile dysfunction, frank impotence, and sexual dissatisfaction including a fear of engaging in sexual activity.

This trial includes older children and adult cases with sickle cell disease actively attending a designated centre for care. Its aim is to compare a treatment modality in documented use with a more easily available alternative, in terms of tolerability and efficacy.

3. BACKGROUND

There are two types of priapism recognised: -

(i) a short self limiting episode lasting up to 4 hours which tends to be recurrent, nocturnal and is not associated with organ damage itself per se, called **stuttering** priapism.

(ii) an **acute major** attack, which requires medical and/or surgical intervention, failure of which can result in impotence.

The time limit for such intervention should be within 6-24 hours of the onset of symptoms. Any age may be affected by priapism but the majority of patients are

under 40 years with 10-25% having an attack in the first decade of life. 75% of patients will have had their first attack by their 20th birthday. Some controversy exists in the literature with regards the association between the two types of priapism. We recently carried out a 5-centre questionnaire survey, which showed a 35% incidence of priapism and a clear relationship of stuttering priapism as a harbinger of an acute major attack (χ^2 ; $p < 0.001$) (Adeyoku *et al* 2002). The mean frequency of attacks was 3 per month (range 3 per year - 4 per week). The mean duration of each attack was 1.25 hours. This relationship has also been reported from the large cohort of patients reported by Emond *et al* in the Jamaican study of sickle cell anaemia (Emond *et al* 1980). It seems therefore possible that prevention of recurrent attacks of stuttering priapism may prevent an acute major attack with its catastrophic consequences.

- Mechanism of Priapism and Rationale for Therapy

Ischaemic priapism is a failure of the penile detumescence mechanism from many causes among which are excessive release of neurotransmitters, blockage of the draining venules (the presumed causative factor in sickle cell disease), paralysis of the intrinsic detumescence mechanism, and prolonged relaxation of the intracavernous smooth muscles. The outcome is a persistently increased intracavernous pressure of 80 to 120 mm Hg and a gradually worsening ischaemic state. Typically, pain will not ensue until 4-6 hours have passed. The degree of ischaemia is a function of the duration of venous occlusion. Alpha-Adrenergic nerve fibres and receptors have been demonstrated in the cavernous trabeculae and surrounding the cavernous arteries, and norepinephrine has generally been accepted as the principal neurotransmitter to control penile flaccidity and detumescence. Animal studies demonstrate that the stimulation of sympathetic nerves or systemic infusion of Epinephrine causes detumescence of the erect penis (Diederichs *et al*, 1991a, 1991b).

Ephedrine is a sympathomimetic agent with direct and indirect alpha adrenergic activity.

- Treatment modalities for priapism.

Various conservative measures have been tried to abort attacks of stuttering priapism. These include hydration, simple and compound analgesia, exercise, tranquillisers, blood transfusion, vasodilators, anticoagulants and lately hydroxyurea. This represents a lack of consensus on the best treatment for this condition.

Diethylsiboestrol, an oestrogen in doses of 5mg, has been used in treating repeated attacks of priapism. The incidence of adverse events is relatively high (20%) in a relatively small number of patients (11 in total). It has feminising side effects and compliance may be a problem.

Oral α -adrenergic agents have been used in a non-systematic fashion to treat stuttering priapism. The most widely used is Etilefrine (Okpala 2002). Most patients were established on a dose of 50 mg modified daily release and that is the dose chosen for the study. Another alpha agonist is Ephedrine, which is a common ingredient in most "off the counter preparations" for common cold and may be a suitable alternative. The minimum effective dose has not been established. The side effect profile of Ephedrine include palpitations, tachycardia, insomnia, anxiety, dry mouth, tremors and these side effects are infrequent (<5%), mild and well understood and may be limited by taking the tablets at night. Furthermore, the doses intended for the study are relatively small and will ensure that side effects are limited. Neither drug is

currently licensed for this indication. Etilefrine is imported into the UK by special arrangement through hospital pharmacies. Ephedrine is broadly available in developing countries but Etilefrine is neither available nor affordable in these parts of the world. Both drugs are not known to be myelosuppressive hence making them suitable options to be combined with other agents such as hydroxyurea, which some patients take to ameliorate the course of their disease. If this study's results are positive, we believe its benefits may be widespread to male patients with sickle cell disease in all countries.

The treatment for an acute major attack of priapism includes outpatient penile aspiration with or without irrigation with α -adrenergic agent such as Epinephrine or Etilefrine (Virag 1996). This approach is only available in designated centres with a large number of patients and specialist urology input and is not available to many patients. Ephedrine and Etilefrine appears to be safe when taken orally, in the doses we propose to use in this study.

Study Objective

- (i) *To assess if oral Ephedrine or Etilefrine taken by patients with sickle cell disease is tolerable and if it reduces the rates of stuttering priapism and/or major attacks of priapism **compared to placebo.***
- (ii) *To see if oral Ephedrine is comparable to Etilefrine in efficacy.*
- (iii) *If it is so, to establish the minimum effective dose of Ephedrine.*

Eligibility criteria

- Must be male patients with a documented history of sickle cell disease irrespective of genotype. (α Thalassemia status will not be determined).
- Patients should be 12 years or over.
- Patients with a known history of stuttering priapism (a short self limiting episode lasting up to 4 hours which tends to be recurrent) attributable to SCD.
- Patients in active attendance at a designated care centre i.e. one visit in the last 6-12 months.
- Patients on a stable dose of hydroxyurea for over 6 months before trial entry can be included provided a baseline "event rate" (on treatment) is established before randomisation and no dose change occurs during trial period
- Patients who received a 'one off' or isolated top up transfusion greater than three months before recruitment date can be entered into study.

Initial discussions about trial entry will be established when patient is in "steady state" and **not** experiencing an acute event

Exclusion criteria

- Patients with sickle cell trait. (Hb A greater than Hb S on alkaline gel electrophoresis or HPLC) will not be eligible for randomisation.
- Patients' known to have elevated blood pressure or a history of cardiac disease.
- Patients with SCD and a documented history of stroke in the past.
- Patients with a history of vessel aneurysm in the past.

- Patient's known to be on MAOI (mono amine oxidase inhibitor drugs) or other drugs with significant interactions with study drugs e.g. tricyclic antidepressants, Reserpine, Phenelzine and Dopamine.
- Patient's known to be intolerant of α -adrenergic drugs.
- Patients with hyperthyroidism.
- Patients on a long-term blood transfusion programme to prevent or treat the complications of sickle cell disease.
- Patients with renal failure (serum creatinine greater than 400 $\mu\text{mol/l}$) are not eligible for the study.

Reasons for withdrawal

- A dose change in the Hydroxyurea during the study period.
- Patients transfused within the duration of the study period are also ineligible for analysis.

Once patients are recruited they will be followed up throughout the study duration on an 'intention to treat basis'.

Study Design(Appendix 1)

This is a randomised double blind placebo controlled trial between two doses of oral Ephedrine (15 mg and 30 mg) and a standard dose of Etilefrine (50 mg).

Recruitment

Patients will be told that priapism is a side effect of Sickle Cell Disease at a confidential interview during a routine clinic visit. Patient information leaflets will be handed to patients in 'steady state' by the local investigator. After 1 –2 weeks, patients who wish to participate will give written informed consent. A drop of blood will be blotted onto Guthrie cards at registration and stored for postage to a central laboratory in the UK.

Phase A. Patients will record prospectively over a six-month (6) period the frequency of attacks and any recognised precipitating event(s). Diaries will be collected at the end of phase A of the study period. Follow up will be 6 weekly in designated centres recognised for care of affected individuals under the supervision of a Consultant Haematologist/Urologist or specialist health care worker. Each centre will nominate a contact person for monitoring purposes. A completed entry form should be sent to Ms Julie Morris Medical Statistics, Wythenshawe Hospital Manchester. M23 9LT, United Kingdom, fax number: 0161-291-5816 at registration on starting Phase A.

Observation only period

The natural history of priapism is highly variable between individuals and even within the same individual over a period of time. It is very important therefore for us to establish the average "true" frequency of attacks or "event rate" before randomisation. A minimum observation period of **3 months** is required in all cases with a maximum of 6 months. There are a variety of self- help measures that patients can adopt to limit

an attack or reduce its frequency such as oral rehydration, moderate exercise, simple or compound analgesia, cold or warm baths (Adeyoku et al 2003). None of these have been systematically evaluated. These should be offered in the first instance to see how effective they are. If the frequency of attacks should increase or an acute attack should ensue during the observation period, then treatment according to local practice such as intracorporeal aspiration of blood with injection of epinephrine should be carried out or even surgery may be necessary. Thereafter, patients may be randomised to receive one of the study drugs (see suggested Care Pathway pg 21). This is at the discretion of the local physician but individualised cases should be discussed with one of the clinical coordinators:- Drs Ade Olujohungbe, Anne Yardumian, Mr Adeyoku or Dr Joshua Wright.

Phase B. Patients will then be randomised in phase B between four arms comprising of study drug, Ephedrine (in two doses 15 mg and 30 mg) and Etilefrine 50 mg and a placebo. Phase B will last 6 months. The Study tablets are white, and will include either placebo, Etilefrine 50 mg or Ephedrine in 15 mg and 30 mg formulations. They will be encapsulated and identical in appearance. Each patient will take two capsules once a day at night for the entire six months duration of phase B. If side effects appear the dosage can be reduced to one tablet for two weeks and notified to the Chief Investigator. If no further side effects occur, this dose is maintained throughout the study period. Tolerability will be assessed by evaluation of the diary for side effects. Grading of the severity adverse events will not be carried out to allow simplicity and consistency between centres. The number of patients still on the trial drug at the end of study period will be noted and the monthly “drop out” rate will be calculated from the diary returns.

Study end points.

- A change in the frequency/severity of attacks of stuttering priapism from baseline data.
- A change in the incidence of an acute (major) attacks of priapism.
- Tolerability of oral Etilefrine (50 mg) or Ephedrine at 15mg or 30mg with respect to side effect profile.

Sample Size

With 80 subjects in each group (320 in all) the study will have 80% power to detect differences of approximately 1.5 attacks per month between the active treatment groups and the placebo group, assuming the average attack rate is 5 per month under placebo, (where the attack rates quoted are geometric means and the common standard deviation of the logged attack rates is 1) The standard deviation estimate is based on data from a previous cohort study of subjects suffering from priapism.

The study will also have 80% power, using a one-sided test at the 5% level, to demonstrate equivalence in the attack rate per month between the active treatment groups, assuming the average attack rate is 4 per month under active treatment, that an average difference in attack rates of less than 1.5 per month indicates effectiveness (where the attack rates quoted are geometric means, the common standard deviation of the logged attack rates is 1, and the true difference in attack rates is zero).

The sample sizes above take account of the multiple comparison tests required with the active treatment groups and also assume an attrition rate of 5%.

Randomisation

This will be carried out using a separate randomisation schedule for each centre, created by the Department of Medical Statistics; South Manchester NHS Trust using computer generated randomised blocks (which will be used to prepare opaque, sealed, consecutively numbered envelopes, each containing the single allocation of a patient to one of the drug groups). The principal investigator at each centre will be responsible for enrolling patients into the study. The pharmacist at those centres will select sequential envelopes to assign patients to designated therapies

It is expected that randomisation will take place near the end of phase A.

Blinding

This will be a double blind placebo controlled study, neither the patient nor the clinician assessing the outcome will be aware of the drug allocation. The study drugs will be packaged by DHP Ltd (Clinical Trial Supplies, Waller House, Elvicta Business Park, Crickhowell, Powys, NP8 1DF) who will be responsible for the provision of the drugs in three monthly child resistant tamper evident caps according to cGMP. The study statistician and the company QP will be the only individuals with access to the codes.

The outcome will be analysed by the Statistician (JM) in Manchester, UK.

Clinical & Laboratory study

Blood pressure will be measured at the beginning of the study, two weeks into Phase B and then six weekly until study completion. A rise in systolic and/or diastolic blood pressure of greater than 20 mm Hg above baseline or above 130/80 mm Hg should lead to discontinuation of study drug and notification to the Trial office.

At recruitment a drop of patient's blood will be blotted on Guthrie cards to confirm diagnosis of sickle cell disease prospectively and to measure variant haemoglobins present. This card will be stored in a waterproof sealed bag and sent to the centres chief investigators laboratory for HPLC analysis.

No specific laboratory monitoring is required throughout the study period.

Diary Keeping

A colour-coded diary (blue) will be issued on entry into trial for collection of baseline data on frequency rates. This will be Phase **A**. Diaries will be reviewed 6 weekly in clinics by designated personnel for a total period of 6 months.

Upon randomisation: - start of phase **B**, a separate diary of a different colour (yellow) will be issued and also reviewed 6 weekly for a total of 6 months marking end of

study. All diaries will be collected at the end of each phase and sent to the medical statistics department, South Manchester. The diaries will **not** differ in each centre but each centre will have a unique centre number allocated to it. As many centres that demonstrate a willingness to randomise patients and collect data systematically in both countries will be encouraged to participate.

Data Management

Patient demographic data and completed diaries will be processed by the Department of Medical Statistics, South Manchester NHS Trust and entered onto a computer spreadsheet. Patient identifiers will not be included on the computer file, and all patient demographic data and diaries will be kept in a locked filing cabinet.

Data Monitoring

An independent data monitoring has been set up to follow the trial progress. The data committee will monitor the data 3 monthly. The trial statistician will be asked to submit a summary of the data three months into phase B for adverse events and tolerability of study drug. Data will be analysed at the end of Phase A and on study completion.

Statistical Analysis

Comparison of changes in attack rates over the period of the study between the active treatment groups and the placebo group will be carried out using analysis of covariance to adjust for baseline rates and a limited number of possible confounding factors.

Equivalence will be assessed by the calculation of confidence intervals for the difference in attack rates.

The analysis will be on an ITT basis, with subjects who discontinue treatment (only a very small number of withdrawals is expected) being followed up as far as is feasible.

Tolerability.

Common side effects of Ephedrine and Etilerfrine have been listed in check boxes on a weekly basis. Other unexpected side effects can be written in manually. How often these side effects occur per week will be noted in the diary by ticking the appropriate box or writing in space provided in phase B diaries.

Serious Adverse Effects

Definition

A serious adverse event (SAE) is defined as any undesirable experience occurring to a patient, whether or not considered related to the investigational drug, which results in:

- a) death
- b) immediate risk of death at the time the observation was made
- c) hospitalisation or prolongation of hospital stay
- d) persistent or significant disability or incapacity

- e) a congenital anomaly or birth defect

Serious adverse effects should be reported within 24 hours of the first full working day or after the weekend to the trials office by filling in the appropriate documentation and faxing it to Julie Morris (fax: 0161-291-5816) and Dr Ade Olujohungbe (fax: 0151-529-3310).

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**LOCAL
HOSPITAL
LETTERHEAD**

APPENDIX A

A randomised placebo controlled study of Ephedrine/Etilefrine for prevention of recurrent (stuttering) attacks of priapism in sickle cell disease.

PATIENT INFORMATION SHEET

Dear Patient

You are being asked to take part in a multi-centre randomised trial this is being conducted in many hospitals throughout the UK and two centres in Nigeria. It has been subjected to ethical review by your local hospital.

Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

RATIONALE FOR STUDY

Priapism is a persistent, painful erection of the penis. It can be caused by a variety of diseases but it is a well-recognised complication of sickle cell disease. Events that precipitate attacks are poorly understood, neither is there an agreed locally or internationally best way to treat this complication. We have some evidence that an acute major disabling attack is preceded by recurrent, short lasting (less than 4 hours) *stuttering* attacks. An acute attack can lead to severe pain, sexual dissatisfaction and impotence and may require major surgery.

We are conducting a clinical trial comparing two drugs Ephedrine and Etilefrine for preventing recurrent attacks of stuttering priapism and its other long-term problems such as impotence and sexual dissatisfaction. We do not know if by preventing such recurrent attacks medically, whether we can prevent a major attack thus reducing the number of people who may have to undergo a surgical operation to relieve it or be treated for impotence.

Cont....

Why have I been offered entry to the study? You have been offered to take part because you are a male patient with sickle cell disease who has stuttering priapism.

We would be grateful if you would consider participating in our trial, which consists of two stages. An initial stage 'A', which lasts 6 months, consists of filling in a diary on how frequently you experience these attacks. Your diary will be reviewed in your normal clinic every 6 weeks during a normal clinic appointment. At the end of six months, you will then be asked to submit the diary and to enter into stage 'B' to be randomised into one of four treatment arms these being; (1). Ephedrine 15 mg (2). Ephedrine 30 mg (3). Etilerfrine 50 mg and (4). Placebo (dummy drug). You will be reviewed initially after two weeks and then every six weeks for a period of 6 months. You will be asked to fill in the study diary.

Neither you nor your Doctor will know what tablets you are taking.

What do we know about the study drugs? Ephedrine is a common nasal decongestant present in most common cold preparations bought over the counter in the UK and in some developing countries. Ephedrine is also licensed for the treatment and prevention of asthma. We are testing two strengths, 15mg and 30 mg of the Ephedrine tablet to see which effective dose is associated with the least side effect(s). You will be asked to take one tablet of study medication at night.

We are also testing Etilerfrine (a drug with a similar action) at a trial dose of 50 mg. Etilerfrine is not licenced in the UK but has been used for treating priapism in the UK, though not in a clinical trial. This drug is licensed for the treatment of low blood pressure in other European countries such as Germany and Spain. The tablets to be used in the trial are identical in appearance. Neither drugs are licensed for this use but both have been used very occasionally in sickle cell disease.

What side effects can I expect? Both drugs have similar side effects. Side effects include; palpitations, tachycardia, anxiety, sweating. In abnormally susceptible patients; chest pain and a rise in blood pressure can rarely occur. The elderly are more susceptible to these effects on the heart. The side effects can be limited by taking the tablets just before going to bed at night. We are also using a low dose of both drugs, which should still be effective. Your local doctor will monitor you for any side effects you may be experiencing during that period and how often you are still getting the attacks and may advise you to stop if you are intolerant of the drugs. You will be asked to fill in your symptom diary.

What happens at the end of the study? At the end of your participation in the study you will receive standard clinical care as decided by your Doctor in discussion with you. All the results will be communicated back to your Doctor. He or she will then discuss subsequent treatment with you either based on the results of the analysis or his suggestion. Even if this drug is shown to be of benefit, it may be some time before it is licensed for use.

Cont....

What else would be involved in the study? We would take a drop of blood from your routine blood sample onto filter paper to re-confirm your exact sickle cell type. There are **no** other additional blood tests required for the purpose of the study. We will check your blood pressure at each clinic visit and review your diary.

What other treatments can I have? There are other treatments available for priapism but none of these have been universally accepted. These include drainage of blood in the erect penis by a needle and injection of a similar drug to cause flaccidity; or surgery. You could have a long period of blood transfusion.

What happens if anything goes wrong? You are free to participate or not and this will in no way affect your subsequent care in the hospital you attend. There is no payment for doctors or patients as this trial is not sponsored by any drug company. If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanism should be available to you. You may withdraw from the study at any time without explaining why.

Will the information be confidential? Yes. Only those involved will be able to look at your records. Your personal details will be available to your local doctor, the trial Medical Statistician and members of the study team.

What benefits may I get from the study? The study may not benefit you. We hope that the study will allow us to decide whether or not the drug works.

If further information is required, you can contact your local investigator or the Chief Investigator.

We hope you will agree to participate.

Many thanks for your anticipated co-operation

Chief Investigator

Name and Address of local investigator

Dr Adebayo Olujohungbe
MD MRCP MRCPATH
Consultant Haematologist
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APPENDIX B

PATIENT CONSENT FORM

Centre Number _____

Patient Number _____

A randomised placebo controlled study of Ephedrine/Etilefrine for prevention of recurrent (stuttering) attacks of priapism in sickle cell disease.

I FREELY AGREE TO PARTICIPATE IN THIS STUDY	Yes	No
I have read the Patient Information Sheet provided	Yes	No
I have had the opportunity to ask questions about the study	Yes	No
I understand that my medical care will not be affected if I do not participate in the research study.	Yes	No
I give consent form my case records to be looked at if necessary for purposes of the study.	Yes	No
I can withdraw at any time without giving a reason	Yes	No
I give permission for my GP to be informed	Yes	No

Name and signature of Participant:

..... **Date:**

Name and signature of Principal Investigator: .

.....**Date:**.....

A randomised placebo controlled study of Ephedrine/Etilefrine for prevention of recurrent (stuttering) attacks of priapism in sickle cell disease.

PATIENT INFORMATION SHEET FOR 12-16 YR OLDS

Dear Patient

You are being asked to take part in a clinical study to find out the best to treat recurrent attacks of painful short lasting erections (stuttering priapism) of the penis, which can occur in male children and adults with sickle cell disease.

If you agree to take part we will take a single blood test to check your sickle cell type at the beginning. The study has two parts. Part A and part B, which lasts six months each. During part A you will be asked to fill in a daily diary of how you feel, so that we know how often you have the problem we are studying. During part B you will be given one of four drugs:

1. Placebo (Dummy drug) 2. Ephedrine 15mg 3. Ephedrine 30mg 4. Etilefrine 50mg.
You will be asked to take one tablet at night for six months.

The study drugs have similar side effects, which include sweating and a fast heart beat, but these are not common at the doses used. You will be asked to fill in a daily diary of any problems you develop for the whole of the study period.

Once the study is finished your doctor will discuss with you future treatments.

You can refuse to take part in the study at any time and it will not affect your care in your hospital..

Please note that we have given your parents/guardian a more detailed information leaflet, which you are welcome to read as well. Please ask us any questions you might have.

We hope you will agree to take part in this study.

APPENDIX D

Local Hospital Letterhead

GP LETTER

Dear Doctor

Your patient with sickle cell disease volunteers a history of **stuttering priapism** (a self limiting episode of penile erection lasting up to 4 hours which tends to be recurrent) and has asked to be considered for entry into a international multi-centre randomised trial, comparing a placebo with two drugs, Ephedrine and Etilephrine. This will involve male patients from the ages of 12 to 65 years. The drugs are to be taken at nighttime and we expect them to have very little or no side effects. There are four arms and your patient has been assigned to Patients will be reviewed every six weeks at the study centre and they can withdraw at any time without giving an explanation. Your patient has been given an information sheet before registration.

If you require any further information, please contactyour local investigator or the Chief Investigator, Dr Ade Olujohungbe, tel: 0151-529-2837.

Yours faithfully

Side Effects and Possible Drug Interactions of Study Drugs:-
PISCES Study

EPHEDRINE	ETILEFRINE
Tachycardia	Tachycardia
Anxiety	Anxiety
Nausea	Nausea
Restlessness	Restlessness
Tremors	Tremors
Hypertension	Hypertension
Cardiac Arrhythmias	Cardiac Arrhythmias & angina
Dry mouth	cannot be excluded
Circulatory disturbances	Circulatory disturbances
Headache	Headaches or pressure in the head

These side effects are rare and the elderly are more susceptible. These adverse effects can be abolished with dose reduction.

Possible Drug Interactions:-

Ephedrine should be avoided in patients on monoamine oxidase inhibitors such as moclobemide, tranylcypromine and phenelzine, which are antidepressants.

It should be avoided in patients on other catecholamines such as Norepinephrine.

It may also increase the effects of Dexamethasone.

Increased risk of arrhythmias with volatile liquid anaesthetics and tricyclic antidepressants. Alcohol may antagonize the effects of Ephedrine but causes no adverse reactions.

Etilefrine may have an increased effect with guanethidine (blood pressure tablets), steroids and other tricyclic antidepressants and monoamine oxidase inhibitors. Beta blockers abolish its effects partially or completely.

APPENDIX E

SERIOUS ADVERSE EVENT REPORT FORM

In this trial it is important that unexpected serious adverse events are reported immediately to the principal investigators.

A serious adverse event (SAE) is defined as any undesirable experience occurring to a patient, whether or not considered related to the investigational drug, which results in:

- f) death
- g) immediate risk of death at the time the observation was made
- h) hospitalisation or prolongation of hospital stay
- i) persistent or significant disability or incapacity
- j) a congenital anomaly or birth defect

Serious adverse effects should be reported within 24 hours of the first full working day or after the weekend to the trials office by filling in the appropriate documentation and faxing it to Julie Morris and Dr Ade Olujohungbe.

DESCRIPTION OF ADVERSE EVENT

Signature Date

Name Position

Please fax to:-

Please fax to:-

Mrs Julie Morris fax: 0161-291-5815
e-mail: Julie_M@FS1.with.man.ac.uk

Or

Dr Ade Olujohungbe fax: 0151-529-3310 e-mail:
ade.Olujohungbe@aht.nwest.nhs.uk

Amended 10.03.05 Version 2

Suggested care pathway for the management of an acute attack of Priapism during PISCES study period

Acute Priapism is an intractable painful erection lasting more than 4hours, which fails to resolve despite optimal medical management.

In order to standardise its treatment in all PISCES study centres, the following is recommended. Treatment should be by a multidisciplinary team with a Urological Surgeon skilled in intracorporeal aspiration and instillation of intracavernous pharmacotherapy. **This treatment algorithm can however be overruled at the discretion of the primary physician of the patient.**

TIME OF STUDY	TREATMENT OPTION
<u>PHASE A</u>	If a patient gets stuttering Priapism during phase A, they should be taught “ <i>self- help</i> ” “measures which can abort or ameliorate an attack such as moderate exercise, rigorous oral hydration with fluids, warm baths. It is important to try to establish a “ true event rate ” before randomisation into phase B. A minimum observation period of 3 months is recommended. If however the frequency and/ or severity of attacks increases, the individual can be randomised earlier to phase B by discussing with the clinical coordinators or withdrawn from the study. It must be emphasised that this is at the discretion of the patient and local doctors and in the best interest of the patient. We would still collect data on the chosen treatment thereafter and its outcome in relation to the frequency of attacks for all recruited patients in the study. If the attacks become prolonged (more than 4 hrs) they should present to the hospital where penile aspiration of blood within the corpora should be carried out with instillation of diluted solution of Phenylephrine. A 19-gauge needle is inserted into one corpus cavernosum. Blood is aspirated and sent for blood gas analysis to document the degree of ischaemia. Blood is then aspirated from the corpora (10-15ml), discarded and replaced with an equal amount of normal saline. This process is repeated until the aspirate is bright red. A solution of phenylephrine is prepared by taking 1ml containing 10 mg and diluting it to 100nl with normal saline. 3-5ml of this dilute solution is then injected into the corpora and this process is repeated at 10-minute intervals until the erection subsides. The patients pulse and blood pressure should be monitored during this procedure. A competent Urological surgeon in collaboration with the study physician should only undertake this manoeuvre.. The date of the attack should be noted and the patient should then be randomised between the four arms of the study drugs and continue as in phase B.
<u>PHASE B</u>	If a patient gets an acute attack during phase B while receiving one of the study drugs, the patient should have intracorporeal aspiration and instillation of a diluted solution. A competent Urological surgeon in collaboration with the study physician should only undertake this manoeuvre. The date of the attack should be recorded in the diary and notified to the study statistician or chief investigator through the local investigator. This event will be classed as a “ <i>treatment failure</i> ”. The code of the randomised treatment arm will be “broken” and the patient should receive subsequent care as determined appropriate by their local physicians/surgeons. We will still be interested in following up the patient long term by filling in the diary with notification of chosen second line treatment option and its outcome.

References

(1)Virag R et al (1996)

Preventive treatment of priapism in sickle cell disease with oral and self-administered intracavernous injection of etilefrine.

Urology: 47(5): 777-781.

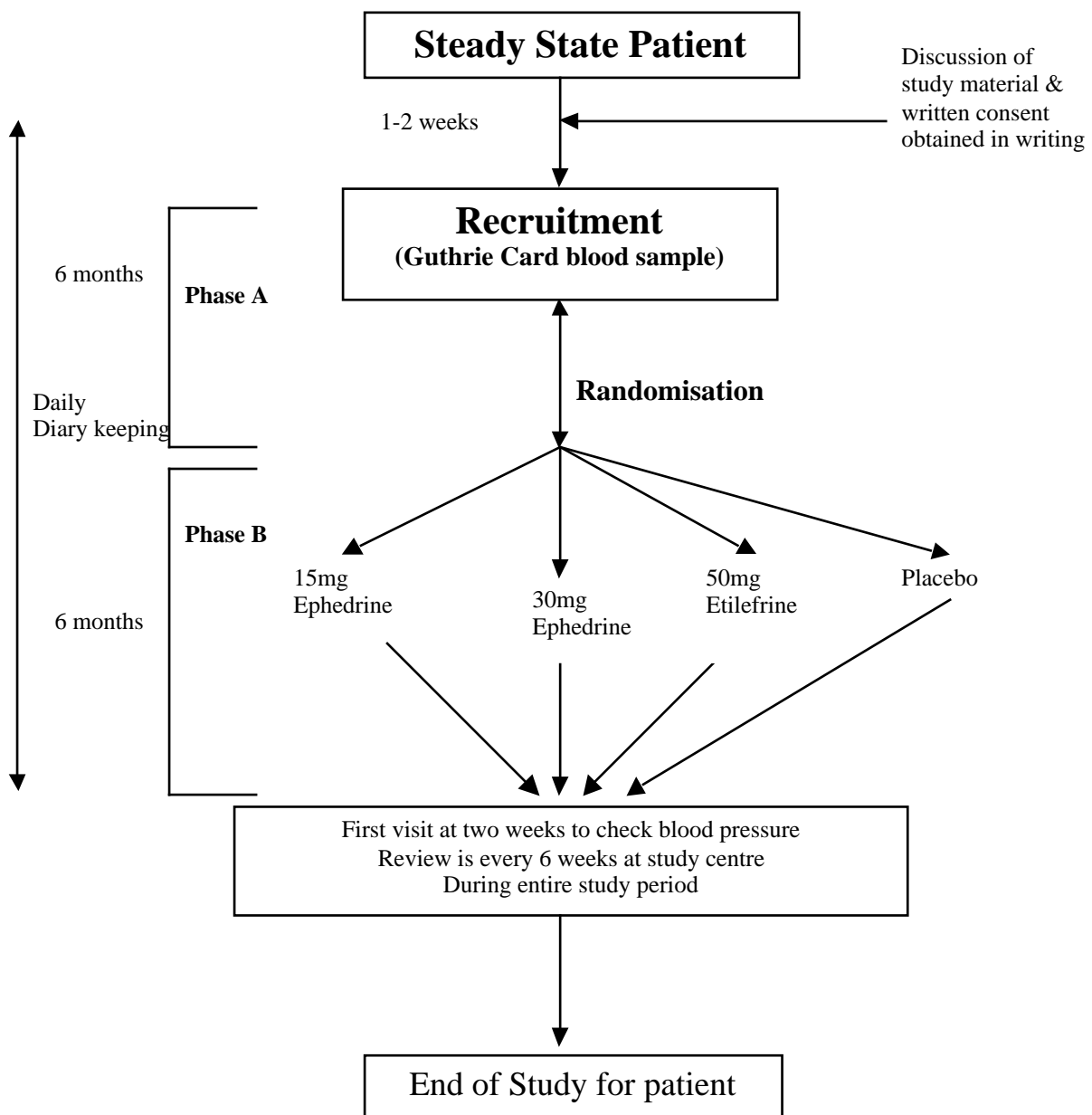
(2)Elpis Mantadakis, David H Ewalt, Joe Don Cavender, Zora R Rogers, and George R Buchanan (2000)

Outpatient penile aspiration and Epinephrine Irrigation for Young Patients with Sickle Cell Anemia and Prolonged Priapism

Blood, 1 January 2000. Volume 95, Number 1

APPENDIX F

Trial of Oral Ephedrine/Etilefrine in Priapism Secondary to Sickle Cell Anaemia



Appendix G

Phase A

PLEASE COMPLETE EACH DAY ENTRY

Baseline BP

Week 1 of 52

Patient Name

	Priapism Attack	Duration	Pain score	What did you
Day 1	Yes / No	hrs		SAMPLE
Day 2	Yes / No	hrs		
Day 3	Yes / No	hrs		
Day 4	Yes / No	hrs		
Day 5	Yes / No	hrs		
Day 6	Yes / No	hrs		
Day 7	Yes / No	hrs		

PLEASE COMPLETE EACH DAY ENTRY

Phase B

Week 27 of 52

Patient Name

SAMPLE

BP

	Priapism Attack	Duration	Tablet taken	Pain score
Day 1	Yes / No	hrs	Yes / No	
Day 2	Yes / No	hrs	Yes / No	
Day 3	Yes / No	hrs	Yes / No	
Day 4	Yes / No	hrs	Yes / No	
Day 5	Yes / No	hrs	Yes / No	
Day 6	Yes / No	hrs	Yes / No	
Day 7	Yes / No	hrs	Yes / No	

Please tick any side effects

- Strong heart beat
- Fast heart beat
- Lack of sleep
- Anxiety
- Dry mouth
- Hand shaking

Others..... 25
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