Identifiers: NCT01242241 **Unique Protocol ID**: H-22091

Title: Propofol in Obese Children

Date: 12 June 2012

Baylor College of Medicine
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MEMORANDUM

TO: OLUTOYIN OLUTOYE
TCH BASED PROGRAMS

FROM: GABRIEL HABIB, M.D., M.S.
Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

DATE: June 20, 2012

RE: **H-22091 - PROPOFOL IN OBESE CHILDREN**

Your request that the above referenced protocol be closed, has been noted and filed with the protocol.

You can access any document related to this closed study via the BRAIN database at any time.

Synopsis:
This study has been completed and the findings have been written up in a manuscript that has been accepted for publication in the journal: Anesthesia & Analgesia

Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

Protocol Number: H-22091
Status: Closed
Initial Submit Date: 11/9/2007

Section Aa: Title & PI

A1. Main Title

PROPOFOL IN OBESE CHILDREN

A2. Principal Investigator

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A3b. Cooperative Agreement

Is this a cooperative agreement protocol?
No

Which institution is the IRB of record?
BCM: Baylor College of Medicine

Section Ab: General Information

A4. Co-Investigators

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A5. Funding Source:

Baylor College of Medicine (Internal Funding Only)

A6a. Institution(s) where work will be performed:

TCH: Texas Children's Hospital

A6b. Research conducted outside of the United States:

Country:
Facility/Institution:
Contact/Investigator:
Phone Number:

If documentation of assurances has not been sent to the Office of Research, please explain:

A7. Research Category:

A8. Therapeutic Intent

Does this trial have therapeutic intent?
Not set yet

A9. ClinicalTrails.gov Registration

Section B: Exempt Request

B. Exempt From IRB Review

Not Applicable

Section C: Background Information

Obesity in children as in adults has rapidly become a public health concern. In the state of Texas, the incidence of childhood obesity is higher than the national average at 20-23% in 4th to 8th graders, with a more marked increase in the minority ethnic groups. The population of obese children presenting for surgery at Texas Children's hospital reflects the state statistics with a recent study showing that 21% of children presenting to the operating room meet the criteria for obesity. Obesity, as defined by the National Health and Nutrition survey is a body mass index (BMI) of greater than 95th percentile. The anesthetic management of obese children poses a variety of significant challenges. These include difficulty with placement of a breathing tube for delivery of anesthesia gases, body positioning to avoid nerve injury and determination of the appropriate dose of anesthetic intravenous agents. It is a common practice to administer anesthetic drugs

based on the real body weight of children. However, obese patients have increased fat composition and altered metabolic state that affects drug distribution and metabolism. The administration of intravenous anesthetic drugs in doses based on the real body weight of these children could result in over dosage and significant hemodynamic consequences particularly hypotension. Large doses of intravenous anesthetic drugs may also result in delayed awakening from anesthesia, and an increase in the duration of hospital stay resulting in a marked increase in health care costs. However, the administration of drugs based on the ideal body weight may result in under-dosing of the anesthetic agents with the risk of inadequate anesthesia and awareness. Such an event could be traumatic and result in psychological effects on the child. Studies in adults have shown that obesity, which can be considered to be a disease state, is a modifier of pharmacokinetics and pharmacodynamics of drugs. There is data to suggest children and adolescents do differ from adults in the manner in which drugs and chemicals are handled but there is sparse data specifically on the effect of obesity on the pharmacokinetics and pharmacodynamics of drugs in children. Therefore, it is important to determine the pharmacokinetics and pharmacodynamics of anesthetic drugs in obese children compared to normal children. Traditionally, the dose of most anesthetic agents is based on the ED 50 or effective dose in 50% of patients, however, as anesthesiologists, ideal situations are those in which unconsciousness is induced in majority or 95 % of patients. Anecdotally, it appears more intravenous medicines are required in obese patients to induce unconsciousness. This study would determine what the ED95 of propofol is in obese and non-obese children.

Section D: Purpose and Objectives

This is a study to test the hypothesis that the dose of propofol (a highly lipophilic sedative hypnotic drug) required for induction of anesthesia will be different in obese children compared to non-obese children.

Section E: Protocol Risks/Subjects

E1. Risk Category

Category 2: Research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects.

E2. Subjects

Gender:
Both

Age:
Adolescent (13-17 yrs), Child (3-12 yrs)

Ethnicity:
All Ethnicities

Primary Language:
English, Spanish

Groups to be recruited will include:
Patients

Which if any of the following vulnerable populations will be recruited as subjects?
Children

Vulnerable populations require special protections. How will you obtain informed consent, protect subject confidentiality, and prevent undue coercion?

During the pre-operative evaluation, the study will be explained to the subject as well as parents/guardians with emphasis on the voluntary nature of participation. Questions will be answered and consent obtained. Assent will also be obtained in children aged 12 years and above. A Spanish translator will be available to Spanish speakers. Subjects will be identified from the operating room schedule made available to the division of pediatric general anesthesia for pre-operative evaluation. Subjects will be children less than 18 years of age presenting for procedures requiring general anesthesia in which propofol use is a planned standard management. Subjects and parents/guardians will be assured that confidentiality of records will be maintained and that subject identifiers will be removed prior to publication of findings. Refusal to participate in the study will not preclude subjects from receiving standard anesthetic care.

E3. Pregnant woman/fetus

Will pregnant women and/or fetuses (as described in 45 CFR 46 Subpart B) be enrolled in the research?

No

E4. Neonates

Will neonates of uncertain viability or nonviable neonates (as described in 45 CFR 46 Subpart B) be enrolled in the research?

No

E5. Children

Will children be enrolled in the research?

Yes

Section F: Design/Procedure

F1. Design

Select one category that most adequately describes your research:

z.z) ARCHIVED DO NOT USE - Other

Discuss the research design including but not limited to such issues as: probability of group assignment, potential for subject to be randomized to placebo group, use of control subjects, etc.

This study will include patients who require general anesthesia with propofol for procedures at Texas Children's Hospital. The patients will be assigned to groups based on their body mass index (BMI). All patients meeting the inclusion criteria will be enrolled. Measurements of body weight and height, which are part of admission vital signs, will be made at the time of patient pre-anesthetic assessment. Patients will be assigned to groups based on their body mass index (BMI). Group A: BMI between 25th and 84th percentile for age(non-obese or healthy weight) and Group B: BMI greater than 95th percentile for age (obese). This study will involve two studies in one. The effective dose of propofol in 95% of non-obese children and 95% of obese children will be determined. Pre determined sequential doses of propofol to be administered are: 1.0 mg/kg, 1.25 mg/kg, 1.5 mg/kg, 1.75 mg/kg, 2.0 mg/kg; 2.25 mg/kg; 2.5 mg/kg; 2.75 mg/kg; 3.0 mg/kg; 3.25 mg/kg; 3.5 mg/kg; 4.0 mg/kg and 4.25mg/kg. The recommended dose range for propofol is 2.5-3.5 mg/kg. The lower doses of 1 or 1.25 mg/kg may insufficiently induce unconsciousness within the specified time but if this occurs, additional medication will be given till a satisfactory level of unconsciousness is attained.The doses of 4.0 and 4.25 mg/kg are beyond the recommended dose range for propofol in children however the purpose of administering propofol is to induce unconsciousness in order for procedures to proceed and the patients will only receive these doses if a satisfactory level of unconsciousness is not achieved with the preceding doses within the expected period. The first patient in each study group will receive the same initial/lowest dose of propofol from the listed doses; the response to this dose of propofol would be deemed positive if there is loss of lash reflex within 20 seconds of administering the dose and negative if there is no response (no loss of lash reflex within 20 seconds). The subsequent patient would receive the next appropriate dose of propofol based on the biased coin design method of sequential dosing (Stylianou M, Flournoy N: Dose finding using the biased coin up-and-down design and isotonic regression. Biometrics 2002; 58:171-7). If patient #1 falls asleep with a given dose of propofol, then patient #2 is randomized to receive either a lower dose with a probability of 0.05 OR the same dose with a probability of 0.95. If patient #1 does not fall asleep with a given dose of propofol, then patient #2 will automatically receive the next higher dose of propofol. In situations where the patient does not lose the lash reflex after 20 seconds, the patient would be documented as having a negative response to the assigned dose of propofol and will be given additional propofol till an adequate level of unconsciousness that will allow the procedure to be performed is achieved.

Inclusion Criteria:

The subject population will include patients between ages 3 -18 years of age presenting for surgery at Texas Children's Hospital

Exclusion Criteria:

The following patients will be excluded from the study: 1.Patients classified as ASA (American Society of Anesthesiology) Class 3 or greater. 2.Patients with documented kidney or liver disease or those presenting for open surgery on the liver or kidney. 3.Patients who will NOT be receiving propofol for induction as part of their anesthetic regimen. 4.Patients who are currently on anti-convulsant medication or receiving drugs with sedative effects. 5. Patients currently being treated for attention deficit disorder. 6. Patients who are

diagnosed with failure to thrive or those with a BMI less than 25th percentile. 7. Patients who are hemodynamically unstable. 8. Patients with egg allergy. 9. Pateints with low levels of albumin

F2. Procedure

Once patients arrive in the holding area a pre-operative assessment will be performed by the nurse practitioners, this includes detailed history taking and a physical examination as well as documentation of all medications the patients are on in addition to their known drug allergies. The vital signs will be obtained which will include the height and weight amongst others. Once the patient meets study criteria, consent will be obtained (and assent in children aged 12 years and above) and the body mass index (BMI) will be calculated from the body weight and height. The patients will be classified at that time into Group A (BMI between 25th and 84th percentile) OR Group B (BMI greater than 95th percentile). An intravenous catheter will subsequently be placed in the hand and the patients will proceed to the procedure area. On arrival there, routine ASA monitors including EKG, pulse oximeter and blood pressure monitors will be placed and lastly, a Bispectral index monitor (BIS monitor) will be placed on the patients¿ forehead. The Bispectral index monitor (BIS) monitor is a monitor that gives a dimensionless empiric number, the BIS value, which correlates with the depth of anesthesia. The BIS value, which ranges from 0 to 100, has been shown to correlate well with the level of hypnosis in adult patients during sedation and general anesthesia. The manufacturers of the BIS monitor have suggested that titrating anesthetics to keep the BIS value between 40 and 60 will provide the optimal depth of anesthesia. There is some preliminary data that suggests that routine monitoring of the BIS level may decrease the incidence of intra-operative awareness in adults considered to be at high risk for this complication e.g. adults on cardiopulmonary bypass. There is limited data on the usefulness of this monitor in children however it is a harmless tool and the information gathered from it (BIS value at time of loss of lash reflex) would be examined retrospectively to see if there is correlation between this value and loss of lash reflex. In addition, your child will be given a syringe full of water to hold tightly in their hand as they fall asleep, the time it takes for their hand grip to weaken, causing the syringe to drop from their hands after receiving propofol will also be noted. These end points: loss of lash reflex and time to weakening of handgrip has been used in previous propofol studies. Obese patients with a body mass index greater than 99% will receive three big breaths of oxygen prior to the beginning of the study in order to compensate for the desaturation that may occur if apnea results from their study dose of propofol. Once monitors have been placed on the patient, intravenous lidocaine 1mg/kg (to a maximum of 60 mg) will be administered prior to the assigned dose of propofol. This is in order to decrease the mild to moderate burning sensation experienced on administration of propofol. The lidocaine would be immediately followed by administration of propofol through a stopcock with 0.5 cc dead space. Propofol administration would be rapidly followed by a flush of 3cc normal saline to ensure the drug enters the circulation. Once the propofol has been flushed in the patient will be checked for loss of lash reflex by stroking the eyelash. If blinking is observed after stroking at 20 seconds, the patient would be deemed to have a negative response to the dose of propofol, this information will be documented and the patient would receive additional propofol titrated to effect, to ensure an adequate level of sedation. The next subsequent patient in this group will then receive the next higher dose of propofol according to the previously stated dosing interval regimen. If there is loss of lash reflex at 20 seconds, the next patient would be randomized to receive either the next lower dose or the same dose administered to the previous patient.

Section G: Sample Size/Data Analysis

G1. Sample Size

How many subjects (or specimens, or charts) will be used in this study?

Local: 85 Worldwide: 85

Please indicate why you chose the sample size proposed:

The up and down study design is characterized by non-independence of data and an unknown distribution, which preclude the development of rules to calculate a sample size for determination of the effective dose of a drug in a certain percentage of patients. As a result, statistical simulations have suggested that approximately 20-40 patients would provide adequate estimates of the target dose in most cases. 40 patients will be evaluated in Group A and 40 in Group B.

G2. Data Analysis

Provide a description of your plan for data analysis. State the types of comparisons you plan (e.g. comparison of means, comparison of proportions, regressions, analysis of variance). Which is the PRIMARY comparison/analysis? How will the analyses proposed relate to the primary purposes of your study?

Data will be analyzed with the use of the isotonic regression estimator with confidence intervals derived by bootstrapping to determine the ED95 of propofol in obese patients. Isotonic regression is a general technique for estimating quantities that are assumed to be non-increasing. This method produces estimates of the probability of toxicity (or estimates of the probability of a positive response in this case) for each dose level,

under the assumption that the dose response function is not decreasing i.e. the higher the dose level the higher the probability of response.

Section H: Potential Risks/Discomforts

Describe and assess any potential risks/discomforts; (physical, psychological, social, legal, or other) and assess the likelihood and seriousness of such risks:

Propofol is a widely used sedative hypnotic agent in both children and adults. Administration of propofol may result in a 30% decrease in the blood pressure. This is usually resolved with administration of fluids being infused during surgery routinely. There is minimal risk to taking part in this study, as patients enrolled will be those that would receive propofol regardless of their participation in the study. A potential risk is that your child does not fall asleep (does not stop blinking when the eyelashes are gently touched) with his/her assigned dose of propofol. If this happens, your child would be noted to have a negative response to the given dose of propofol and more propofol would be given to make sure that he/she is in an adequate state of deep sleep (anesthesia) before proceeding with their procedure. Another risk maybe that your child receives a dose of propofol that may cause a decrease in the blood pressure. This is commonly seen when children receive medicine to fall asleep for procedures. The blood pressure usually returns to normal within a few minutes. If not, fluids or additional medicines are given to bring the blood pressure back to normal levels. An additional potential discomfort to receiving propofol involves a mild burning sensation, which sometimes occurs on injection. Precautions will be taken to decrease this discomfort by injecting lidocaine through the intravenous catheter prior to propofol administration.

Section I: Potential Benefits

Describe potential benefit(s) to be gained by the individual subject as a result of participating in the planned work.

There is no direct benefit to the patient for participating in this study.

Describe potential benefit(s) to society of the planned work.

This study will allow a better understanding of the response of obese children to this lipophilic, sedative -hypnotic agent and would allow for proper dose adjustment which will in return, lead to improved care for this increasing segment of our population.

Do anticipated benefits outweigh potential risks? Discuss the risk-to-benefit ratio.

Anticipated benefits of this study long term do outweigh the potential risks. The only potential risk to patients is loss of confidentiality. The possible benefits to society are greater than potential risks of this study. Therefore the risk-to-benefit ratio is favorable for this study.

Section J: Consent Procedures

J1. Waiver of Consent

Will this research require a waiver of consent and authorization?

No

Will additional pertinent information be provided to subjects after participation?

No

Explain why providing subjects additional pertinent information after participation is not appropriate.

J1a. Waiver of requirement for written documentation of Consent

Is this research subject to FDA regulations?

No

Explain how the research involves no more than minimal risk to the participants, and the specifics demonstrating that the research does not involve procedures for which written consent is normally required outside of the research context.

Explain how the only record linking the participant and the research would be the consent document, and how the principal risk would be potential harm resulting from a breach of confidentiality, and how each participant will be asked whether he or she wants documentation linking the participant with the research and their wishes will govern.

J2. Consent Procedures

Who will recruit subjects for this study?

PI
PI's staff

Describe how research population will be identified, recruitment procedures, any waiting period between informing the prospective participant and obtaining consent, steps taken to minimize the possibility of coercion or undue influence and consent procedures in detail.

Patients who require general anesthesia for their procedures will be identified from the Texas Children's hospital operating room schedule that is made available to the pediatric anesthesia division. Voluntary patient participation will be emphasized during recruitment of patients. Anesthetic care will have no bearing on whether or not the patient is involved in this study. The PI or PI¿s staff will obtain standard written consent from the parent or guardian of each patient. For the purposes of this study, consent can be obtained from only one parent. Assent will also be obtained in children aged 12 years and above. The assent form that will be used is attached in section S of the protocol. A Spanish translator and a short Spanish version of the consent form will be made available for Spanish speakers; this is also attached in section S.

Are foreign language consent forms required for this protocol?

Yes

Which of the following ways will you document informed consent in languages other than English?

Short-Form consent documents

J3. Privacy and Intrusiveness

Will the research involve observation or intrusion in situations where the subjects would normally have an expectation of privacy?

No

J4. Children

Will children be enrolled in the research?

Yes

J5. Neonates

Will non-viable neonates or neonates of uncertain viability be involved in research?

No

J6. Consent Capacity - Adults who lack capacity

Will Adult subjects who lack the capacity to give informed consent be enrolled in the research?

No

J7. Prisoners

Will Prisoners be enrolled in the research?

No

Section K: Confidentiality

Will research data include health information by which subjects can be identified?

Yes

Where will research data be kept? How will such data be secured?

The data will be kept locked in a filing cabinet with no patient identifiers in the PI's office. A separate Excel spreadsheet linking patient information with the unique patient identifier will be kept in a password protected computer as will the database.

Who, besides the PI, the study staff, the IRB and the sponsor, will have access to identifiable research data?
No one else.

Will you obtain a Certificate of Confidentiality for this study?
No

Please further discuss any potential confidentiality issues related to this study.
NA

Section L: Cost/Payment

Delineate clinical procedures from research procedures. Will subject's insurance (or subject) be responsible for research related costs? If so state for which items subject's insurance (or subject) will be responsible (surgery, device, drugs, etc). If appropriate, discuss the availability of financial counseling.
There will be no cost to the patient related to this study.

If subjects will be paid (money, gift certificates, coupons, etc.) to participate in this research project, please note the total dollar amount (or dollar value amount) and distribution plan (one payment, pro-rated payment, paid upon completion, etc) of the payment.

Dollar Amount:
0

Distribution Plan:

Section M: Genetics

How would you classify your genetic study?

Discuss the potential for psychological, social, and/or physical harm subsequent to participation in this research. Please discuss, considering the following areas: risks to privacy, confidentiality, insurability, employability, immigration status, paternity status, educational opportunities, or social stigma.

Will subjects be offered any type of genetic education or counseling, and if so, who will provide the education or counseling and under what conditions will it be provided? If there is the possibility that a family's pedigree will be presented or published, please describe how you will protect family member's confidentiality?

Section N: Sample Collection

None

Section O: Drug Studies

Is this study placebo-controlled?
No

Does the research involve a drug or biologic (including radioactive drugs) that is not approved by the FDA?
No

Will the research involve a radioactive drug?
No

Section P: Device Studies

Does this study need an IDE?
No

Regarding your device study, could potential harm to subjects be life-threatening?
No

Regarding your device study, could potential harm to subjects result in permanent impairment of a body function?
No

Regarding your device study, could potential harm to subjects result in permanent damage to a body structure?
No

Section Q. Consent Form(s)

None

Section R: Advertisements

None