PROTOCOL

Background

1. Provide the scientific background, rationale and relevance of this project.

INSTRUCTIONS

- This should include a referenced systematic evidenced-based review when possible.
- If this study involves qualitative research explain the major constructs of your study.
- Do not state in this section what you plan to do in this study. This information should be entered later under "What will be done in this protocol?"
- Do not include the bibliography in this section.
- For studies submitted under the Expedited review criteria, this section need not be more than a few paragraphs.
- For those studies where data will be analyzed collaboratively by multiple sites doing a similar study for which there is no common protocol (Collaborative Site Analysis Study) include a description of the common scientific goals/ procedures/data points.
- If this is a FIVE YEAR UPDATE make sure the information throughout the protocol includes the most current information.

Post-surgery pain management is critical for ensuring timely patient recovery and minimizing complications. Part of the multimodal approach to managing severe acute pain in the days following surgeries is the use of nerve blocks. The relatively short-lived effect of commonly used local anesthetics recently prompted the development and subsequent approval of a liposomal formulation of bupivacaine (Exparel; Pacira Pharmaceuticals, Parsippany, New Jersey). It has demonstrated favorable pharmacokinetics compared to bupivacaine HCl, with a slower release into blood stream of up to 96 hours after administration, following a single dose wound infiltration at the end of various surgeries (summarized in (1)). Studies using other modes of administration reported similar results (2, 3).

Thoracic surgeries pose an exceptional challenge as they are one of the most painful surgeries and poor pain-management contributes to reduced quality of life and severely delayed recovery (4, 5). The anesthesiology protocol within the Enhanced Recovery After Surgery (ERAS) program at medical centers across the world aim to increase patient comfort after surgery while reducing complications and use of opioids. As a common part of this protocol, intercostal nerve blocks with liposomal bupivacaine are regularly utilized for reduction of post-thoracotomy pain and studies show that it may be just as or more effective than bupivacaine HCl for treatment of pain, decreasing hospital stays and reducing incidence of complications (6-8).

Despite its frequent use in the surgical room for nerve blocks, the pharmacokinetics of a single dose injection of liposomal bupivacaine at the intercostal nerves has never been investigated. The aim of this study is to assess the pharmacokinetics of liposomal bupivacaine injected at the intercostal nerves to aid in the standardization of post-thoracotomy pain management. Further, the information gleaned from this study will allow for the optimal use of additional local anesthetics, particularly those administered intravenously, for the purpose of obtaining maximal pain relief while minimizing the occurrence of local anesthetic toxicity.

Objectives/Hypothesis

INSTRUCTIONS:
If this study involves biomedical research clearly state the objectives and hypotheses and clearly define the primary and any secondary outcome measures. If this study involves qualitative research clearly state your research hypothesis or question.

This section should not include information already included in other sections such as background information or information from the procedures section.

The intent of this prospective study is to evaluate the serum concentrations of liposomal bupivacaine following a surgeon administered, single dose injection at the intercostal nerves, at the start of thoracotomies. The primary end points will be to assess the time to peak serum concentration/s of liposomal bupivacaine (T_{max}) and peak serum concentration/s (C_{max}) after a single-dose injection in the intercostal nerves. We will also determine pharmacokinetic parameters such as area under the serum concentration-time curve (AUC) and time apparent terminal elimination half-life ($T_{1/2}$). In doing so, we will obtain serum bupivacaine concentrations at various times following wound infiltration. Additionally, we will monitor pain levels in the patients through the 96-hour period after intercostal nerve block injection.

Study Design: Biomedical

1. Will controls be used?
No

►IF YES, explain the kind of controls to be used.
Answer/Response: N/A

2. What is the study design?

Example: case series, case control study, cohort study, randomized control study, single-blind, double-blind, met-analysis, systematic reviews, other. You may also view the IRB-HSR Learning Shot on this topic to help you answer this question. (http://www.virginia.edu/vpr/irb/learningshots/Writing_protocol_June09/player.html

Pharmacokinetic study of single-dose surgeon administered liposomal bupivacaine

3. Does the study involve a placebo?
No

►IF YES, provide a justification for the use of a placebo
Answer/Response: N/A

Human Participants

Ages: **>18___**
Sex: **_Male and Female___**
Race: **__Any__**

Subjects- see below

INSTRUCTIONS: For question 1-4 below insert an exact #. Ranges or OPEN is not allowed. This # should be the maximum # you expect to need to enroll (i.e. sign consent) If you are only collecting specimens the number of participants should equate to the # of specimens you need. If you are collecting only data from a chart review the number should designate the number of subjects whose medical records you plan to review. Age/ Sex/Race criteria should designate the demographics of participants from whom you will obtain the specimen/data.

1. **Provide target # of subjects (at all sites) needed to complete protocol.**

INSTRUCTIONS: If this is NOT a database protocol, this number should be the same as the number of subjects needed to obtain statistically significant results.

15

2. **Describe expected rate of screen failure/ dropouts/withdrawals from all sites.**

We estimate a 25% rate of withdrawal/failure/dropout. This percentage also includes those patients who decline to consent. As such, we will aim to consent 20 patients.

3. **How many subjects will be enrolled at all sites?**

INSTRUCTIONS: This number must be the same or higher than the # from question # 1 in order to account for the # of screen failures, dropouts, withdrawals described in question # 2.

20

4. **How many subjects will sign a consent form under this UVa protocol?**

INSTRUCTIONS: If the protocol does not have a consent form- the number listed here should reflect such things as the number of subjects from whom specimens will be obtained, the number of charts to be reviewed etc.

20

Inclusion/Exclusion Criteria

INSTRUCTIONS:

- The inclusion and exclusion criteria should be written in bullet format.
- *This item applicable if the study will require consent (verbal or written).* Unless there is a scientific reason for not recruiting a certain type of vulnerable population(e.g. not

enrolling fetuses, neonates or children in a study regarding Alzheimer's) list the following vulnerable populations under either Inclusion or Exclusion criteria below: pregnant women, fetuses, neonates, children, prisoners, cognitively impaired, educational or economically disadvantage, non- English speaking subjects .

- If you will not enroll subjects who do not speak English because certain procedures cannot be carried out if the subject does not speak English (e.g. a survey is not validated in other languages) insert the following as an Inclusion Criteria: Willingness and ability to comply with scheduled visits and study procedures.
- If this is a collection of only retrospective* specimens or data, the inclusion criteria must include a start and stop date for when specimens/ data will be collected.
- The stop date must be prior to the version date of this protocol.
- *Retrospective: all specimens are in a lab at the time this protocol is approved by the IRB. All data exists in medical records or records from previous studies at the time this protocol is approved by the IRB.

1. List the criteria for inclusion
   - >18 years of age
   - Undergoing thoracotomy

2. List the criteria for exclusion
   - Non-English speaking
   - Pregnant women
   - Prisoners
   - Weighing <50 kg
   - Allergy to local anesthetics
   - Patients unable to understand the risks and benefits of the study and to consent for themselves

3. List any restrictions on use of other drugs or treatments.
N/A

Statistical Considerations

1. Is stratification/randomization involved?
No

►IF YES, describe the stratification/ randomization scheme.

INSTRUCTIONS:
The stratification factors and/or the randomization plan should be identified. If there is no randomization component or important patient characteristics that will be used in treatment allocation or data analysis, a statement to this effect should be included.

Stratification factors: These are pretreatment patient characteristics which could be balanced across treatment arms by design or may be used to determine starting dose or treatment allocation.

If randomization is going to be used, the details of the randomization plan should be described.

The description should include:
--the method and timing of randomization
--the type of randomization scheme that will be used in the study
--whether or not the randomization masked/blinded/if so, then to whom is it masked/blinded
--who has access to the randomization scheme

N/A

►IF YES, who will generate the randomization scheme? N/A

_____ Sponsor
_____ UVa Statistician. Insert name Answer/Response:
_____ UVa Investigational Drug Service (IDS)
_____ Other*:* Specify Answer/Response:

2. What are the statistical considerations for the protocol?

The objectives section and the statistical section should correspond, and any objective for which analysis is unfeasible should be deleted. Also, the estimates and non-statistical assumptions of the statistical section should be supported by discussion in the background section.

The answer to this question should include:
--Study Design/Endpoints

--Recap of study objectives and endpoint definitions. An assessment of how study objectives will be assessed by identifying & defining which endpoints will be used to assess each component of the study objectives.
--The study design should include contingencies for early stopping, interim analyses, stratification factors (If applicable), and any characteristics to be incorporated in analyses.
--The power/precision of the study to address the major study endpoint(s), the assumptions involved in the determination of power/precision.
--If statistical hypothesis testing is included then specify the null and alternative hypotheses, the test statistic, and the type I and II error rates
--If precision of an estimate, then provide a definition for precision
--If other, then specify

This is a prospective pharmacokinetic study investigating the pharmacokinetic parameters of liposomal bupivacaine injected at the intercostal nerves by the surgeon at the start of a thoracotomy. The primary endpoint of this study is to evaluate the time to peak serum concentration/s of liposomal bupivacaine (T_{max}) as well as maximal serum concentration/s (C_{max}). Additional end-points will include the assessment of area under serum concentration-time curve (AUC) and observed terminal elimination half-life of liposomal bupivacaine ($T_{1/2}$). These parameters will allow us to generate a pharmacokinetic profile of liposomal bupivacaine injected in the intercostal nerves by determining serum bupivacaine concentrations at various set times following wound infiltration at the intercostal nerves. This study will only have one group and a sample size of 15 subjects.

We do not anticipate stopping this study early. We may conduct an interim analysis of the pharmacokinetic data to assess whether the chosen blood draw times are sufficient to properly analyze the pharmacokinetics. In other words, if after interim analysis we note undetectable levels of the anesthetic at the first few time points or if we do not reach peak plasma concentration by the last time point, we will adjust blood draws to reflect these results in order to obtain the most complete pharmacokinetic data and to minimize blood draws.

3. Provide a justification for the sample size used in this protocol.

Include the anticipated accrual rate, the accrual goal for the study, including accrual goals by strata if appropriate, adjustments for drop-outs etc. and study duration.

Answer/Response:
The data to aid in the determination of sample size calculation are inadequate. However, published studies investigating the pharmacokinetics of liposomal bupivacaine all enrolled a small number of patients. The most relevant and similar to our study is the data published by Viscusi *et al*. As such, our determination of sample size is based on this previous report. Viscusi *et al*. assessed the pharmacokinetics of 266mg liposomal bupivacaine injected in the epidural space (3). Here, the total subject number was 7 and the confidence intervals for T_{max} were very large: 8 – 48 hours with the median being 24 hours. We believe that a sample size of 15 subjects for our study would be sufficient to obtain better confidence intervals for our T_{max} target. We anticipate that the drop-out rate will be 25% and as such, will aim to consent 20 patients and anticipate that the study will last for 3 months.

4. What is your plan for primary variable analysis?

Include a sketch of the analysis to assess primary study objectives.

Answer/Response: N/A

5. What is your plan for secondary variable analysis?

Include the following: --A sketch of the analysis to assess secondary study objectives. --For phase III studies, the power/precision of the study to address the secondary objective(s).

Answer/Response: N/A

6. Have you been working with a statistician in designing this protocol?
Yes

IF YES, what is their name?
Answer/Response: Eric Schneider, Ph.D.

7. Will data from multiple sites be combined during analysis?
N/A

INSTRUCTIONS: IF YES, answer the following questions

7(a). Does the study involve randomization?
No

IF YES, will randomization be done at each site or among sites?
Answer/Response: N/A

7(b). Has the sample size calculation considered the variation among sites?
N/A

7(c). When combining the data from multiple sites to assess the study results, is the effect of the treatment to be tested (or the association to be tested) assumed to be the same across sites or vary among sites? What is the modelling strategy?
N/A

7(d). Is there a common protocol used in all sites?
N/A

IF NO, how will differences among sites, such as those related to the implementation, inclusion criteria, patient characteristics, or other sites characteristics, be considered to assess the study results?
Answer/Response: N/A

Study Procedures-Biomedical Research

1. What will be done in this protocol?

INSTRUCTIONS:
This should include everything that will be done as part of this protocol. Do not repeat information that is included in other sections such as Background or Hypothesis sections.
This section should include an indication of which research interventions if any offer a prospect for direct benefit and which interventions (invasive measurements, collection of blood, tissue, data, surveys, etc.) are being done solely to answer a research question

and generate generalizable knowledge. If the interventions done solely for research purposes are associated with greater than minimal risk they need to be justified. Describe and justify any control and experimental arm and include method, dose, and duration of drug administration. Reference any claim of clinical equipoise if applicable.

If you are obtaining specimens or data, provide information regarding the type of specimen/data, amount of specimen needed and how the specimen/data will be obtained and what analysis will be done with the specimen/data.

Special note for studies with waiver of consent/waiver of documentation of consent: Include a statement regarding how subjects will be recruited. For other studies this information is captured in Recruitment does not need to be duplicated in this section.

In this study, patients who are undergoing thoracotomies will be consented separately from the surgery itself. Patients will be consented for the study on the day of the surgery in the Surgical Admission Suites (SAS), prior to being taken to the OR. The study participants will be given a standard (266 mg/20ml) single dose injection of liposomal bupivacaine by the surgeon at the start of the surgery. Immediately prior to the injection of the local anesthetic, 5 ml of blood will be drawn from the patient via the arterial line. The arterial line will be placed as part of standard surgery procedure and not for the purposes of the study. Blood will then be drawn from the patient after the injection of the local anesthetic at 5 mins, 15 mins, 30 mins, 1, 2, 4, 8, 12, 24, 48, 72 and 96 h. Each blood draw will be 5 ml.
The arterial line will not remain in the patient for the purposes of the study and will be removed per standard procedure. If more blood samples are needed after the arterial line is removed, we will first attempt to obtain blood an existing venous catheter. If blood cannot be obtained this way, a venipuncture will be performed.
Blood samples will be analyzed for the following pharmacokinetic parameters: area under the serum concentration-time infinity (AUC), maximum observed serum concentration (C_{max}), time to attain C_{max} (T_{max}), and apparent terminal elimination half-life ($T_{1/2}$).
At the same time of blood samples, pain scores will be recorded on a standard ten-point pain scale. These pain scores will be omitted if the patient is under general anesthesia.

2. If this protocol involves study treatment, explain how a subject will be transitioned from study treatment when they have completed their participation in the study.

Example: If the subject will be taking an investigational drug, will they need to be put back on an approved drug when they have completed the study? If yes, explain how this will be accomplished and who will cover the cost. If the subject has a device implanted will it be removed? Again- who will cover the cost of the removal?
Instructions: Answer NA if this study does not involve a study treatment.

Answer/Response: N/A

Subject Compliance with Study Procedures

1. **Explain how the study team will monitor the subject for compliance with the study procedures.**
   (e.g. study team will administer study drug/ study interventions, study drug inventory of dispensed and returned drug, diary etc.)
   The blood draws will first be done by surgery personnel followed by the post-surgery care team. A member of the study team will be present at all blood draws.

2. **Describe criteria for when a subject is considered to be non-compliant with study procedures.**
   (e.g. subject returns more than 20% of the study drug, subject misses 20% of study visits)
   Answer/Response: Subject declines to complete all of the blood draws.

Bibliography

INSTRUCTIONS: Provide a current bibliography supporting the hypothesis, background and methodology including references to papers and abstracts that have resulted from previous work by the investigator and references to the work of others.

References

1. Hu, D., Onel, E., Singla, N., Kramer, W.G., and Hadzic, A. (2013) Pharmacokinetic profile of liposome bupivacaine injection following a single administration at the surgical site. *Clin.Drug Investig*. **33,** 109-115
2. Davidson, E.M., Barenholz, Y., Cohen, R., Haroutiunian, S., Kagan, L., and Ginosar, Y. (2010) High-dose bupivacaine remotely loaded into multivesicular liposomes demonstrates slow drug release without systemic toxic plasma concentrations after subcutaneous administration in humans. *Anesth.Analg*. **110,** 1018-1023
3. Viscusi, E.R., Candiotti, K.A., Onel, E., Morren, M., and Ludbrook, G.L. (2012) The pharmacokinetics and pharmacodynamics of liposome bupivacaine administered via a single epidural injection to healthy volunteers. *Reg.Anesth.Pain Med*. **37,** 616-622
4. De Cosmo, G., Aceto, P., Gualtieri, E., and Congedo, E. (2009) Analgesia in thoracic surgery: review. *Minerva Anestesiol*. **75,** 393-400
5. Wenk, M., and Schug, S.A. (2011) Perioperative pain management after thoracotomy. *Curr.Opin.Anaesthesiol*. **24,** 8-12
6. Khalil, K.G., Boutrous, M.L., Irani, A.D., Miller, C.C., Pawelek, T.R., Estrera, A.L., and Safi, H.J. Operative Intercostal Nerve Blocks With Long-Acting Bupivacaine Liposome for Pain Control After Thoracotomy. *The Annals of Thoracic Surgery*. **100,** 2013-2018
7. Mehran, R.J., Walsh, G.L., Zalpour, A., Cata, J.P., Correa, A.M., Antonoff, M.B., and Rice, D.C. (2017) Intercostal Nerve Blocks With Liposomal Bupivacaine: Demonstration of Safety, and Potential Benefits. *Seminars in Thoracic and Cardiovascular Surgery*.
8. Rice, D.C., Cata, J.P., Mena, G.E., Rodriguez-Restrepo, A., Correa, A.M., and Mehran, R.J. Posterior Intercostal Nerve Block With Liposomal Bupivacaine: An Alternative to Thoracic Epidural Analgesia. *The Annals of Thoracic Surgery*. **99,** 1953-1960