Surgical Savvy

SUMMER 2015, ISSUE 2
www.surgicalresearch.org

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SRA CERTIFICATION SUCCESS STORY

RENAE HALL, a Surgical Research Anesthetist (SRA) at Wake Forest Institute of Regenerative Medicine (WFIRM) Jesse Meredith's Surgery Center, tells us about her experience with the Academy and obtaining her SRA certification.

Q: Please give us some information on your background and current job role.

I grew up on a family farm and have always enjoyed taking care of animals. After high school, I attended Central Carolina Community College in Sanford, NC and became a Registered Veterinary Technician. I joined Wake Forest School of Medicine in 2007 as a Laboratory Animal Technician. In 2011 I became part of Wake Forest Institute of Regenerative Medicine (WFIRM) Jesse Meredith's Surgery Center. Here I learned more hands on skills and found my interest in anesthesia. In October 2012 at the Annual Academy of Surgical Research Meeting in Charlotte, NC, I became a Surgical Research Anesthetist (SRA). After receiving my certification I became a lead technician for all types of species at the institute. My duties and responsibilities include evaluating an animal before and after a surgical

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operation, following a sedation protocol, administering anesthesia and other pain relief agents, performing diagnostic tests, administering fluids, monitoring vital signs, operating specialized monitoring equipment, updating medical charts and supervising/teaching lower level veterinary technicians and support staff.

Q: How long have you been involved with the ASR? Was this the first time you attended the ASR meeting and what did you think of it?

I have been involved with the ASR since April 2012 when I first submitted my case logs and narratives to sit for the SRA Exam. This was the first time I had attended an ASR meeting. At first I felt overwhelmed but soon gained confidence once I knew I had passed the SRA Exam. I knew then I was a true member of this excellent surgical group and felt honored.

Q: What motivated you to take the SRA exam?

Two things motivated me to become a Surgical Research Anesthetist. One motivator was that no one else at WFIRM or at the entire Wake Forest School of Medicine had mastered this accomplishment. The second was that once I started learning about this field I couldn't get enough of it. I wanted to learn as much as I could and be the best that I could be.

Q: What are your thoughts on the exam?

I thought the SRA Exam was very thorough and organized. I liked the two parts based on a lecture and hands on practicum approach. In a quiet testing setting the hands on practicum was the best it could be in that type of situation. The exam was only 200 questions total, which was a good number that didn't overwhelm you.

Q: What advice would you give to people studying for the test?

I would set aside designated study time for the exam. Since the ASR sends out the acceptance letters for testing in July you only have until October to study. Purchase in advance all the books and materials in preparation for the SRA exam after you submit your case logs and narratives. Once you get the acceptance letter and materials, get organized into categories and study one category at a time. When you feel like you understand that topic move to the next one. Make notes throughout the materials to go back in reference in a flash when needed. Main key here is to stay organized; allow enough study time to get through all the testing material and save time at the end for a review. When it gets testing time, get to the testing site early. Make sure you know exactly where to go, eat a good breakfast and get a good night's sleep.

Surgical Research Anesthetist (SRA)

The SRA certification is intended for the technician who works as an anesthetist who also has responsibilities as part of the surgical team that include aseptic preparation and peri-operative care of surgical patients. The SRA candidate must have documented experience with at least two species as reflected in an anesthetic case log.

Surgical Research Technician (SRT)

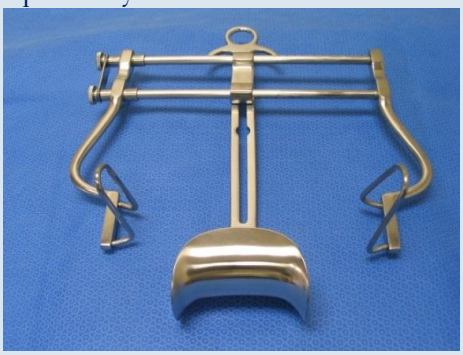
The SRT certification is intended for technicians who perform minor surgical procedures, such as peripheral vessel cannulation, indwelling pump implantation, subcutaneous implantation, etc. A minimum of two different procedures need to be documented in a surgical case log.

Surgical Research Specialist (SRS)

The SRS certification is intended for the surgeon who performs major surgical procedures, such as those which penetrate a body cavity, or orthopedic manipulations, vessel and/or nerve anastomosis, etc. A minimum of two different major procedures in two species need to be documented in a surgical case log. If the majority of work is performed in rodents, then 4 different procedures need to be performed.

Balfour Retractor

A very common retractor, it is used to hold open abdominal incisions during laparotomy.



Finochietto Retractor

A retractor used for spreading the ribs during thoracotomy. Named after Enrique Finochietto, a prominent surgeon at the start of the 1900's. Enrique Finochietto from Argentina, had 67 inventions credited to him during his lifetime.

Weitlaner Retractor

Properly pronounced "VIGHT-lahn-er", it is named after Franz Weitlaner, an Italian born surgeon in the early 1900's. This retractor and Weitlaner derived retractors are used in many different surgical applications and organ sites, though most well known as a shallow tissue retractor in orthopedic and neurological cases.

How Clean is Your Skin?

Lynsey Gregory, BSc (Hons), LAT

The skin has an ambient environment for controlled bacterial growth; this includes commensal bacteria which protect the host from pathogenic bacteria. Resident gram-positive bacteria such as *Staphylococcus aureus* are notoriously pathogenic in the skin and in order for the bacteria to be pathogenic they must be able to adhere to, grow on or invade the host. Performing surgeries on a patient can create an environment for these pathogens to invade, adhere to or grow on the host.

Surgical site infections (SSI) increase morbidity and mortality rates and raise costs to healthcare providers. In England, between 1% - 10 % of patients develop a wound infection following surgery (Tanner 2012). It is estimated that 5% of patients in the US suffer from SSI complications from all clean-contaminated operations performed annually (Hemani, Lepor 2009). A Spanish study concluded that the total cost of an SSI to be $97,000, which included costs to the hospital, primary care, the patient and the economy.

To help prevent SSI, skin preparation before a surgical procedure is critical. There are many different solutions used for preparing the surgical site and the surgeons. The most common active ingredients used are chlorhexidine gluconate and iodophors (such as povidone iodine). These can be prepared as either aqueous or alcoholic solutions.

The ideal antiseptic solution should be:

- Active against a broad range of Gram positive and Gram negative bacteria, viruses and fungi
- Fast acting
- Have residual effect
- Not inactivated by organic material such as blood or dirt
- Non-irritant and non-toxic

Aqueous-based solutions containing iodophors have widespread use because of their broad spectrum antimicrobial properties, efficiency and safety on nearly all skin surfaces.

Povidone-iodine (PVP-I) kills a range of Gram positive and Gram negative bacteria, viruses and fungi, it contains iodine that the povidone releases slowly which kills bacteria quickly but does not have a residual effect. Iodine is inactivated by organic material so should be applied only to clean skin. PVP-I is applied to the skin in a 2 step scrub and paint technique.

Chlorhexidine gluconate (CHG) kills a range of Gram positive and Gram negative bacteria, viruses and fungi, and binds to the top layer of the skin which results in persistent activity. It works by disrupting bacterial cell membranes; it is also more resistant to neutralization by blood products. This agent is used in both patient site preparation and a hand-scrubbing, showering antiseptic prior to surgery.

Alcohol-based solutions: ethyl and isopropyl alcohol are the 2 most effective antiseptic agents available. Alcohol is fast and short acting, killing a range of Gram positive and Gram negative bacteria, viruses and fungi.

Alcohol-based solutions that contain CHG or iodophors have sustained and durable antimicrobial activity that lasts long after the alcohol evaporates. Alcohol dries on skin within minutes of application so can be applied in a 1 step preparation method. They should not be applied to mucous membranes.

DuraPrep® surgical solution is an alcohol-based antiseptic solution containing iodine povacrylex and isopropyl alcohol. ChloraPrep® is also an alcohol-based antiseptic solution containing CHG and isopropyl alcohol. These antiseptics are applied in 1 step, dry in minutes on hairless skin and both solutions maintain antimicrobial activity for up to 48 hours. They have effective broad spectrum antimicrobial properties, including *Staphylococcus* species. DuraPrep® leaves a water insoluble film on the skin surface and accomplishes a 6-fold bacterial log reduction within 1 minute of contact. It also has effectiveness in wet surgical environments.

In multiple studies carried out on aqueous-based and alcohol-based antiseptic solutions each agent has effective properties at reducing SSI's. Alcohol-based solutions with iodophors containing iodine have a larger range of effectiveness against all microbes with immediate and long lasting antiseptic properties.

In conclusion, when preparing a surgical site be mindful of the type of surgery being performed and use the most appropriate level of antiseptic to keep the skin as clean as possible before and after the procedure is carried out.

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The ASR Educational Foundation

Teresa Gleason talks with Devra Olson about the Foundation

- **What is the ASR Educational Foundation?**

  The ASR Educational Foundation is a 501 (c) (3) nonprofit organization supporting the education of preclinical experimental surgical candidates.

Mission of the ASR Educational Foundation

The mission of the ASR Education Foundation shall be to advance the profession of surgical research through supported educational activities. Continuing education awards shall be made in a non-discriminatory basis to selected individuals working in the surgical research field.

- **When was it founded and by whom?**

  The Foundation was the brainchild of Tom Long who felt that some technicians were unable to obtain certification due to lack of financial support for meeting travel from their companies. It was founded in 2012.

- **How do you qualify for financial assistance in attending ASR or sitting for certification?**

  To qualify for an award there is a grant application located on the ASR website – these are reviewed by the committee on an individual basis for awards.

- **Why did you become involved in the Educational Foundation?**

  I became involved the year after I served on the board as Immediate Past President. This is how the position has traditionally been filled; however, any active ASR member will be considered as Chair or as a member of the Foundation committee.

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Short-acting and Long-acting Buprenorphine Therapeutic Drug Levels Following Single Subcutaneous Administration in Diabetic Yucatan Miniswine

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ABSTRACT

Sustained and controlled analgesia for animals involved in potentially painful procedures, such as surgery, is required for animal welfare and ethical considerations. Many analgesics are available to Laboratory Animal Veterinarians but the pharmacokinetic and pharmacodynamic data are not always available for every species. This is the situation for miniswine and porcine models. Standard short-acting buprenorphine HCl (BUP), an opioid, is routinely used in swine models on a BID basis (dose range 0.005-0.02 mg/kg im, sc or iv) while BUP SR (Sustained Release) is dosed at approx. 10-fold levels in large animals. The published data supporting this porcine BUP regimen or the use of Sustained Release (SR) buprenorphine (BUP SR) in swine is quite limited, thereby forcing investigators to favor on the side of caution which can be expensive. Therefore, we designed a study to assess the PK for buprenorphine analgesics in Yucatan miniswine. The diabetic Yucatan was selected because we chemically induce, place VAPS, and maintain a large herd of these animal models. Four castrated male alloxan diabetic animals weighing approximately 30 kg were used in a complete cross-over design. For standard buprenorphine HCl animals were dosed subcutaneously (left flank fold) with either 0.01 mg/kg (low-dose) or 0.02 mg/kg (high-dose), while for sustained release buprenorphine the dose was either 0.12 mg/kg (low-dose) or 0.24 mg/kg (high-dose) s.c. in left flank-fold. Washout was set at 9d before animals were redosed with another formulation. For the shorter acting buprenorphine, blood samples were collected at pre-dose, 0, 15, 30, 60, 120, 240 and 480 minutes (8 timepoints targeted). For the sustained formulation, samples were collected at pre-dose, 0, 30, 60, 90, 240 and 480 minutes, and 12h, 24h, 48h, 72h, and 96h (12 timepoints targeted). Buprenorphine was analyzed in K2EDTA plasma samples by liquid-liquid extraction and LC-MS/MS (quantitation range 50 to 5000 pg/mL). Results were reported in picograms/mL of plasma. All data were quality controlled and outliers removed before summary statistics were calculated and plotted. Results for buprenorphine high- & low-dose plasma drug profile curves showed that BUP peaked at 2192 pg/ml for the high-dose and 842 pg/mL for the low dose. Following single s.c. administration, short-acting BUP drug was onboard in plasma for 240-480 min (above 0.1 ng/mL efficacious threshold for 480 min or 8 hrs). Results for buprenorphine SR high- & low-dose plasma drug profile curves showed that BUP SR peaked at 1795.5 pg/ml at 240 min (high-dose) and peaked at 1531.8 pg/mL (low dose) at 30 min. Sustained release drug was present in plasma for 96 hrs for both high- & low-dose (above 0.1 ng/mL). In conclusion, these data suggest that these dose levels provide sufficient plasma levels of drug for analgesia (>0.1 ng/mL) for at least 8 hr (short-acting BUP) or for at least 96 hr (long-acting BUP SR). Standard pharmacokinetic parameters were calculated.

Keywords: 1) Analgesia, 2) Yucatan miniswine, 3) Buprenorphine HCl or Buprenorphine SR

INTRODUCTION

Sustained and controlled analgesia for animals involved in potentially painful procedures, such as surgery, is required for animal welfare and ethical considerations. Many analgesics are available to veterinarians but pharmacokinetic and pharmacodynamic data are not always available for every species. Standard buprenorphine HCl (BUP), an opioid, is routinely used in swine models on a BID basis (dose range 0.005-0.02 mg/kg im, sc or iv), while BUP SR (Sustained Release) is dosed at approx. 10-fold levels in large animals. The published data supporting this porcine regimen or the use of buprenorphine sustained release (BUP SR) in swine is quite limited, thereby forcing investigators to favor on the side of caution which can be expensive. We designed a study to assess the pK for buprenorphine analgesics in Yucatan miniswine. The diabetic Yucatan was selected because we chemically induce, place subcutaneous vascular access ports (VAPS), and maintain a large herd of these animal models.

METHODS

Four castrated male alloxan diabetic (db) animals weighing approximately 30 kg were used in a complete cross-over design. Buprenorphine HCl (Buprenex™ Injection, 0.3 mg/mL. Reckitt Benckiser Pharmaceuticals) and Buprenorphine HCl SR 10mg/ml (SR Veterinary Technologies/ZooPharm, Windsor, CO) was obtained. For BUP, animals were dosed subcutaneously (left flank fold) with either 0.01 mg/kg (low-dose) or 0.02 mg/kg (high-dose), while for BUP SR the dose was either 0.12 mg/kg (low-dose) or 0.24 mg/kg (high-dose), also dosed s.c. in left flank-fold. Washout was set at 9d before animals were redosed with another formulation. For the BUP, blood samples were collected at pre-dose, 0, 15, 30, 60, 120, 240 and 480 minutes (8 timepoints targeted). For the BUP SR, samples were collected at pre-dose, 0, 30, 60, 90, 240 and 480 minutes, and 12h, 24h, 48h, 72h, and 96h (12 timepoints targeted). Buprenorphine was analyzed in K2EDTA plasma samples by liquid-liquid extraction and LC-MS/MS (quantitation range is 50 to 5000 pg/mL). Results were reported in picograms/mL of plasma. All analytical data were quality controlled and outliers removed before summary statistics were calculated and plotted.

Non-compartmental analysis was applied to the drug concentration – time data. Pharmacokinetic analysis was performed using Phoenix WinNonlin 6.3 (Pharsight Corporation, Mountain View, CA). Pharmacokinetic parameters were calculated separately for each individual animal using the raw data and nominal blood sampling time points. Group means were also tabulated. For PK modeling purposes, plasma drug concentrations reported as less than the lower limit of quantification were designated as 0 in the analysis data set. The following PK parameters were estimated: Cmax, Tmax, T1/2, and AUC. AUC values were determined by the method of linear trapezoidal linear interpolation.

RESULTS

Buprenorphine plasma drug profile curves showed that BUP peaked at 2192 pg/ml for the high-dose and 842 pg/mL for the low dose (Table 1 and Figure 1). Short-acting BUP drug was in plasma for 480 min (above 0.1 ng/mL efficacious threshold for 8 hrs). BUP SR plasma drug profile curves showed peaks at 1795.5 pg/ml at 240 min (high-dose) or at 1531.8 pg/mL (low dose) at 30 min (Table 2 and Figure 2). Sustained release drug was present in plasma for at least 96 hrs for both high- & low-dose (above 0.1 ng/mL). Table 3 presents pK analysis parameters by drug group (includes Cmax Tmax, T1/2, Clast, Tlast, AUClast, AUCo, Vz/F, Cl/F, MRTlast). Of significance, the higher dose BUP SR reached

RESULTS (CONTINUED)

Tmax quicker than did the lower dose SR (5.4 vs. 9.1 hr). Two of 4 high dose SR animals exhibited considerable variability (Tmax: 1.5 & 12 hr) from the other two animals Tmax of 4 hours each.

Table 1. High vs. Low Dose SA Buprenorphine Dosed Subcutaneously In db Yucatan: Group Plasma Means (pg/mL) Over Time (N=4)

	pK Timepoint (mins)						
	predose	15 min	30 min	60 min	120 min	240 min	480 min
Mean BUP Low	76.5	474.5	642.75	695.25	502.75	397.5	352.75
Mean BUP High	130.00	1985.00	2192.00	1905.00	1128.75	821.00	428.75

Figure 1. High vs Low Dose SA Buprenorphine Dosed s.c. In db Yucatan Miniswine: Group Plasma Means Over Time (N=4)

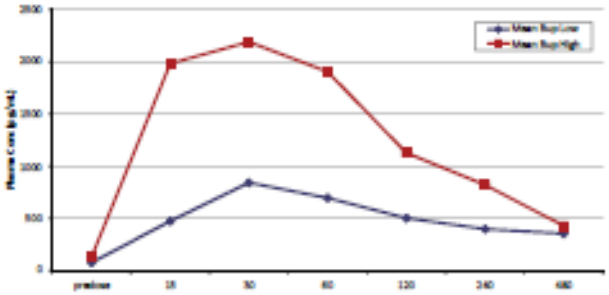
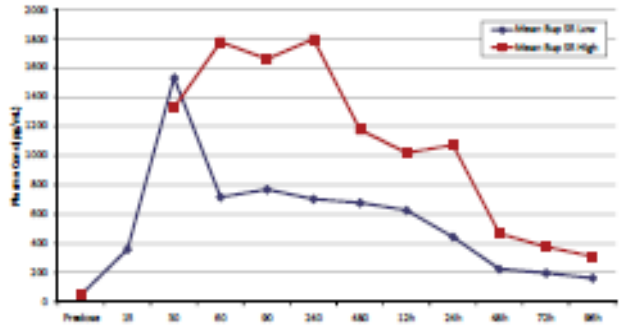


Table 2. High vs. Low Dose Buprenorphine SR Dosed Subcutaneously In db Yucatan: Group Plasma Means (pg/mL) Over Time (N=4)

	pK Timepoint (mins)											
	Pre dose	15 min	30 min	60 min	90 min	240 min	480 min	12h	24h	48h	72h	96h
Mean BUP Low	49	390.5	1531.75	716.75	768.75	703.25	677.75	627	443.75	225.25	196	182.75
Mean BUP High	49		1327	1776.25	1659.5	1765.5	1177.5	1019.25	932.75	488	377.75	311.5

Figure 2. High vs. Low Dose Buprenorphine SR Dosed s.c. In db Yucatan Miniswine: Group Plasma Means Over Time (N=4)



RESULTS (CONTINUED)

Table 3. Buprenorphine PK Parameters in Yucatan Miniswine: Group Mean Data (N=4)

Group	Cmax (pg/mL)	Tmax (hr)	T1/2 (hr)	Clast (pg/mL)	Tlast (hr)	AUClast (hr*pg/mL)	AUCinf (hr*pg/mL)	Vd/F (mL/kg)	Cl/F (mL/hr/kg)	MRTlast (hr)
1- BUP Low Dose	843	0.5	4.1	353	8	3090	4570	15689	2560	3.5
3- BUP Hi Dose	2260	0.5	3.1	429	8	8110	11300	7966	1780	2.9
5- BUP SR Low Dose	1920	9.1	111.8	183	96	35300	81000	326707	2020	31.8
4- BUP SR Hi Dose	2090	5.4	89.3	312	96	66100	108000	271586	2250	33.8

DISCUSSION

The 2-way crossover design used in this pharmacokinetic protocol added balance in that all animals received all combinations of drugs (treatments). Short-acting buprenorphine was present in plasma above the reported human minimally effective concentration for analgesia (0.1 ng/mL, Evans & Easthope, 2003) for at least 8 hrs for both high- & low-dose groups. Sustained release buprenorphine was also present in plasma above the reported human minimally effective concentration for analgesia for at least 96 hrs for both high- & low-dose groups. Our study clearly illustrate that these dose levels in miniswine provide sufficient plasma levels of drug for putative analgesia (>0.1 ng/mL) for at least 8 hr (short-acting BUP) or for at least 96 hr (long-acting BUP SR) periods in Yucatan miniswine. These findings are consistent with clinical in house experience on post-surgical analgesia at this CRO.

The group mean pK parameter for Tmax suggested that the higher dose BUP SR reached Tmax earlier than did the lower dose SR (5.4 vs. 9.1 hr). Two of 4 high dose SR animals exhibited considerable variability (Tmax: 1.5 & 12 hr) from the other two animals Tmax of 4 hours each.

CONCLUSION

In conclusion, these data show that these dose levels provide sufficient plasma levels of drug for analgesia (>0.1 ng/mL) for at least 8 hr (short-acting BUP) or for at least 96 hr (long-acting BUP SR). This is consistent with manufacturer's notice that buprenorphine SR provides analgesia for 72 hours in large laboratory species and also consistent with post-surgical clinical analgesia assessments in our miniswine.

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Test Tips Answers:

1. A 2. B 3. D