

# HARTLEY COMMENTARY

Summer 2008

## Welcome

Recently, I read a quotation by the famed architect Frank Lloyd Wright that reminded me of you, my clients and friends, and the care that you provide to patients. Wright attributes the price of success to “dedication, hard work, and an unremitting devotion to the things you want to see happen.” I believe each of us lives by this credo and it is my pleasure to be of service to you and your patients.



I am extremely pleased to tell my California-based clients that Hartley Medical is now better positioned to help you provide seamless care for your patients



hospitalized within Sutter Health’s extensive Northern California network. As the new preferred pharmacy for sterile compound pharmaceuticals, your hospitalized patients will now have immediate access to Hartley Medical products. This assures your patients of the same high-quality therapeutics they receive from you as outpatients – and provides you with peace of mind. Our Hartley Medical team is always working to expand our preferred pharmacy status to new hospitals and systems throughout the country. We want to do all we can to support the care of your patients while hospitalized.

In this issue of *Hartley Commentary*, I preview the upcoming 15th Annual Napa Pain Conference. I certainly hope you will join your colleagues and me at the conference, as it is an outstanding opportunity for professional development. Eric Grisby, MD, continues to have my sincere appreciation for bringing together the distinguished speakers and providing a venue for networking within our industry.

To help further your understanding of two key intrathecal medications, this issue contains a review of the hydrochloride drugs clonidine and bupivacaine. As always, I am available to you to discuss these drugs or any other questions that you may have. I can be reached via email at [wstuart@hartleymedical.com](mailto:wstuart@hartleymedical.com) or by phone at 888.671.2888.

Best regards,

*William Stuart*



## *Inside this issue*

Welcome .....	1
Clonidine: A Review .....	2
Bupivacaine: A Review .....	3
USP 797 Update .....	3
Napa Pain Conference Highlights .....	4
For Your Information .....	4

## *Quality Service for You and Your Patients*

Hartley Medical offers the latest cutoff time in the U.S. for delivery of therapeutics. Order by 4 p.m. Pacific Time for next-day delivery.

### **Contact us at:**

*Pain Staff:*

[pain@hartleymedical.com](mailto:pain@hartleymedical.com)

*Telephone:* 888 671 2888

*Facsimile:* 800 648 8550

*Website:* [HartleyMedical.com](http://HartleyMedical.com)

## Clonidine: A Review

Each issue of *Hartley Commentary* provides a discussion of one or more specific therapeutic agents that are administered intraspinally. For some readers this is a helpful review and, for others, an introduction to the drug.

### About Clonidine

The drug clonidine hydrochloride was synthesized in 1962 as a derivative of a known alpha sympathomimetic drug, naphazoline, which proved to be an effective treatment for mild to severe hypertension. Clonidine was discovered by scientists at Boehringer and marketed under the brand name of Catapres. It is classified as an alpha 2 adrenergic agonist for the treatment of high blood pressure. The drug acts centrally to inhibit sympathetic tone on systemic blood vessels and thereby reduces hypertension.

More recently, clonidine was discovered to have analgesic properties when administered intraspinally. Currently, it is administered for the treatment of chronic and neuropathic pain.

Clonidine has been studied extensively for the treatment of pain. Ackerman<sup>1</sup> published findings on the clinical effectiveness of intraspinal clonidine in 15 patients treated for either neuropathic chronic pain or cancer pain. All patients received single dose injections of clonidine. Patients reported a significant decrease in pain by at least 50 percent utilizing VAS Scale. The Polyanalgesic Consensus Conference 2007 publication recognized clonidine as a second-line drug.

K.S. Filos<sup>2</sup> conducted a double blind study of 20 patients with intrathecal clonidine. The drug was shown to be effective in the relief of secondary pain during a Cesarean section. In this study, patients were receiving 150 micrograms intrathecally versus saline, and their scores demonstrated a significant relief of pain.

### Stability

Clonidine displays stability with many narcotic opioid analgesics, as well as anesthetics, and can be administered as a sole agent for the treatment of pain via an implantable infusion pump. It is stable in various concentrations with opioid analgesics. Stability studies of long-term use of intrathecal clonidine have been documented as far back as the early 1990s. One study by Lawrence Trissel<sup>3</sup>, et al, showed physical and chemical stability of low and high-concentration morphine in combination with clonidine hydrochloride in plastic syringes. The study established the stability of morphine sulfate, 5 and 50 mg/ml with clonidine, 250-4000 mcg/ml for 60 days. At the conclusion of this study, there was no significant degradation of morphine



sulfate or clonidine hydrochloride content when stored in plastic syringes at 4°C and 23°C.

A.M. Classen, et al<sup>4</sup>, performed a study analyzing the stability of morphine, bupivacaine and clonidine within the Medtronic infusion device. This study showed the chemical stability of a combination of morphine sulfate, 50 mg/ml, bupivacaine, 20 mg/ml, and clonidine, 2000 mcg/ml. These combination solutions were placed in the reservoir of an implantable infusion pump and stored at 4°C and 37°C for 90 days.

Investigators studied each drug at various points in time, starting with day one and then assessing after 30, 60, and 90 days. High performance liquid chromatograph (HPLC) was used to determine quantitative analysis. At the conclusion of the study, all three drugs remained stable up to 90 days.

### Dosing Considerations

Clonidine is an effective drug for the treatment of pain, but therapy should be introduced slowly starting with initial doses of 50 to 100 micrograms per day. Clonidine dosing should be based upon the patient's condition, pain level, age, weight, and pre-existing conditions. Discontinuing a patient's treatment with intraspinal clonidine therapy should be done in a cautious manner. A slow titration to remove the clonidine from intraspinal infusion should also be performed. At the conclusion of therapy or after the complete withdrawal of clonidine, consider oral or topical treatment of clonidine for a period of three to seven days to prevent adverse reactions.

Clonidine has a solubility of 76.9 mg/ml at room temperature, 20°C. Clonidine hydrochloride in solution exists in a non-ionic form. This property allows it to penetrate the brain to a much greater degree; it also enables the drug to have a positive effect on tissues and receptors within the brain to relieve systemic vascular tone, thereby giving it anti-hypertensive properties. Side-effects associated with clonidine are hypotension, drowsiness and lethargy.

1 Journal of Pain and Symptom Management, 2003, Volume 26, pages 668-677

2 Journal of Anesthesiology, 1992, (77), pages 267-274

3 International Journal of Pharmaceutical Compounding, Volume 6, No. 1, January, 2002

4 Journal of Pain and Symptom Management, December, 2004

## Bupivacaine: A Review

Bupivacaine is a local and central nervous system anesthetic drug originally discovered in 1957 along with mepivacaine. German chemical engineers isolated bupivacaine from a compound called cinchocaine. Bupivacaine, which has a unique structural design, produces nerve blocks for up to eight hours and is considered a second-line drug for the treatment of pain by the Polyanalgesic Consensus Conference. This drug is often combined with opioid analgesics and, in some cases, is administered as the sole agent for the relief of neuropathic pain. When combined with other drugs such as hydromorphone, morphine, fentanyl or sufentanil there was no drug induced toxicity or complications observed.

### Key Studies Establish Stability

Many long-term studies have been performed regarding intrathecal administration of bupivacaine with clonidine or analgesics for the relief of pain. One particular study, again by Lawrence Trissel<sup>4</sup>, showed stability of low and high-dose concentrations of morphine sulfate with bupivacaine when packaged in plastic syringes. The study looked at morphine, 5 mg/ml in combination with bupivacaine hydrochloride, 2.5 mg/ml in sodium chloride 0.9%. The findings indicated that there was no loss of morphine or bupivacaine concentrations in the samples that were stored at 4°C and 23°C for 60 days.

Additionally, Trissel studied the stability of morphine sulfate, 50 mg/ml and bupivacaine, 25 mg/ml also stored at 4°C and 23°C. This study also concluded that there was no loss of potency for up to 60 days. In another study by K.R.Hildebrand<sup>5</sup>. et. al., the objective was to show that the drug was effective for relief of pain when administered through an implantable drug delivery device. In this particular study, commercially available bupivacaine at 7.5 mg/ml was incubated at 37°C for 12 weeks within an implantable infusion device. It was revealed that concentrations remained greater than 96 percent in the implantable drug delivery systems.

Stability of bupivacaine is well documented in many other publications. A December 2004 article in the *Journal of Pain and Symptom Management* showed bupivacaine hydrochloride, 20 mg/ml, morphine sulfate, 50mg/ml and clonidine, 2mg/ml to be stable within an implantable infusion device for 90 days.

### Recommended Dosing

At Hartley Medical, we recommend that the starting dose of bupivacaine be maxed out at approximately 1 to 5 milligrams per day. The upper doses of bupivacaine should not exceed 15 milligrams per day. However, various pain physicians in the western

United States have utilized bupivacaine for the treatment of both cancer and non-cancer pain, with doses ranging from 30 to 40 mg/day.

### Pivotal Role as Anti-Microbial

A very significant study of bupivacaine was published by Per H. Rosenberg, M.D., and Olli V. Renkonen<sup>6</sup>. The authors examined the anti-microbial activity of bupivacaine and morphine against 10 strains of bacteria. Bupivacaine was studied with various microorganisms, in particular *E. coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* and epidermis. The concentrations of bupivacaine examined were 0.5 mg/ml and 1.25, 2.5, and 5 mg/ml. Bupivacaine in concentrations of 2.5 mg/ml inhibited growth of *Staph. epidermis* strain and *Staph. pyogenes* as well as *Streptococcus pneumoniae*. Morphine showed no growth-inhibiting activity against bacteria.

The study's bottom line is that bupivacaine spurs anti-bacterial activity against common pathogens. More significantly, bupivacaine has specific inhibitory effects on *Staphylococcus aureus* and *Staphylococcus epidermis* commonly found on human skin.

Bupivacaine has a maximum solubility at 40 mg/ml at room temperature. However, bupivacaine's solubility increases with temperature; therefore, bupivacaine in concentrations exceeding 40 mg/ml can be stable in an implantable infusion device at 37°C. However, bupivacaine 40mg/ml stability may be compromised when combined with other drugs within an implantable infusion device.

<sup>4</sup> *ibid.*

<sup>5</sup> *The Clinical Journal of Pain* (17): 239-244 2001

<sup>6</sup> *Anesthesiology*, Vol. 62, pages 178-179, 1985

## USP 797 Update

At Hartley Medical, we strive to maintain the optimal environment for compounding sterile drugs. Long before the United States Pharmacopeia (USP) Chapter 797's guidelines for sterile compounding were introduced, we initiated an effective environmental monitoring program that incorporates advanced technology.

The previous issues of *Hartley Commentary* discussed our means of monitoring microbial air quality (use of passive plates during the last decade and the augmentation of this practice with an active air-sampling program) and our comprehensive air quality management program that monitors for very small dust particles, 0.3 to 5.0 microns in dimension, which can transport bacteria. (*continue to page 4*)

# The Napa Pain Conference Provides Unparalleled Opportunities

I certainly hope that all of you will consider joining us at the October 3-5, 2008 15th Napa Pain Conference with Neuromodulation and Wine in Napa Valley.

A faculty of internationally known physicians specializing in neuromodulation and pain management will present at the gathering. Keynote speakers include Elliot Krames, MD, editor of *Neuromodulation* and one of the founders of The National Pain Foundation, as well as Eric Grigsby, MD, founder and medical director of SpectrumCare Pain Treatment Center in Napa.

Lectures and workshops will cover such topics as the neurobiology of pain; chronic cancer pain; back pain; neuromodulation of the brain for stroke and stroke recovery; spinal cord stimulation for angina; deep brain stimulation for pain, movement and psychiatric disorders; spinal cord and peripheral nerve stimulation; and motor cortex stimulation. The conference is targeted to physicians, physician assistants, and allied healthcare professionals.

Michelle Byers of MB Business Consulting will again direct a series of business management workshops, including sessions on successful billing and coding, avoiding HR issues, and effective public relations. I attended her session last year and learned a lot.

#### Medical faculty members include:

Eric Grigsby, MD  
Elliot Krames, MD  
Allen Burton, MD  
David Caraway, MD, PhD  
Lisa Stearns, MD,  
Giancarlo Barolat, MD

Jamie Henderson, MD  
Leo Kapural, MD  
Robert Levy, MD  
Phil Starr, MD  
Lawrence Poree, MD

This year the program will also include a Weekend Wine College, with a focus on the science of winemaking, the art of pairing food, and wine-blending techniques. Friday evening will feature a special dinner in the Wine Caves at Pine Ridge Winery.

Due to the popularity of the conference, I suggest you register as soon as you can by contacting [Michellebyers@roadrunner.com](mailto:Michellebyers@roadrunner.com) or at 415-518-5391.

## For Your Information

Medicare has made a carrier change for California, Nevada and Hawaii. Starting this summer, the new Medicare intermediary for these states will be Palmetto GBA of Columbia, S.C. Its website is: <http://www.palmettogba.com>. At this time, we are unsure as to billing procedures and reimbursement rates. As they become available, we will include pertinent information in this newsletter.

## USP 797 Update (continue from page 2)

In this issue, I want to discuss equipment associated with USP 797 for the elimination of bacteria and inanimate microbial or inanimate particles for appropriate sterile compounding. USP 797 requires that pharmacies compound sterile products within a Class 100 environment. Classification 100 is an old standard of the Federal 209-E, stating air classifications of Class 1 through 1,000,000, calibrations and defining air cleanliness. Therefore, a Class 100 Laminar Air Flow Workbench (LAFW / IV Hoods) is defined as providing air quality with no more than a hundred 0.5 micron-size particles to be contained within a cubic foot of air. The ISO 9000 Publication has now revised those past standards, defining the new classification of ISO with a number between 1 and 10. The ISO standards stipulate that Class 100 filtration devices represent an ISO classification of 5. With regard to ISO 5 classification, the concentration of air particles cannot exceed 3,520 per cubic meter. The two standards are differentiated through conversion of particle content to the metric system.

At Hartley Medical, we utilize Class 10 IV hoods that deliver a filtration of no more than 10 particles per cubic foot. The average compounding pharmacy is utilizing Class 100 LAFW/IV Hoods. Our greater filtration capacity provides an optimum environment for sterile compounding and exceeds federal standards.

In addition, our IV hoods are tested for microbial and non-viable air particles. USP 797 states that sterile compounding pharmacies will certify the IV hoods every six months. However, at Hartley Medical we certify our IV hoods every 120 days to closely monitor their function and detect any problems in filtration sooner. For microbial testing we employ a Bioscience SAS 100 Air Sampler. This device will draw 1,000 liters of air across a growth medium plate, detecting the microbial load that could exist in the IV hood area.

At Hartley Medical, we are ahead of both federal and state guidelines affecting sterile compounding. Please review the Polyanalgesic Consensus Conference publication discussing pharmacy compounding and compare its standards with those of Hartley Medical.

**Disclaimer.** The information contained in this publication is provided "as is" and without warranty, express or implied. Hartley Medical assumes no responsibility for any damages of any kind resulting from use of the products and procedures contained herein.

