Introduction to Enduracaine™ PAT

Background, Development, and Clinical Experience

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Background and Overview

According to Miller's **Anesthesia**, the practice of anesthesiology is the rendering of a human being insensible to pain while maintaining and promoting the life functions and muting or overriding noxious responses to painful stimuli. From the time that earliest people tried to use plants and alcohol to alter responses to pain, the search for a single agent that can do all these things has been a continuing theme in the practice of medicine. With the introduction of ether in the nineteenth century, it was thought that the goal was attained.[12] Unfortunately, no single pharmaceutical agent is a perfect anesthetic, so research has continued to attempt to identify the characteristics of the perfect agent.

As in all human knowledge endeavors, there have been cycles of fashion in approach to the problem. Anesthesia consists generally of four parts: Relief of pain; promotion of life functions; attenuation of noxious reflexes; and, frequently, the provision of amnesia for the experience. Almost simultaneously with the development of ether, efforts began to render parts of the body insensible with cocaine, the earliest known local anesthetic.[13] The intellectual tension between regional anesthesia with local anesthetics and general anesthesia resulted in two schools of research and practice that were often seen as competitive rather than complementary.[11] Techniques were touted for their "purity" and a jaundiced eye was cast on proponents of one school attempting to integrate techniques of the other. But as cycles go on and thought processes alter, the

complementarity of regional anesthesia techniques combined with general anesthesia techniques has slowly evolved.[25]

The tremendous injury toll during the second World War brought redoubled efforts in the development of regional anesthesia techniques as the general anesthesia techniques of the time were poorly suited to the serious trauma coming from the battlefields, with many deaths occasioned using newly available agents such at thiopental sodium, also called pentothal. This barbiturate made possible the rapid induction of general anesthesia, but at a cost of a severe burden on physiology dealing with major trauma. Deaths were abundant.[12] This did serve as a driver to the development of regional anesthesia techniques. After the war, these techniques of nerve block, epidural, and spinal anesthesia continued to develop. Again, anesthesiology practices tended to favor one set of techniques over the other rather than seeking complementarity. General anesthesia became the ascendant technique, as newer agents minimized the disadvantages of agents like ether and pentothal.

The introduction of powerful narcotics in the 1980's seemed to point to the "purer" technique that had always been envisioned. Unfortunately, the tremendous successes of drugs such as fentanyl overshadowed the negative features of their use. Rapid accommodation (tachyphylaxis) by the human body to the effects of the narcotics created issues in post-operative pain management that were addressed with prolonged narcotic therapy, creating issues of dependence and adverse physiologic responses (such as the slowing

or elimination of normal bowel motility), which impacted recovery from the ever more extensive surgical procedures that have become possible as technology has improved and advanced.[23]

As well, initiatives such as the demands by accrediting organizations that patient pain perception be treated as a "fifth vital sign", in addition to the objective signs of temperature, heart rate, blood pressure, and respiratory rate, contributed to an explosion in the use of narcotic drugs in the perioperative period, despite the known and emerging adverse consequences of the chronic use of opioids, including delays in the recovery process of patients undergoing bowel resections.[1] It is into this situation that the programs for "enhanced recovery after surgery", or ERAS, began to be developed.[19] These programs looked at the development of multiple approaches to the management of post-operative pain issues, rather than relying solely on opioids, with the issues attendant to their use. Led by colorectal surgery interests, then joined by anesthesiology specialists, integration of multiple techniques and agents, with a goal of dramatically reducing opioid use, began to develop.

Concomitant with these developments, an opioid "crisis" bloomed in the United States, with record numbers of prescriptions for opioids being written and a vast illegal drug market developed. All of this is reported near daily in the national media. Medicaid, which provides health insurance services for millions of Americans, reports that 12% of their beneficiaries have a substance abuse issue.[1] The costs for this epidemic nationally, according to the Department of Health

and Human Services, is estimated at $55 billion annually in health and social costs, with another $20 billion estimated for emergency and inpatient care for opioid poisoning. Indeed, on the average day in the US, more than 650,000 prescriptions for opioid drugs are written, the majority being for acute pain situations.[23] The most common acute pain situation is in the perioperative period.

While it is impossible to ascribe a single cause to a complex and multifactorial problem, it seems intuitively obvious that many people gain their initial exposure to opioids as a result of a medical intervention.[5] In surgery, which by its nature produces a painful condition, there is abundant research which demonstrates that patients whose pain is well-controlled in the immediate perioperative period go on to consume dramatically less pain medication than patients who do not receive excellent immediate analgesia. Indeed, perioperative development of narcotic dependence is probably both under-recognized and under-treated.[25]

For the past four decades of my own clinical practice, I have seen the shift from combining regional anesthetic techniques as a routine part of an anesthetic intervention, to relying almost totally on narcotic analgesics, to a resurgence of interest in regional anesthetic techniques as an important pain control modality. With the development and availability of ultrasound-guided regional anesthetic techniques, there has been both increased interest and increased success with all types of peripheral nerve blocks.[26]

Health Facts, an online reviewer of healthcare in the United States, reports that there were some 50 million surgeries in the US in 2009, the last year for which comprehensive numbers are available.[24] Based on even a modest increase of 2% per annum, that would bring us to over 60 million operations in the US by the current date. Estimates range closer to 70 million. With the newly insured millions coming to the healthcare marketplace due to changes in Federal insurance regulations, that number seems unlikely to decrease soon.[12,25]

Of the more than 60 million surgical procedures annually in the US, again based on my own clinical perspective as an anesthesia provider for nearly 40 years, there is a vast unmet need for a low toxicity, long-duration local anesthetic to increase the utility of regional anesthetic techniques. My own professional estimate of the number of surgeries in which an effective regional anesthetic technique can be combined with other anesthetic modalities to achieve excellent post-operative pain control without undue reliance on opioids is between 50 and 70% of all operations. The number of regional anesthetic techniques is large and growing.[7,8,14] The continuing decline in the price for high quality ultrasound instruments will make these available to every size of clinical practice. Regional anesthetic techniques have a very long history of safety and efficacy. It has been primarily the technical aspects of block placement that has hindered the general acceptance of many of these techniques in a wider practice setting.[3,4]

Additionally, a limiting factor in the use of regional anesthetic techniques has been the absence of a very long-acting local anesthetic, which also does not exhibit undue toxicity.[22] Unfortunately, the primarily available long-acting local anesthetic is the drug bupivacaine, in various incarnations. This drug exhibits serious and until recently, untreatable, cardiac toxicity which can lead to death, in a dose-dependent manner. Unfortunately, the treatment introduced for treating bupivacaine toxicity is not 100% effective. There have also been multiple attempts to reduce toxicity by reconfiguring the bupivacaine molecule, resulting in drugs such as ropivacaine and levobupivacaine, which, while less toxic inherently, also do not have adequately prolonged duration of effect.[13] This problem continues to be the focus of vast effort, largely centering on reconfiguring bupivacaine in some manner.

For toxicity reasons, bupivacaine has not been recommended for use in children under 12 years of age, and only with caution in older children.[14] This has changed very recently with FDA approving a pediatric indication for liposomally encapsulated bupivacaine, despite the highly variable research results into the product.[34] The small therapeutic index (the difference between the effective dose and the lethal dose of a medication, expressed as a multiple of the effective dose) for bupivacaine has hampered the development and application of regional anesthetic techniques overall.[13, 16] One of the reasons for the great popularity of ultrasound guidance in regional anesthesia is that it becomes possible to limit the volume of drug used in regional anesthesia, to counter the extreme cardiac toxicity associated with bupivacaine in larger

doses. The tradeoff for use of smaller volumes of drug is shorter duration and less generous coverage of the relevant nerve supply with blocks such as the transversus abdominus plane (TAP) block of the abdomen.[2,6,9]

Several drug developers (including Pacira, Heron, Durect, and Flexion) have developed or are developing novel drug delivery applications to enhance the duration of regional anesthetic techniques. In the case of Pacira, this has been to treat bupivacaine to turn it into a liposomally encapsulated moiety, with a slow delivery to minimize the toxicity issues. Durect has an acetate-based moiety to achieve the same result. Unfortunately, the parent compound is not rendered less toxic, merely less available. And with the Pacira product, mixing the product with another local anesthetic other than more bupivacaine can destroy the liposomal encapsulation, thereby increasing exposure to high levels of bupivacaine, according to the package insert for the product.

As a matter of clinical practice, such mixing of local anesthetics to combine the benefits of speedier onset with a slower onset product is extremely common in clinical practice. Probably the most used local anesthetic infiltration (whether periarticular or in wound margins), in the US and Europe, is a combination of lidocaine (a very benign local anesthetic) with the much more toxic bupivacaine.[10] One of the drawbacks to delayed release moieties is that it is very difficult to use a very slow-release drug product to establish local anesthesia without partnering it with a more rapid onset agent. One way to deal with this with the Pacira product has been to mix their product with regular

bupivacaine injection.[34] While this is said not to disrupt the liposomal structure, it does increase the total exposure to bupivacaine. The adverse toxic properties of the underlying bupivacaine moiety are present in each of the several available or proposed reformulations of bupivacaine.

The major impactor in the delivery of surgery care has been the development of the ERAS protocol—enhanced recovery after surgery. Having been developed initially for major abdominal bowel procedures, the protocol features are spreading to bariatric, cardiovascular, and other surgical specialties. The benefits of ERAS, including the ability to resume normal nutrition quickly, and allowing the avoidance of other physiologically adverse effects, continues to expand the need for effective regional adjuncts.[2,3,4] Studies of the ERAS protocol have been striking in the reduction in hospital stay, morbidity, overall cost, and patient satisfaction. There is now a vigorous national movement to ever greater acceptance of the ERAS regime.[5,6]

Development

Concomitant with the implementation of ERAS, the use of the TAP block (transversus abdominis plane), and other plane blocks, have grown in popularity, for their ability to reduce the consumption of narcotics in the post-operative period. The data are clear that these blocks are major contributors to improved patient outcomes in those having major abdominal procedures. The limiting feature has been the duration of effect achievable with the anesthetic

agents currently available. Because of the nature of the nerve distribution in the tissue plane wherein the block is placed, the volume of drug limitations associated with bupivacaine products has negatively impacted the ability to cover the broadest levels of innervation to the affected structure.[9]

It was in this atmosphere that several years ago we became motivated to investigate safer alternatives to ever-greater quantities of bupivacaine in the ERAS protocol. We looked at several commonly available local anesthetic agents and at the common intraoperative practice of mixing shorter and longer acting and faster and slower onset agents in combination with each other to produce:

1. Greater safety
2. Longer duration of effect
3. Greater volume of agent that could be employed
4. Minimal adverse effects on cartilaginous and other body structures

The drugs we reviewed included several short- and long-acting local anesthetics.[11,12,17] By comparing the physical and physiological properties of the local anesthetics lidocaine and tetracaine, we hoped to gain quick onset and long duration with a combination of two very safe drugs, which have been in the clinical setting since the end of World War II. There are many decades of experience behind these agents and their safety profiles are outstanding.[18] One of the significant clinical features of tetracaine, which has been used for decades for spinal anesthesia, is that adding epinephrine to that drug

intrathecally appears to significantly extend its duration of effect. As well, it is known that adding epinephrine to lidocaine significantly increases its safety margin (raising the toxic dose from 3mg/kg to 7mg/kg).[15] Optimal concentrations of epinephrine are already known and for local anesthetics, that concentration appears to be a 1:250,000 solution.[10]

The lidocaine product is stable at room temperature. The tetracaine product is a refrigerated item, in its aqueous form. Epinephrine, USP, is also stable at room temperature, alone and in solution with lidocaine.[29,30,32] There is a lyophilized preparation of tetracaine, called niphanoid tetracaine, which is no longer manufactured in the US, but which is stable at room temperature. All three drugs are somewhat light sensitive. Lidocaine is an amide-type local anesthetic and tetracaine is an ester-type local anesthetic. The aqueous tetracaine product is mildly thermolabile, undergoing spontaneous ester hydrolysis at higher temperatures (>25C), with principal degradation products of para-aminobenzoic acid and diethylaminoethanol. On prolonged standing at higher room temperatures, tetracaine solutions have the disadvantage of yielding small quantities of precipitated 4-n-butylaminobenzoic acid as a hydrolysis degradation product, crystals of which cause turbidity of the solution.[17,18]

Tetracaine undergoes ester hydrolysis by plasma pseudocholinesterases with the degradation products excreted in the urine. The liver metabolizes lidocaine rapidly, and the kidneys excrete metabolites and unchanged drug.

Biotransformation of lidocaine includes oxidative N-dealkylation, ring hydroxylation, cleavage of the amide linkage, and conjugation. N-dealkylation, a major pathway of biotransformation, yields the metabolites monoethylglycinexylidide and glycinexylidide. The pharmacological/ toxicological actions of these metabolites are similar to, but less potent than, those of lidocaine. Approximately 90% of lidocaine administered is excreted in the form of various metabolites, and less than 10% is excreted unchanged. The primary metabolite in urine is a conjugate of 4-hydroxy-2, 6-dimethylaniline.[12]

Both local anesthetic products are mild bases, with lidocaine having a pKa of 7.8 and tetracaine having a pKa of 8.2. The pKa of epinephrine is 8.5. The drugs are generally not reactive with each other in aqueous solution. A combination product in an aqueous format would thus likely require refrigeration to maintain stability of the tetracaine moiety. The adjustment of pH for storage of the tetracaine product, as formulated by Akorn, is to 3.5-5.5, per its product information. This is coincidentally the optimal storage pH for the lidocaine/epinephrine product, as formulated. While we know that the FDA generally favors single moiety drug products, the most used long-acting local anesthetic product in the US is bupivacaine, which is a racemic mixture (also available with epinephrine), so we were not embarking on new ground with the product.[27,28] As well, as we have stated, it is typical medical practice to mix shorter and longer acting local anesthetics to achieve quicker onset and longer duration at the point of use in the operating room or other treatment setting.[31]

Local Anesthetic	Potency and Lipid Solubility/Duration of Action
AMIDES	
Bupivacaine and levo-Bupivacaine	4/4
Etidocaine	4/4
Lidocaine	2/2
Mepivacaine	2/2
Prilocaine	2/2
Ropivacaine	4/4
ESTERS	
Chloroprocaine	1/1
Cocaine	2/2
Procaine	1/1
Tetracaine	4/3

1= least; 4= greatest

pKa of Local Anesthetics

Local Anesthetic	pKa
AMIDES	
Bupivacaine and levo-Bupivacaine	8.1
Etidocaine	7.7
Lidocaine	7.8
Mepivacaine	7.6
Prilocaine	7.8
Ropivacaine	8.1
ESTERS	
Chloroprocaine	9.0
Cocaine	8.7
Procaine	8.9
Tetracaine	8.2

(After Miller et al)

Further, it is well known that mixtures of local anesthetic drugs are no more toxic than their parent compounds. (And no less toxic, in the case of the various bupivacaine congeners).[15] Clinical judgment and trial with the known and approved substituents, compounded on site, led us to the combination product which we call Enduracaine.™ PAT This product is a mixture of three drugs: lidocaine, tetracaine (2-(Dimethylamino)ethyl p-(butylamino)benzoate monohydrochloride), and epinephrine (L-adrenaline). The ratios are as follows: 0.4% lidocaine, 0.2% tetracaine, and 1:250,000 epinephrine. We have prepared the product ourselves as follows: For every ten milliliters of resultant product, we used 8 ml of 0.5% lidocaine with 1:200,000 epinephrine, NDC 0409-3177-01, which is packaged as a 50 ml vial. The balance is 2 ml of 1% tetracaine per 10 ml resultant, which is provided as a 2 ml ampoule, NDC 17478-045-32.

These solutions do not contain preservatives such as methylparaben, rendering them suitable for use in the epidural space and for every type of nerve block or wound infiltration. Point of use mixing in the operating room is a common, indeed a decades old practice, usually using a mixture of bupivacaine and lidocaine. Adding epinephrine to solutions is commonly done in the operating room as well and literature supports this as a reasonable practice.[10]
We have standardized a mixture of the agents to obtain the longest duration of effect with a minimal side effect profile.[29]

Given the performance and benefits we have observed clinically, Ventis Pharma has decided to make an off-label use version of Enduracaine™ PAT

available to answer what we believe is a pressing need for a low toxicity, high efficacy product in the American clinical setting.

To review, tetracaine is an amino-ester class local anesthetic. Clinicians have used it for a variety of purposes in the US since the early 1930s, but its most common use today is as a topical ophthalmic anesthetic for short procedures on the surface of the eye, as well as the ears and nose. The primary injectable role has been for spinal anesthesia, another indication, and for which it has been employed in the US for some seven decades with a notable safety record. The World Health Organization (WHO) lists tetracaine as an essential drug. It is relatively inexpensive in comparison to other local anesthetic agents. Even though tetracaine has never been approved by the US FDA for use by injection, due to its usage predating the modern FDA, tens of millions of spinal administrations have been carried out safely for many, many years. Toxic doses are generally thought to be between 1.5 and 3.0 mg/kg, but adverse toxicity is rarely seen. Those with sensitivity to para-aminobenzoic acid derivatives may be susceptible to allergic reactions, but such reactions are relatively uncommon.[15,18]

Allergies to local anesthetics are rare and are more common with ester-type local anesthetics than with amide types such as lidocaine. More often, the allergic response is caused by a metabolite, preservative, or unrelated adjuvant substance. At times, an apparent allergic reaction can be brought on by anxiety. Lidocaine was approved as a local anesthetic in the US in November

1948. It has an enormously long record of safety, and efficacy. It is prescribed well over 2 million times a year in the US. It is often prescribed in a formulation combining epinephrine. The maximum recommended dose is up to 7mg/kg with the lidocaine/epinephrine combination. Toxicity is most often seen with unintentional injection of a therapeutic amount into the circulation, rather than into tissues, in attempts to produce local anesthesia.[26]

Due to the inherent safety, efficacy, and versatility of these two local anesthetics, combining them to produce a compound that offers quick onset of local anesthesia and long duration, has seemed prudent. A combination of low dose lidocaine hydrochloride with epinephrine, USP with low dose tetracaine hydrochloride USP, have produced a product that offers many advantages over any local anesthetic product containing the very toxic local anesthetic bupivacaine.[11] We call this combination product Enduracaine™ and have obtained very long duration local anesthesia with minimal motor effects and very minimal toxicity or other intolerance to the combination. The Enduracaine™ product consists of 0.4% lidocaine with 0.2% tetracaine and 1:250,000 (4mcg/ml) epinephrine.

We have consistently found that the product produces short acting motor effects and very long pain-relieving effects in all types of procedures and with all types of nerve and plane blocks as well as when used for local infiltration. The very low toxicity and minimal side effect profile allows the prescriber to use up to 1.5 ml/kg of the Enduracaine™ product, permitting a maximum dose that does

not exceed recommended guidelines for maximal dosing. Given that tetracaine is immediately metabolized upon entry into the circulation, issues for combined toxicity of the two agents have not been seen, in our own series of over 5000 patients who have received the product to date.

We can state, with due consideration for FDA guidance regarding claims of opioid sparing effects for local anesthetics, that this product is apparently extremely safe, extremely effective, and far longer acting than any of the long-acting local anesthetic products currently on the market. Because of the very low toxicity of the components, we have used it confidently in children over the age of 12 with excellent results and no evident problems. We have not used the product in neonates and very young children, due to the necessity for normal liver function and enzyme synthesis to metabolize ester-type local anesthetics. We have seen significant decreases in both opioid use overall and decreases in length of hospital stay for procedures such as bowel resections in patients who have received Enduracaine™ transversus abdominis plane blocks for that procedure. In sum:

a. Very low toxicity per prescribing information for lidocaine and tetracaine
b. Effective in nearly all local and regional anesthesia applications (not recommended for topical use or for spinal anesthesia)
c. Can be used for epidural anesthesia
d. Very long-acting pain relief when used as directed. (There is no virtue to trying to use lowest possible volume of drug to produce local anesthetic block since toxicity is so low. This allows adequate volume for all regional

anesthesia and local infiltration applications, unlike all bupivacaine containing products.[20,21]

e. Adequate dosing for volume/plane blocks thus is not compromised by toxicity issues.
f. Cost-effective since no other drug must be mixed with Enduracaine™ PAT to initiate and to maintain local anesthesia, unlike, for example, with Exparel™, which is not a complete product in and of itself. It is priced at 60% less than liposomally encapsulated bupivacaine.
g. Easy to mix and use.
h. Decreases substantially the need for supplemental pain relief measures because of longer duration of effect.
i. Incidence of allergy or adverse reaction is extremely low clinically.
j. FDA approval for an easier to use kit and specific indications is in process, though use of existing USP FDA accepted products is legally permissible for off-label applications.

As of summer 2021, the product will be available in a 50 ml kit, comprised of a 50 ml vial of 0.4% lidocaine and 0.2% tetracaine. The package includes a syringe containing 0.2mg of 1:1000 epinephrine, USP, to be added just prior to use. While this version requires refrigeration, the bag-type packaging system awaiting FDA acceptance will be shelf stable from minus 20 C to plus 50 C. That version is expected to be approved by late 2022 (Ventis correspondence).

Clinical Experience

In our principal clinical venue, a colorectal and general surgeon, began to use the product on patients undergoing bowel resections. His results have been interesting both for near elimination of post-operative opioids, and for decrease of a day and a half of the average length of stay for colon resections. The surgeon was able to use a significantly larger volume of Enduracaine™ PAT in his surgeon-administered TAP blocks[21] because of the much greater safety margin than that of bupivacaine. His observed duration of effect with the TAP block has been generally greater than 36-48 hours and his major abdominal surgery patients have nearly eliminated the use of opioids post-operatively.[20,21] We believe that the ability to use at least 50 ml of the combination product per side versus 30 ml in toto of the bupivacaine standard allows for greater coverage of the nerve distribution of the abdominal wall. The increased duration of action is in accordance with expectations, given the relative potencies of the substituent drugs. The place for TAP block in intraabdominal surgeries is extremely well established clinically.[9,19]

This surgeon's high degree of satisfaction with his clinical sample led an orthopedic surgeon colleague, to employ the combination for local infiltration of the periarticular areas of patients undergoing total knee arthroplasty (TKA). This infiltration technique accounts, by the way, for approximately 70% of the local analgesia employed for TKA, with only a minority of knee replacement

patients receiving one or more of several other regional anesthesia techniques, which may involve blocks of the femoral, saphenous, peroneal, sciatic, or obturator nerves, in various combinations.[26]

The third experience of our general surgeon colleague is in pediatric (>12 years) patients undergoing appendectomy. These patients also did very well with regional blockade after operation. Given the large safety margin of the substituents in the drug product, and that the local anesthetics have been used in the pediatric population for decades, we felt confident that the product posed far less risk than bupivacaine would have posed, and that the opportunity to achieve excellent pain relief without opioid use justified reliance on regional anesthetic techniques. Obviously, while these results are anecdotal, they come from a general surgeon and an orthopedic surgeon, both of whom are extensively experienced. As the product is made available, we hope to see more formal studies undertaken to substantiate these findings.

I have myself used Enduracaine™ PAT successfully for several years while developing the product, for every type of regional anesthetic application, including epidurally and for major extremity blocks, without any apparent adverse effects on any patient. Duration of effect is a function both of drug combination AND volume of drug deposited in the requisite area. We have had excellent duration (generally greater than 36 hours) with all types of blocks. Results summaries are most interesting for what they do not describe: there is no evidence of any adverse effect of the use of the Enduracaine™ PAT product.

While the physicians and anesthetists in our group did not expect to find any particular result, the hope was that extended duration of pain relief would be realized to the extent that other physicians in our clinical setting would consider adopting the product for its prolonged duration of effect. This is indeed what we observed.

Head-to-head study with bupivacaine 0.25% plain remains necessary since this is the most used concentration and drug currently being employed. Even when bupivacaine 0.5% is employed, it is typically diluted half and half with lidocaine products, resulting in a 0.25% concentration. Liposomal bupivacaine was approved on the strength of a comparison with saline. In our own practice we see, with Enduracaine™ PAT and a larger volume of drug (e.g., up to 50ml per side for most plane blocks), that the duration is greater than 36 hours generally. We have seen the same duration more than 36 hours with TAP blocks.

Surgeon satisfaction was high, to the extent that users were unwilling to return to previous mixtures after experience with Enduracaine™ PAT, but the reports are most remarkable for the higher numbers of patients being able to be discharged on the next post-operative day, compared to those receiving other local anesthetics.

Summary

While our results are admittedly non-random and non-blinded, the conclusion was that the surgeons viewed the mixture as a significant improvement over their prior techniques, for patient satisfaction, decreased use of opioids, and faster ambulation post-operatively. One of the orthopedists did use a combination of bupivacaine and tetracaine on some of his patients but his own conclusion was that the combination was not superior to Enduracaine™ PAT. While the orthopedist accumulated a large amount of observational data, albeit anecdotal, it is very interesting that he found the lidocaine, tetracaine, and epinephrine combination preferable for his periarticular infiltrations and continues to use the combination for that purpose.

Enduracaine™ PAT appears to be met with approval by the surgeons who use it. The same is true with my own and my anesthesia colleagues' experiences in anesthesia using the product for regional blocks. The combination of predictability, duration, efficacy, and safety is not matched by another product currently available for use in the United States. The product is safe enough to be used in older children up to the opposite extreme of age. It can be utilized by infiltration periarticularly, infiltration into soft tissue, and in every type of regional block, including in the epidural space.

Enduracaine™ PAT produces excellent sensory blockade with only moderate motor blockade. The sensory block routinely exceeds the motor block. In our initial planned packaging, the drug will be provided in a ready to use, 50 ml

single use vial of aqueous solution. We believe that a safe dose of the product is up to 1.5 ml per kg of body weight. Our existing patient experience reflect the use of the product in doses up to that amount. We are proceeding with developmental work on a lyophilized tetracaine product with a lidocaine and epinephrine diluent in a single unit for easy reconstitution, which will provide room temperature stability for storage.

Commercial pricing for the product will be far more affordable than for the various bupivacaine products either on the market or upcoming to the market, according to Ventis Pharma, who expect to be priced approximately 60% less costly overall than the cost of liposomal bupivacaine. There is no new or untried technology involved in the creation of the product and the substituents are not inherently costly, despite tetracaine solution prices having soared due to having only a single manufacturer in the marketplace. Lyophilization is not a new technology and, indeed, formerly in the US until 2010, a lyophilized version of tetracaine was available. The manufacturer discontinued that product because of decreasing demand for its use in spinal anesthesia, then the most common application of tetracaine by injection.

The benefit to patients in terms of decreased opioid use, long duration of pain relief, minimal toxicity, and the early ability to ambulate, participate in pulmonary hygiene and physical therapy and experience a shorter hospital stay combine to recommend the use of the product. The decades long history of safety and efficacy of the substituents is outstanding and unlikely to produce

any hidden surprises in wider patient application. Having done many hundreds of blocks with the product and achieved excellent duration of effect with a vanishingly small side effect profile, significant adverse effects appear to be unlikely. Objective clinical study of Enduracaine™ PAT appears likely to support the large body of anecdotal and historical evidence behind the substituent's safety and efficacy.

Footnotes:

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