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CME ARTICLE

Three Therapies for the Scrap Heap: Sarapin, Vertebroplasty, and Caudal Epidural for Chronic Low Back Pain

Clifford Gevirtz, MD, MPH

Learning Objectives: After participating in this activity, the physician should be better able to:

1. Analyze the evidence regarding the use of Sarapin as an additive to nerve blocks.
2. Evaluate the efficacy of vertebroplasty for osteoporosis-related vertebral fractures.
3. Assess the efficacy of caudal epidural corticosteroid injection for chronic lumbar radiculopathy.

There is a progression of knowledge and technique throughout medicine, in that therapies are discovered, popularized, challenged, and then discarded as outmoded. Many therapies that were the cutting edge 50 years ago are now considered obsolete or outright dangerous, such as insulin shock therapy for depression.

In This Issue

The key in deciding which therapies should be abandoned is the randomized controlled trial (RCT). A properly performed RCT has the power to separate out the problem of observer bias that often accompanies new techniques. It provides the data we need to discern whether a new technique or drug is truly superior to the standard approach.

In this article, we review 3 therapies that have long been a staple among pain specialists. Careful review of their efficacy, however, calls into question whether they should continue to command a place in our armamentarium against pain.

Sarapin

Sarapin (High Chemical Company) is a suspension of powdered *Sarracenia purpurea* (pitcher plant) in alkaline solution. More than 70 years ago, it was observed to be of value in relieving pain of neuropathic origin. The drug was used in a series of several thousand cases, and it was claimed that the preparation acted through its effect on sensory nerves, relieving neuralgic pain without

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change in skin sensation and while having no effect on motor nerves.

Bates and Judovich[1] state: "In no instance has there been any motor weakness after injection of peripheral nerves, nor loss of touch, pressure, pinprick, and temperature sensibility."

Early experiments that used controls with procaine, saline, and water showed prolonged duration of effect in favor of the pitcher plant preparation. Toxicity tests revealed that it was harmless in clinically used concentrations, and no evidence of tissue coagulation or sclerosis could be demonstrated.

As stated by Bates,[2] "Controls of [procaine], saline and water were used, and the results recorded. The key numbers of these various ampules were changed several times, and on analysis in each series, it was found that Sarapin produced prolonged relief in contrast to fleeting or negative results with the other solutions. In a number of instances, patients who had been injected with [procaine], with only a short period of relief of pain, obtained prolonged relief by a subsequent injection of pitcher plant distillate."

In an attempt to demonstrate the effectiveness of Sarapin in prolonging the action of neural blockade with improved pain relief, Manchikanti et al[3] conducted a prospective, continuous, double-blind trial including 500 consecutive patients undergoing either caudal epidural injections; cervical, thoracic, lumbosacral facet joint nerve blocks; and/or intercostal nerve blocks, or a combination thereof. Each patient was treated with 2 blocks with the treatments that were double-blind and prospective. Each patient acted as his or her own control.

The results were drawn from 500 patients who received a total of 828 treatments, once with Sarapin and once without. There

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were no significant statistical differences between these groups, either with pain relief measured by numeric pain scale or duration of significant relief defined as 50% or greater relief.

In a more basic science approach, Harkins et al[4] sought to determine the local anesthetic efficacy using an animal model, the horse, in which they tested Sarapin in a unilateral abaxial sesamoid block model at 2 dose levels: 2 and 10 mL per site.

Although many patients and practitioners have found some measure of relief with Sarapin, a rigorous clinical trial and basic science evaluation do not find any merit in its use.

Cutaneous pain was induced with a light/heat lamp, and analgesia was assessed by measuring the hoof-withdrawal reflex latency period. Neither dose of Sarapin altered hoof-withdrawal reflex latency in this experimental model tested over a 2-week period. On the basis of the demonstrated efficacy of this local anesthetic model, it seems clear that Sarapin has no significant classical local anesthetic actions in the horse, and probably not in other species either.

Clearly, although many patients and practitioners have found some measure of relief with Sarapin, a rigorous clinical trial and basic science evaluation do not find any merit in its use.

Vertebroplasty

Vertebroplasty was first performed in France in 1984 to treat compression fractures caused by bone cancer or bone metastasis, and later to treat compression fractures caused by osteoporosis. Percutaneous vertebroplasty was introduced in the United States in 1994 and has become widely available since 1997 as a treatment for pain associated with compression fractures due to osteoporosis. The number of procedures performed for osteoporotic compression fractures has grown exponentially.

A 1998 study by Deramond and colleagues[5] reported 80 patients with rapid and complete pain relief in more than 90% of osteoporotic cases. The follow-up in this case series ranged from 1 month to 10 years with evidence of prolonged pain relief.

However, when Kallmes et al[6] conducted a prospective randomized placebo-controlled trial, a surprising result occurred. In their study, all patients underwent the assigned intervention (68 vertebroplasties and 63 simulated procedures). The baseline characteristics were similar in the 2 groups. At 1 month, there was no significant difference between the vertebroplasty group and the control group in either Roland Disability Questionnaire score (difference, 0.7; 95% confidence interval [CI], −1.3 to 2.8; $P = 0.49$) or pain rating (difference, 0.7; 95% CI, −0.3 to 1.7; $P = 0.19$). Both groups had immediate improvement in disability and pain scores after the intervention.

Although the 2 groups did not differ significantly on any secondary outcome measure at 1 month, there was a trend toward a higher rate of clinically meaningful improvement in pain (a 30% decrease from baseline) in the vertebroplasty group (64% vs 48%, $P = 0.06$). At 3 months, there was a higher crossover rate in the control group than in the vertebroplasty group (43% vs 12%, $P < 0.001$). There was 1 serious adverse event in each group.

Similarly, Buchbinder et al[7] performed a multicenter, randomized, double-blind, placebo-controlled trial in which participants with 1 or 2 painful osteoporotic vertebral fractures that were of less than 12 months' duration and unhealed, as confirmed by MRI, were randomly assigned to undergo vertebroplasty or a sham procedure.

Participants were stratified according to treatment center, sex, and duration of symptoms (<6 weeks or ≥6 weeks). Outcomes were assessed at 1 week and at 1, 3, and 6 months. The primary outcome was overall pain (on a scale of 0 to 10, with 10 being the maximum imaginable pain) at 3 months. The authors documented no beneficial effect of vertebroplasty as compared with a sham procedure in patients with painful osteoporotic vertebral fractures, at 1 week or at 1, 3, or 6 months after treatment.[7]

Vertebroplasty appears to confer no benefit over a sham procedure (notwithstanding the receipt of local anesthesia) or over usual care, and it poses some risk.

Many clinicians have criticized these studies unfairly, but RCTs such as this are the only truly valid means of establishing or refuting the efficacy of vertebroplasty. Personal anecdote and observational studies are biased toward overestimating treatment benefits for many reasons.

All participants in the Kallmes et al[6] and Buchbinder et al[7] trials had symptoms for 8 weeks or less, refuting the contention that benefits are more likely if the treatment is given early. The 2 trials were more than adequately powered to achieve the primary efficacy aim of detecting a 2.5-unit advantage of vertebroplasty over placebo with respect to the pain score. Because the mean effect of vertebroplasty has consistently been shown to be close to zero in randomized trials in which participants in both treatment groups had improvement over time, it is doubtful that there would be subgroups of patients who would benefit from the procedure. The only way that a proportion of patients could receive a large benefit from vertebroplasty would be if the condition of another subgroup of patients became much worse, a scenario that does not reflect the available data.

Participants in both trials were typical of patient populations seen in routine care, and they also shared comparable baseline characteristics, including levels of pain and disability, with participants in other vertebroplasty studies. As indicated by the stringent selection criteria in both trials, all enrolled patients had, by definition, unhealed "acute" or "subacute" vertebral fractures.

Buchbinder et al concluded: "Vertebroplasty appears to confer no benefit over a sham procedure (notwithstanding the receipt

of local anesthesia) or over usual care, and it poses some risk… It would be neither appropriate nor moral to offer this treatment in routine care."[7]

These results were confirmed by yet another randomized prospective trial by Rousing et al.[8]

However, many clinicians remain unconvinced by these trials and some researchers continue to try to prove these findings wrong.

Anselmetti et al[9] studied 2251 patients with osteoporosis (1811 women; average age, 65 years) suffering from back pain for vertebral collapses that were confirmed by MRI. The participants underwent a clinical interview; their medical treatment, pain grade, quality of life, and extent of vertebral fracture were reviewed. Vertebroplasty was performed in 1542 patients (1302 women; average age, 73 years) when optimal medical treatment (such as bisphosphonates, teriparatide, analgesics, and back brace) did not help to relieve pain or improve quality of life for patients over a 3-month period.

After vertebroplasty, patients continued to receive medical treatment with a rheumatologist. In 1494 patients (96.9%), the average pretreatment pain score on the 11-point visual analog scale (VAS) was 8.2 ± 1.8, and it dropped "significantly" to an average of 1.1 ± 1.6 after vertebroplasty treatment.

The story of these procedures offers a glimpse of the ways in which CER may influence medical practice and health care expenditures.

A patient's ability to manage everyday life—such as washing, dressing, or standing—was measured by the commonly used Oswestry Disability Questionnaire (ODQ), which was completed by patients before and after vertebroplasty. The ODQ scores changed from an average of 68.7 ± 7.6% to 18.5 ± 8.2%. Long-term follow-up (average, 31.2 months) in 1017 patients (857 women; average age, 72 years) showed the VAS significantly dropping from 7.9 ± 1.5 to 1.3 ± 1.7. Of the 757 patients wearing a back brace before vertebroplasty, 683 could stop wearing one after treatment.

But again, this is a very large case series and does not answer what would have happened without intervention.

The Future of Comparative-Effectiveness Research

The story of these procedures offers a glimpse of the ways in which comparative-effectiveness research (CER) may influence medical practice and health care expenditures.

Early studies of these procedures were neither randomized nor blinded, and because the symptoms of compression fractures often abate over time without intervention, the lack of adequate controls made it impossible to know whether improvements that followed treatment would have occurred even without surgery. Furthermore, neither procedure was risk free; reported complications included compression fractures, cement leakage, pulmonary complications, paraplegia, and death.

In a scenario that is likely to be repeated frequently as CER gains greater acceptance and support, randomized trials of vertebroplasty eventually followed the observational studies that had fostered the initial enthusiasm. If the consequences of that research are not yet fully apparent, their potential importance is. If better-designed studies had been conducted initially and translated into practice earlier, the reduction in US health care expenditures would be considerable.

CER treats effectiveness as a balance of benefits and harms; when the risks associated with a procedure outweigh its clinical benefits, it is appropriate and ethical to limit its use. Both the clinical need and the desire to avoid wasteful expenditures were part of the rationale for subjecting these procedures to comparative studies.

Furthermore, consensus that these procedures were promising but unproven led several countries to make them available on an interim-coverage basis. These arrangements, in effect from 2006 through 2010, allowed the procedures to be performed in everyday practice while further evidence was generated.

Trials conducted during that period suggested that vertebroplasty did not improve outcomes. As mentioned earlier, studies of vertebroplasty produced varying results, but the highest-quality trials cast doubt on the benefit and raised additional safety concerns. In a randomized but nonblinded trial by Kallmes et al,[6] patients who underwent vertebroplasty and controls had similar reductions in disability and pain scores, with a trend toward a higher rate of clinically meaningful improvement in pain (30% decrease from baseline) in the vertebroplasty group that neared statistical significance (64% vs 48%, $P = 0.06$).

These studies illustrate the difficulty of inferring the effects of treatments for a condition with a variable time course.

In a randomized, blinded trial by Buchbinder et al,[7] vertebroplasty did not have a statistically significant advantage over placebo in any measured outcome over 6 months, although pain diminished in both groups.

These studies illustrate the difficulty of inferring the effects of treatments for a condition with a variable time course, particularly when its manifestations are strongly influenced by placebo effects. But the studies at best cast doubt on the magnitude of any benefits from these procedures and at worst established their ineffectiveness.

The findings led U.S. and other payers to revisit their interim funding decisions. To improve safety and quality and to respond to pressures for fiscal responsibility and efficiency in health care, payers are deciding to limit or withdraw coverage for vertebroplasty. In late 2010, the Blue Cross Blue Shield Association's

Medical Advisory Panel confirmed its decision that neither procedure met its criteria for established effectiveness, and in Canada, the Ontario Health Technology Advisory Committee ruled that vertebroplasty should not be considered the standard treatment for osteoporotic vertebral fractures.

Any CER agenda strives for improved safety and quality of care. By identifying relative ineffectiveness, CER may also improve the health care system by freeing up resources to be used for safer and more effective forms of care. Savings from limiting the use of care that has not been proved effective can be substantial, whether the intervention is new or has already been disseminated.

A 50% reduction in the use of vertebroplasty and kyphoplasty—a similar procedure that involves inserting a balloon in the affected vertebrae to restore some height lost to the compression fracture—would deliver annual savings of $450 million; an 80% reduction would save about $725 million annually. Because these figures are based on costs rather than charges or payments, they are highly conservative. And although these figures seem small relative to US health care expenditures, the procedures are not among the most common. Furthermore, savings are large in relation to the $1.1 billion that Congress allocated to CER in the 2009 American Recovery and Reinvestment Act. When the Patient-Centered Outcomes Research Institute, created by the Affordable Care Act, is fully operational, its budget is expected to reach $500 million annually, or just two thirds of the potential savings each year from diminished use of just these 2 apparently ineffective procedures.

Caudal Epidurals for Chronic ("Not Acute") Low Back Pain

Iverson et al[10] conducted a blinded, RCT to assess the efficacy of caudal epidural corticosteroid or saline injection in chronic lumbar radiculopathy in the short (6 weeks), intermediate (12 weeks), and long term (52 weeks).

Caudal epidural corticosteroid or saline injections are not recommended for chronic lumbar radiculopathy.

They enrolled 461 patients presenting with lumbar radiculopathy for more than 12 weeks. A total of 328 patients were excluded for cauda equina syndrome, severe paresis, severe pain, previous spinal injection or surgery, deformity, pregnancy, ongoing breastfeeding, warfarin therapy, ongoing treatment with nonsteroidal anti-inflammatory drugs, body mass index greater than 30, poorly controlled psychiatric conditions with possible secondary gain, or severe comorbidity.

They then randomized the remaining patients into groups receiving subcutaneous sham injections of 2 mL of 0.9% saline, caudal epidural injections of 30 mL of 0.9% saline, and caudal epidural injections of 40 mg of triamcinolone acetonide in 29 mL of 0.9% saline. Participants received 2 injections with a 2-week interval.[9]

They collected Oswestry disability index scores and European quality of life measure (EQ-5D) and VAS scores for low back pain and for leg pain.

The original power calculations required the inclusion of 41 patients per group. They did not allocate 17 of 133 eligible patients because their symptoms improved before randomization.[10] All groups improved after the interventions, but they documented no statistical or clinical differences between the groups over time. For the sham group (n = 40), estimated change in the Oswestry disability index from the adjusted baseline value was −4.7 (95% CI, −0.6 to −8.8) at 6 weeks, −11.4 (−6.3 to −14.5) at 12 weeks, and −14.3 (−10.0 to −18.7) at 52 weeks.

For the epidural saline intervention group (n = 39) compared with the sham group, differences in primary outcome were −0.5 (−6.3 to 5.4) at 6 weeks, 1.4 (−4.5 to 7.2) at 12 weeks, and −1.9 (−8.0 to 4.3) at 52 weeks; for the epidural corticosteroid group (n = 37), corresponding differences were −2.9 (−8.7 to 3.0), 4.0 (−1.9 to 9.9), and 1.9 (−4.2 to 8.0). Analysis adjusted for duration of leg pain, back pain, and sick leave did not change this trend. Iverson and co-authors[9] concluded that caudal epidural corticosteroid or saline injections are not recommended for treatment of chronic lumbar radiculopathy.

In 2007, a report from the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology[11] addressing the use of caudal epidural injections for chronic pain stated: "It is concluded that epidural steroid injections for lumbosacral radicular pain have no impact on average impairment of function, on need for surgery, or on long term pain relief beyond 3 months, and their use for the indications are not recommended."

In contrast, Conn et al[12] state there is excellent evidence (Agency for Healthcare Research and Quality level II-1 or II-2) for caudal epidural injections in managing chronic pain after lumbar laminectomy syndrome and spinal stenosis. This dichotomy of opinion points out that when conducting systematic reviews, erroneous conclusions can be reached that will fall when robust randomized trials are conducted.

Conclusion

These 3 therapies still have their advocates, but from an evidence-based perspective, they need to be consigned to the scrap heap. It makes no sense to cling to therapies that are of marginal or no benefit to our patients. Clinicians must be vigilant in assessing new treatments—and even those that are not so new—based on data from clinical RCTs. ■

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Update on Risk of Overdose of IV Acetaminophen in Pediatric Patients

Acetaminophen is one of the safest analgesics, even for children—except when the dose is too high. In 2011, the FDA approved an IV formulation of acetaminophen (IVA). In 2011, the availability of this formulation for mild to moderate acute pain provides a new analgesic option for adult and pediatric patients of age 2 years and older.

But the formulation also comes with a potential risk of overdose in children if prescribers and those who administer the drug do not pay close attention. Most pediatricians, pediatric nurse practitioners, and pediatric specialty units and hospitals are already used to mindfully calculating dosages for children, but the potential for a huge error of the magnitude involved with IVA makes it worthwhile to give special attention to this formulation.

Most events have involved a 10-fold dosing error in small children caused by calculating the dosage in milligrams, but then administering the solution in milliliters.

Past Concerns About Over-the-Counter Pediatric Overdose

In the last several years, over-the-counter liquid formulations with acetaminophen have been changed to a lower concentration industry wide, after some confusion led to inadvertent overdosing. In that case, it was attributed to parents being unaware of how much higher the concentration of the drug was in infant drops, compared with "junior" liquids, and accidentally overmedicating their children.

In the case of IVA, the dosing, prescribing, and administration are performed by professionals, but there is still a high risk of error unless physicians and other members of the care team are aware of the reason a mix-up could occur. It is not unlike mix-ups that occur because 2 drugs have similar names, but in this case, the error potential is because of, for lack of a better term, look-alike numbers. In fact, the potential error can result in a child getting 10 times the normal dose.

Special Article Reports 23 Overdoses—One Fatal—in United Kingdom

In a special article published in the journal *Pediatrics*, February 1, 2012, Richard Dart, MD, PhD, and Barry Rumack, MD,[1] both from the Rocky Mountain Poison and Drug Center in Denver, Colorado, wrote that in 2010, regulatory authorities in the United Kingdom reported 23 cases of single or repeated dosing errors using the IV form of acetaminophen in children younger than 1 year. One of the cases was fatal.[1]

"Most events have involved a 10-fold dosing error in small children caused by calculating the dosage in milligrams, but then administering the solution in milliliters. The solution is 10 mg/mL; therefore, a 10-fold overdose occurs," Dart and Rumack[1] wrote.

The formulation approved by the FDA for use in the United States is also 10 mg/mL (Ofirmev, Cadence Pharmaceuticals). The approval is for use in patients of age 2 years and older, although other countries have not put a minimum age on the approval and off-label use in the United States is inevitable, Dart and Rumack[1] wrote.

"… [O]ff-label use can be anticipated, because it is used in young children internationally, and this age group often has difficulty with oral administration," wrote the authors. "Hospitalists and intensivists can anticipate cases of iatrogenic dosing errors of intravenous acetaminophen in young children."[1]

An Infamous Case Leads to Foundation Advocating for System-Wide Approach to Patient Safety

One of the most tragic and humbling pediatric errors involved Maryland toddler Josie King, in 2001. Josie had been recovering nicely from first- and second-degree burns at the Johns Hopkins Hospital in Baltimore. After 10 days in the pediatric intensive care unit, she was transferred to intermediate care with the expectation of going home a few days later. But there were serious errors in diagnosing, dosing, and observing the patient—and failure to listen to the mother's concerns about her daughter, until it was too late. After a rescue, a communication failure led to a nurse delivering a dose of methadone that killed the 18-month-old child.

Outraged that such a thing could happen in what is by some measures the best hospital in the country, the child's parents sued the hospital and won a settlement. But Hopkins then reached out to the King family to speak to staff about what happened. That rare collaboration grew to the family using the settlement to create a foundation named after their child—the Josie King Foundation—and work in partnership with Peter Pronovost, MD, PhD, toward effecting change in the system errors that endanger patients.

Pronovost is professor of anesthesiology and critical care medicine and surgery at the Johns Hopkins University School of Medicine, also holding faculty appointments in the Department of Health Policy and Management at Johns Hopkins' Bloomberg School of Public Health and in the School of Nursing. He is medical director of the Center for Innovation in Quality Patient Care and director of the Quality and Safety Research Group.

To learn more, go to the Josie King Foundation website at www.josieking.org. The site includes several resources for professionals and for patients and families.

Although many new analgesics have been approved more recently, the fact is that acetaminophen is the most widely used analgesic and antipyretic currently approved in the United States. Acetaminophen is also a first-line choice for pain in the World Health Organization step-ladder approach to pain management.

Despite the risk of overdosing because of the milligrams/milliliter mix-up potential, IVA may have some built-in safety: it does not undergo first-pass hepatic metabolism.

The authors recommend a combination of being prepared for overdose and proactively providing intensive education to health care professionals who work with children and might be involved in the administration of the IV formulation of acetaminophen.

For example, they suggest the following steps:

1. Head off potential errors by raising awareness. Clinicians in pain management should become proactive and initiate consultations between themselves and hospital pharmacy staff, nurses, and nurse practitioners whenever IVA is to be added to the formulary.
2. Overcommunicate. Prescribers should write the prescribed dosage in both milligram *and* milliliter forms to prevent confusing the amount with the volume of the drug.
3. Initiate a rapid response to overdoses if they occur. If an overdose is discovered, Dart and Rumack wrote, appropriate management should be initiated immediately, using the Rumack-Matthews normogram as a guide. If needed, the clinician should also administer acetylcysteine, the antidote for acetaminophen overdose.

   The authors write that evaluation of a patient with overdose with the IV formulation is similar to an overdose of the oral drug, including drawing a serum acetaminophen concentration 4 hours after the infusion was started or as soon as possible after that. If the serum acetaminophen concentration plots above the treatment line on the Rumack-Matthew nomogram, treatment with acetylcysteine should be initiated.
4. Report the overdose. Health care providers are encouraged to contact their regional poison center (1-800-222-1222) so that dosing errors will be reported, and the experience with this new product can be accumulated.

Lonnie Zeltzer, MD, director of the Pediatric Pain Program at Mattel Children's Hospital at the University of California, Los Angeles (UCLA), and professor of pediatrics, anesthesiology, psychiatry, and biobehavioral sciences at UCLA's David Geffen School of Medicine, said IV formulations of acetaminophen require staff to be at their vigilant best when calculating doses and administering it to pediatric patients. Zeltzer also is a member of the editorial advisory board of *Topics in Pain Management.*

"IV acetaminophen can be a rapid way to anticipate and mitigate an acute pain event within a clinical and monitored setting," said Zeltzer via an e-mail interview with *Topics in Pain Management*. "As with all IV-administered medications, care should be taken in the administration process to avoid accidental overdosing. This includes writing orders in both milligrams and milliliters, double-checking what the pharmacist has given to the nurse or physician to administer, and education of the clinical team about IVA."

Advantages of IV Formulation

Despite the risk of overdosing because of the milligrams/milliliter mix-up potential, IVA may have some built-in safety: it does not undergo first-pass hepatic metabolism. Unlike oral acetaminophen, IVA bypasses the liver because of the IV administration.

There are other differences between IVA and oral acetaminophen, as follows:

"Based on modeling," Dart and Rumack wrote, "intravenous infusion is predicted to produce a peak acetaminophen concentration in the liver 50% less than the concentration produced by the same oral dose."[1]

Using that model, they wrote, it is highly unlikely that a 10-fold IV overdose of the drug would lead to production of more N-acetyl-p-benzoquinone imine (NAPQI), the toxic metabolite triggered by acetaminophen.

Metabolism of IV Formulation Differs From Oral

In last month's issue of *Topics in Pain Management* (March, Vol. 27, No. 8), Editor Clifford Gevirtz, MD, MPH, gave an update on IVA across all patient populations and described how the drug is metabolized:

"In both children and adults, acetaminophen is metabolized by the liver via 3 major pathways: glucuronidation (approximately 60%), sulfation (approximately 25%), and oxidation (approximately 10%). In neonates and infants, sulfation is the major metabolic pathway due to delayed maturity in the glucuronidation pathway. Minor metabolic pathways for acetaminophen include hydroxylation, methoxylation, and hydrolysis, wrote Gevirtz."[2]

"It is important to note that within the therapeutic dosage range, small amounts of N-acetyl-p-benzoquinone imine (NAPQI), a toxic intermediate, are produced by the cytochrome P450 CYP2E1 enzyme. Normally, this NAPQI is then conjugated with intracellular glutathione to produce a nontoxic thiol metabolite, which is excreted in the urine. When a supratherapeutic dose is taken or when there is significant depletion of glutathione stores, NAPQI is produced in larger amounts, which can result in hepatotoxicity."[2]

Studies Show Few Adverse Events

In studies of IVA in both children and adults, adverse events were not different from placebo. The most common adverse reactions in patients treated with IVA were nausea, vomiting, headache, and insomnia in adult patients, and nausea, vomiting, constipation, pruritus, agitation, and atelectasis in pediatric patients.

One important consideration is that because the antipyretic effects of IVA may mask fever in patients treated for postsurgical pain, for example, it may in turn mask the signs of postoperative infection and sepsis.

But, on the whole, IVA has advantages in pediatric use. Unlike aspirin, for example, acetaminophen is not associated with a risk of Reye syndrome in children with viral illnesses. The safety and effectiveness of IVA for the treatment of acute pain and fever in pediatric patients 2 years of age and older is supported by evidence from adequate and well-controlled studies of IVA in adults.

IVA for acute pain and fever in pediatric patients 2 years of age and older is supported by evidence from adequate and well-controlled studies in adults.

In a consensus statement of the assessment and management of acute pain in infants, children, and adolescents, the American Academy of Pediatrics Committee on Psychological Aspects of Child and Family Health (AAP Committee) and the American Pain Society Task Force on Pain in Infants, Children, and Adolescents (APS Task Force)[3] have recommended that pediatricians should "anticipate painful experiences" and "use a multimodal approach to pain management."

They noted that the use of nonopioid analgesics, such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), in combination with opioids can reduce the amount of opioids required to achieve adequate analgesia. In the view of the AAP Committee/APS Task Force, the goal of acute pain treatment is "to control the pain as rapidly as possible," and when the child needs immediate pain relief, IV administration is indicated.

And because acetaminophen is a centrally acting analgesic without the anti-inflammatory effects, it can be combined with an NSAID for multimodal analgesia. Such multimodal analgesia has shown to reduce opioid consumption, and therefore reduce adverse effects from opioids. ■

Editor's Note: Dart and Rumack have disclosed that they were part of a group of consultants retained by Cadence Pharmaceuticals to develop recommendations for management of overdose of IV acetaminophen.

References

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With More Drugs Available, Multimodal Approach to Analgesia Can Reduce Need for Opioids in Acute Perioperative Setting

With a growing number of injectable drugs available to manage perioperative pain, anesthesiologists and surgeons have a more effective arsenal of medications that can reduce or even eliminate the need for opioids.

Raymond Sinatra, MD, PhD, professor emeritus of anesthesiology at Yale School of Medicine, presented a comprehensive report of several agents and how they can be combined to relieve patients' pain more effectively, at the New York State Society of Anesthesiologists (NYSSA) Post-Graduate Assembly (PGA) last December in New York City.[1]

"Multi-modal—or mechanistic—analgesia is the simultaneous use of different agents or forms of analgesia delivery that suppress pain transmission in the peripheral and central nervous systems," according to Sinatra's prepared materials.

He compared the multimodal approach to analgesia with the way other disease states, such as diabetes, hypertension, asthma, and infection, are treated with multiple therapeutic measures.

Medications that can be used in the perioperative setting now include the following:

- Injectable nonsteroidal anti-inflammatory drugs (NSAIDs), such as injectable ibuprofen and ketorolac;
- Cyclooxygenase-2 inhibitor (celecoxib) injections;
- Intravenously administered acetominophen;
- Injectable ketamine;
- Injectable glucocorticoids;
- Injectable benzodiazepines such as diazepam and lorazepam; and
- Injectable and transdermal alpha agonists such as clonidine.

The list is substantial: the upside of that is that various medications that can attack pain from peripheral and central nervous system transmission—and inflammation—can mean deeper effect. It also allows for many choices, so that if one of the drugs is contraindicated for a particular patient, another one might work.

A multimodal approach requires that the practitioner have a broader knowledge base to be able to prescribe effectively and avoid adverse drug interactions or toxicity.

So what is the downside? The sheer number of medications available and the need for a more complicated dosing regimen means that multimodal analgesia has some inherent challenges: More medications are administered, so the cost could be higher, for one thing. But a multimodal approach also requires that the practitioner have a broader knowledge base to be able to prescribe effectively and avoid adverse drug interactions or toxicity.

Data suggest ibuprofen has greatest efficacy when administered preoperatively.

And once patients are discharged, if they are to continue a multimodal approach at home, it could raise problems in compliance for patients who are elderly or otherwise challenged in following a more complex regimen.

Here, as follows, is a summary of some of the specific information on each type of drug, as Sinatra presented to attendees at the NYSSA-PGA:

Injectable NSAIDs, Such as Injectable Ibuprofen and Ketorolac

NSAIDs reduce local inflammation and can prevent both peripheral hyperalgesia and central sensitization and are useful in managing surgical and posttraumatic musculoskeletal pain and visceral pain. They can be useful in augmenting opioid and neural blockade.

Ketorolac, however, must be used with caution because of the risks of platelet dysfunction. It has been removed from the European market and has dose restrictions in the United States.

Ibuprofen injections have been approved since 2009 and may offer greater safety, but ibuprofen should never be administered as a rapid IV bolus. It can be used before surgery, intra- and postoperatively. Data suggest the drug has greatest efficacy when administered preoperatively.

Celecoxib is well suited for preincisional dosing because it is not associated with impaired platelet function.

Cyclooxygenase-2 Inhibitor (Celecoxib)

Although injectable coxibs have not been approved for use in the United States, and orally administered celecoxibs have been associated with cardiovascular risks with long-term use, orally administered celecoxib is available for acute pain management. It can be given to patients with a small sip of water 2 hours before induction of anesthesia.

Sinatra noted that celecoxib is well suited for preincisional dosing because it is not associated with impaired platelet function. Postoperatively, it can be taken every 12 hours for 5 days or longer.

One disadvantage, however, is that it cannot be taken by postoperatively by patients who have not been advanced to an oral liquid diet.

Another is that it comes with a mandated black-box warning about risks of cardiovascular and cerebrovascular thrombosis with long-term use.

IV Acetaminophen

See last month's issue of *Topics in Pain Management* (*TPM* March, Vol. 27, No. 8), for the CME article by *TPM* Editor Clifford Gevirtz, MD, MPH, for an update on IVA.

Injectable Ketamine

Ketamine could play an important role in preventing acute pain from progressing to chronic pain. Although ketamine's mechanism of action remains unclear, it is a nonselective N-methyl-D-aspartate (NMDA) receptor antagonist in the central nervous system. NMDA receptor activation leads to continuous cell firing that may lead to secondary sensitization and changes in neural connections.

Ketamine could play an important role in preventing acute pain from progressing to chronic pain.

The drug is demonstrated to potentiate opioid analgesia while providing an opioid-sparing effect. It is especially useful for opioid-tolerant patients. Complications include hyperdynamic cardiovascular responses and psychomimetic reactions.

Injectable Glucocorticoids

Injectable glucocorticoids provide an anti-inflammatory effect and could be a safe and useful substitute for patients who have contraindications to NSAIDs.

Injectable Benzodiazepines Such As Diazepam and Lorazepam

Injectable benzodiazepines can be useful in reversing surgery-related muscle spasm and the pain associated with it—something that opioids are generally ineffective at.

They can be combined with oral corticosteroids, opioids, and NSAIDs on the basis of the severity of the symptoms.

But benzodiazepine adverse effects include sedation, dizziness, habituation, and memory impairment, and these agents can exacerbate opioid-related respiratory depression and somnolence. So physicians should consider decreasing opioid doses by 20% to 25%.

Adding clonidine to opioid analgesia is useful for patients with high-grade opioid tolerance.

Injectable and Transdermal Alpha Agonists

Alpha adrenergic agonists such as clonidine and dexmeditome enhance endogenous analgesia. Adding clonidine to opioid analgesia is useful for patients with high-grade opioid tolerance or in those who are highly sensitive to opioids. Epidural solutions offer greater potency, but should be used only in healthy adults because they are associated with hypotension in debilitated and hypovolemic patients.

Injectable dexmedetomidine is more selective and has a shorter duration of action than clonidine. It has not been specifically approved by the FDA for treatment of postoperative pain. Some data show a 66% reduction in morphine use for patients in the early postoperative period after major inpatient surgery in clinical trials.

However, dexmedetomidine is also associated with increased postoperative sedation and bradycardia, requiring prolonged monitoring in the postanesthesia care unit. Sinatra said its usefulness may be most suited to being an analgesic adjuvant for highly opioid-dependent patients or those with significant intolerance to opioids. ■

Reference

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Coming Soon:

- CME Article: Opioid Rotation—Methods and Cautions
- Update on the Washington State Pain Care Act
- Medical Schools Found Lacking in Pain Education

Topics in Pain Management CME Quiz

To earn CME credit, you must read the CME article and complete the quiz and evaluation assessment survey on the enclosed form, answering at least 70% of the quiz questions correctly. **Select the best answer and use a blue or black pen to completely fill in the corresponding box on the enclosed answer form.** Please indicate any name and address changes directly on the answer form. If your name and address do not appear on the answer form, please print that information in the blank space at the top left of the page. Make a photocopy of the completed answer form for your own files and mail the original answer form in the enclosed postage-paid business reply envelope. Your answer form must be received by Lippincott CME Institute by **March 31, 2013.** Only two entries will be considered for credit.

Online quiz instructions: To take the quiz online, **log on to your account at http://www.topicsinpainmanagement.com,** and click on the "CME" tab at the top of the page. Then click on "Access the CME activity for this newsletter," which will take you to the log-in page for **CME.lwwnewsletters.com.** Enter your *username and password for this screen as follows*: Your ***CME username*** will be the letters LWW (case sensitive) followed by the 12-digit account number above your name on the paper answer form mailed with your issue. Your ***CME password*** will be **1234**; this password ***may not*** be changed. Follow the instructions on the site. You may print your official certificate ***immediately***. Please note: Lippincott CME Institute, Inc., ***will not*** mail certificates to online participants. **Online quizzes expire at 11:59 pm Pacific Standard Time on the due date.**

1. **A prospective randomized trial of Sarapin demonstrated no significant statistical differences between groups, either with pain relief measured by numeric pain scale or duration of significant relief defined as 50% or greater relief.**
   A. True
   B. False

2. **Harkins et al clearly demonstrated the local anesthetic efficacy of Sarapin using an animal model.**
   A. True
   B. False

3. **In two randomized prospective trials, patients in both the vertebroplasty and placebo groups had immediate improvement in disability and pain scores after the intervention.**
   A. True
   B. False

4. **The Buchbinder et al trial demonstrated no beneficial effect of vertebroplasty as compared with a sham procedure in patients with painful osteoporotic vertebral fractures, at 1 week or at 1, 3, or 6 months after treatment.**
   A. True
   B. False

5. **Buchbinder et al concluded: "Vertebroplasty appears to confer benefit over a sham procedure while it poses some risk."**
   A. True
   B. False

6. **CER treats effectiveness as a balance of benefits and harms; when the risks associated with a procedure outweigh its clinical benefits, it is appropriate and ethical to limit its use.**
   A. True
   B. False

7. **By identifying relative ineffectiveness, CER may also improve the health care system by freeing up resources to be used for safer and more effective forms of care. Savings from limiting the use of care that has not been proved effective can be substantial, whether the intervention is new or has already been disseminated.**
   A. True
   B. False

8. **A 50% reduction in the use of vertebroplasty and kyphoplasty would deliver annual savings of $450 million; an 80% reduction would save about $725 million annually.**
   A. True
   B. False

9. **The Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology, addressing the use of caudal epidural injections for chronic pain stated: "it is concluded that epidural steroid injections for lumbosacral radicular pain have no impact on average impairment of function, on need for surgery, or on long term pain relief beyond 3 months."**
   A. True
   B. False

10. **Iverson et al concluded that caudal epidural corticosteroid or saline injections are recommended for treatment of chronic lumbar radiculopathy.**
    A. True
    B. False

NEWS IN BRIEF

Study Finds Benefit from Conservative Approach to Management of Spinal Stenosis-Related Pain

Patients with lumbar central spinal stenosis might benefit from receiving lumbar interlaminar injections with or without corticosteroids, according to the preliminary results of a randomized, double-blind, active-control trial.

The trial is being led by Laxmaiah Manchikanti, MD, associate clinical professor of anesthesiology and perioperative medicine at the University of Louisville in Kentucky, with co-authors including Frank J.E. Falco, MD, associate professor of pain medicine and rehabilitation at Temple University Medical School in Philadelphia.

The preliminary results were published in January in the journal *Pain Physician*.[1] The full text is available online for free at www.painphysicianjournal.com.

Manchikanti et al sought to fill a void in the existing literature about the effectiveness of some conservative approaches. They sought to determine whether interlaminar epidural injections of local anesthetic could provide long-lasting pain management or relief from the low back pain and leg pain that are secondary to lumbar spinal stenosis, and whether that relief could be achieved with or without the addition of corticosteroids.

They found that existing studies and evidence synthesis were deficient because they were performed without fluoroscopy and with varying doses and combinations of drugs.

The authors acknowledge that the lack of a placebo arm and the fact that these are preliminary studies are both limitations qualifying their results, but nonetheless report results that merit further study. They continue to gather data on the total of 120 patients participating in their study. So far, preliminary results include data for 60 of the patients.

Participants were randomized into 2 groups: group I received injections of local anesthetic (lidocaine 0.5%) only, and group 2 received local anesthetic combined with nonparticulate betamethasone. Physicians performed the injections with fluoroscopy guidance in an ambulatory surgery setting, with midazolam and fentanyl if needed. They entered the lumbar interlaminar space at L5/S1, or one space below the stenosis level, attempting to direct the flow toward the involved segments. All patients were treated with the injections, but they were not assigned any other treatments, such as physical therapy or bracing.

Outcome measurements were taken at 3, 6, and 12 months.

The authors found that patients in both groups reported significant pain relief and improvement in Oswestry Disability Index (ODI) scores at 12 months. Group 1, with local anesthetic (LA) only, reported 70% significant pain relief at 12 months, and Group 2, with LA and betamethasone, reported 63% significant pain relief.

The pattern continued with scores on the ODI—Group 1 scored 70% improvement on the ODI, while Group 2 (LA with betamethasone) scored 60% improvement. ■

Reference

1. Manchikanti L, Cash KA, McManus CD, et al. Lumbar interlaminar epidural injections in central spinal stenosis: Preliminary results of a randomized, double-blind, active-control trial. *Pain Physician*. 2012;15:51-63.

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