

Device Improves Articular Injection Outcomes

BY DENISE NAPOLI

A combination of ultrasound and a novel two-barrel syringe significantly decreased the nonresponder rate in intra-articular injections compared with a traditional, palpation-guided, single-barrel syringe method, according to findings from a study of 148 patients.

In fact, the nonresponder rate fell a sig-

nificant 62%, from 28.4% in the traditional injection method group to 10% with the new, ultrasound-guided method.

Moreover, the ultrasound-guided technique reduced pain at 2 weeks by 75% compared with the traditional method.

The study was randomized but not double-blinded, since both the physician and patient could see which method was used, and was presented at the Western Regional Meeting of the Amer-

ican Federation for Medical Research.

The novel injection method consisted of manual palpation of the joint, followed by superficial marking and assessment with ultrasound to “define the anatomy, determine the presence of effusion, and confirm the optimal anatomic approach,” Dr. Kye S. Park of the University of New Mexico, Albuquerque, said in an interview.

Then, using a two-syringe needle

known as the reciprocating procedure device (RPD), one barrel delivered local anesthesia and performed aspiration, if necessary, while the second barrel injected the therapeutic agent—in this study, triamcinolone acetonide.

“It’s a two-barrel syringe, and essentially you control it with one hand,” Dr. Park said. “You aspirate and inject by pushing one or the other plunger. Normally when you put in a one-barrel traditional syringe, when you inject, you’re pressing your flexor. Then to aspirate, you have to pull out. With this, you’re using the same motion to inject and aspirate, but when you push one plunger to aspirate, the other [chamber of the syringe] is the one that’s actually filling up with fluid,” he explained.

The traditional method used palpa-



COURTESY, DR. KYE S. PARK

A physician uses ultrasound and the reciprocating procedure device.

tion-guided injections with a standard needle.

The average patient age in the ultrasound group was 52 years, compared with 56 years in the traditional group. In both groups, more than 80% of patients were female, and nearly three-quarters had inflammatory arthritis. Pain was assessed on a 0- to 10-cm visual analog scale (as opposed to the more conventionally used 0- to 100-mm scale). Nonresponders were defined as having significant persistent joint pain that was rated as being greater than or equal to 5 cm at 2 weeks following treatment.

Although physicians are becoming more aware of the benefits of ultrasound-guided intra-articular injections, the RPD is still relatively unknown among rheumatologists, said Dr. Park. It is particularly useful if a rheumatologist intends to be the sole operator of both the ultrasound and the needle, because the physician does not need to change positions, he added.

However, both ultrasound and the RPD add cost—the ultrasound itself can cost an additional \$75-\$150 per procedure, and the RPD tacks on an extra \$1.50 per injection. The use of ultrasound about doubles the time it takes to perform the injection. Therefore, regarding “the implications of something like this being used widespread, there obviously needs to be a cost analysis,” said Dr. Park.

Dr. Park said that the utility of the new method is especially pronounced in dry joints (without effusion), where “the actual space between the cartilage and the

Continued on following page

AMRIX®

(Cyclobenzaprine Hydrochloride Extended-Release Capsules)

Rx Only

Brief Summary of Prescribing Information. The following is a brief summary only. Please see full Prescribing Information for complete product information.

DESCRIPTION

AMRIX® (Cyclobenzaprine Hydrochloride Extended-Release Capsules) is a skeletal muscle relaxant which relieves muscle spasm of local origin without interfering with muscle function. The active ingredient in AMRIX extended-release capsules is cyclobenzaprine hydrochloride, USP.

AMRIX extended-release capsules for oral administration are supplied in 15 and 30 mg strengths.

INDICATIONS AND USAGE

AMRIX is indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions. Improvement is manifested by relief of muscle spasm and its associated signs and symptoms, namely, pain, tenderness, and limitation of motion.

AMRIX should be used only for short periods (up to two or three weeks) because adequate evidence of effectiveness for more prolonged use is not available and because muscle spasm associated with acute, painful musculoskeletal conditions is generally of short duration and specific therapy for longer periods is seldom warranted.

AMRIX has not been found effective in the treatment of spasticity associated with cerebral or spinal cord disease or in children with cerebral palsy.

CONTRAINDICATIONS

- Hypersensitivity to any component of this product.
- Concomitant use of monoamine oxidase (MAO) inhibitors or within 14 days after their discontinuation.
- Hyperpyretic crisis seizures and deaths have occurred in patients receiving cyclobenzaprine (or structurally similar tricyclic antidepressants) concomitantly with MAO inhibitor drugs.
- During the acute recovery phase of myocardial infarction, and in patients with arrhythmias, heart block conduction disturbances, or congestive heart failure.
- Hyperthyroidism.

WARNINGS

AMRIX is closely related to the tricyclic antidepressants, e.g., amitriptyline and imipramine. In short term studies for indications other than muscle spasm associated with acute musculoskeletal conditions, and usually at doses somewhat greater than those recommended for skeletal muscle spasm, some of the more serious central nervous system reactions noted with the tricyclic antidepressants have occurred (see WARNINGS, below, and ADVERSE REACTIONS section of full Prescribing Information).

Tricyclic antidepressants have been reported to produce arrhythmias, sinus tachycardia, prolongation of the conduction time leading to myocardial infarction and stroke. AMRIX may enhance the effects of alcohol, barbiturates, and other CNS depressants.

As a result of a two-fold higher cyclobenzaprine plasma levels in subjects with mild hepatic impairment, as compared to healthy subjects, following administration of immediate-release cyclobenzaprine and because there is limited dosing flexibility with AMRIX, use of AMRIX is not recommended in subjects with mild, moderate or severe hepatic impairment.

As a result of a 40% increase in cyclobenzaprine plasma levels and a 56% increase in plasma half-life following administration of AMRIX in elderly subjects as compared to young adults, use of AMRIX is not recommended in elderly.

PRECAUTIONS

General

Because of its atropine-like action, AMRIX should be used with caution in patients with a history of urinary retention, angle-closure glaucoma, increased intraocular pressure, and in patients taking anticholinergic medication.

Information for Patients

AMRIX, especially when used with alcohol or other CNS depressants, may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

Drug Interactions

AMRIX may have life-threatening interactions with MAO inhibitors. (See CONTRAINDICATIONS.) AMRIX may enhance the effects of alcohol, barbiturates, and other CNS depressants. Tricyclic antidepressants may block the antihypertensive action of guanethidine and similarly acting compounds. Tricyclic antidepressants may enhance the seizure risk in patients taking tramadol (ULTRAM® [tramadol HCl tablets, Ortho-McNeil Pharmaceutical]) or ULTRACET® [tramadol HCl and acetaminophen tablets, Ortho-McNeil Pharmaceutical].

Carcinogenesis, Mutagenesis, Impairment of Fertility

In rats treated with cyclobenzaprine for up to 67 weeks at doses of approximately 5 to 40 times the maximum recommended human dose, pale, sometimes enlarged, livers were noted and there was a dose-related hepatocyte vacuolation with lipidosis. Cyclobenzaprine did not affect the onset, incidence, or distribution of neoplasia in an 81-week study in the mouse or in a 105-week study in the rat. At oral doses of up to 10 times the human dose, cyclobenzaprine did not adversely affect the reproductive performance or fertility of male or female rats.

A battery of mutagenicity tests using bacterial and mammalian systems for point mutations and cytogenic effects have provided no evidence for a mutagenic potential for cyclobenzaprine.

Pregnancy

Pregnancy Category B: Reproduction studies have been performed in rats, mice, and rabbits at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cyclobenzaprine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because cyclobenzaprine is closely related to the tricyclic antidepressants, some of which are known to be excreted in human milk, caution should be exercised when AMRIX is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of AMRIX has not been studied in pediatric patients.

Use in the Elderly

The plasma concentration and half-life of cyclobenzaprine are substantially increased in the elderly when compared to the general patient population (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Elderly in full Prescribing Information). Accordingly, AMRIX should not be used in the elderly.

ADVERSE REACTIONS

The most common adverse reactions in the two 14-day clinical efficacy trials are presented in Table 1.

Table 1: Incidence of the Most Common Adverse Reactions Occurring in ≥3% of Subjects in Any Treatment Group in the Two Phase 3, Double-Blind AMRIX Trials			
	AMRIX 15 mg N = 127	AMRIX 30 mg N = 126	Placebo N = 128
Dry mouth	6%	14%	2%
Dizziness	3%	6%	2%
Fatigue	3%	3%	2%
Constipation	1%	3%	0%
Somnolence	1%	2%	0%
Nausea	3%	3%	1%
Dyspepsia	0%	4%	1%

In a postmarketing surveillance program (7607 patients treated with cyclobenzaprine 10 mg TID), the adverse reactions reported most frequently were drowsiness, dry mouth, and dizziness.

Among the less frequent adverse reactions, there was no appreciable difference in incidence in controlled clinical studies or in the surveillance program. Adverse reactions which were reported in 1% to 3% of the patients were: fatigue/tiredness, asthenia, nausea, constipation, dyspepsia, unpleasant taste, blurred vision, headache, nervousness, and confusion. The following adverse reactions have been reported in post-marketing experience or with an incidence of less than 1% of patients in clinical trials with the 10 mg TID tablet:

Body as a Whole: Syncope; malaise.

Cardiovascular: Tachycardia; arrhythmia; vasodilatation; palpitation; hypotension.

Digestive: Vomiting; anorexia; diarrhea; gastrointestinal pain; gastritis; thirst; flatulence; edema of the tongue; abnormal liver function and rare reports of hepatitis, jaundice, and cholestasis.

Hypersensitivity: Anaphylaxis; angioedema; pruritus; facial edema; urticaria; rash.

Musculoskeletal: Local weakness.

Nervous System and Psychiatric: Seizures, ataxia; vertigo; dysarthria; tremors; hypertonia;

convulsions; muscle twitching; disorientation; insomnia; depressed mood; abnormal sensations;

anxiety; agitation; psychosis, abnormal thinking and dreaming; hallucinations; excitement;

paresthesia; diplopia.

Skin: Sweating.

Special Senses: Ageusia; tinnitus.

Urogenital: Urinary frequency and/or retention.

DRUG ABUSE AND DEPENDENCE

Pharmacologic similarities among the tricyclic drugs require that certain withdrawal symptoms be considered when AMRIX (Cyclobenzaprine Hydrochloride Extended-Release Capsules) is administered, even though they have not been reported to occur with this drug. Abrupt cessation of treatment after prolonged administration rarely may produce nausea, headache, and malaise. These are not indicative of addiction.

OVERDOSAGE

Although rare, deaths may occur from overdose with AMRIX. Multiple drug ingestion (including alcohol) is common in deliberate cyclobenzaprine overdose. As management of overdose is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment. Signs and symptoms of toxicity may develop rapidly after cyclobenzaprine overdose; therefore, hospital monitoring is required as soon as possible.

All patients suspected of an overdose with AMRIX should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage and emesis is contraindicated.

The principles of management of child and adult overdose are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

DOSAGE AND ADMINISTRATION

The recommended adult dose for most patients is one (1) AMRIX 15 mg capsule taken once daily. Some patients may require up to 30 mg/day, given as one (1) AMRIX 30 mg capsule taken once daily or as two (2) AMRIX 15 mg capsules taken once daily.

It is recommended that doses be taken at approximately the same time each day.

Use of AMRIX for periods longer than two or three weeks is not recommended (see INDICATIONS AND USAGE).

Dosage Considerations for Special Patient Populations: AMRIX should not be used in the elderly or in patients with impaired hepatic function (see WARNINGS).

HOW SUPPLIED

AMRIX extended-release capsules are available in 15 and 30 mg strengths, packaged in bottles of 60 capsules.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN. IN CASE OF ACCIDENTAL OVERDOSE, SEEK PROFESSIONAL ASSISTANCE OR CONTACT A POISON CONTROL CENTER IMMEDIATELY.

Distributed by
Cephalon, Inc., Frazer, PA 19355
Manufactured by Eurand, Inc., Vandalia, Ohio 45377

AMRIX is a trademark of Cephalon, Inc., or its affiliates.
©2004, 2006, 2007 Cephalon, Inc., or its affiliates. All rights reserved.

AMR002a Rev. 4/2008

Cephalon
deliver more.®

RA Patients on Anti-TNF-Alpha Agents at Risk for Herpes Zoster

BY MARY ANN MOON

Rheumatoid arthritis patients who are taking monoclonal anti-tumor necrosis factor- α agents such as infliximab and adalimumab may be at increased risk for developing herpes zoster, according to a report.

An analysis of data from the German RABBIT (Rheumatoid Arthritis Observation of Biologic Therapy) registry, initiated in 2001 to track the long-term safety and effectiveness of biologic agents in rheumatoid arthritis (RA), showed a significant association between reactivation of latent varicella zoster virus and treatment with this class of anti-TNF- α drugs, said Dr. Anja Strangfeld of the German Rheumatism Research Centre Berlin and her associates.

The investigators examined data on 5,040 patients who were treated in 2001-2006 at more than 150 German outpatient clinics and private practices specializing in rheumatology.

A total of 82 patients developed 86 cases of herpes zoster, including 12 cases that required hospitalization. Of these, 39 were temporally linked to adalimumab or infliximab, compared with 23 cases linked to etanercept and 24 linked to conventional RA therapies.

The incidence of herpes zoster was 11.1 per 1,000 patient-years in patients who were taking the monoclonal anti-TNF- α antibodies, compared with 8.9 per 1,000 patient-years for etanercept and 5.6 per 1,000 patient-years for conventional therapies.

After the data were adjusted, the risk for

herpes zoster remained elevated only for patients taking adalimumab or infliximab. In a subgroup of patients who switched from conventional therapies to these anti-TNF- α drugs, the risk for herpes zoster increased after the switch, the investigators said (JAMA 2009;301:737-44).

The database used in this study has been supported by an unconditional joint grant from Essex Pharma, Wyeth Pharma, Amgen, Abbott, F. Hoffmann-La Roche Ltd., and Bristol-Myers Squibb Co. ■



© DR. JAYAKAR THOMAS/DERMATLAS/HTTP://WWW.DERMATLAS.ORG

This 25-year-old man complained of severe pain associated with vesicles and crusts on a red base over the right fourth and fifth thoracic dermatomes.

Continued from previous page

synovium is really small. So when we put a needle in, we're finding that sometimes we're not in the place we think we are, and we're actually injecting into subcutaneous tissue," he said. "What we can see in real time with ultrasound is the synovial space actually expanding when you put in fluid." And while he conceded that joints with large effusions (less than 10% of joint injections) may stand to benefit less from this technique, "In a joint without effusion that has collapsed down (90% of injections), it's a benefit. And that is the great majority of injections."

Ultrasound-guided injections may also benefit obese patients. "We're finding we need much larger or longer needles to get into those joint spaces. So it's been tremendously helpful in those areas."

One of Dr. Park's research colleagues, Dr. Wilmer Sibbitt, was a developer of the Food and Drug Administration-approved reciprocating procedure device, now marketed by Avanca Medical Devices Inc. He reported having no other conflicts to disclose. ■

Diabetes | A whole new perspective

Are you looking at every part of diabetes?

You might be missing GLP-1. It's a natural hormone that helps regulate glucose metabolism. It also slows gastric emptying, promotes satiety, and plays a significant role in beta-cell function.¹ Its multiple actions throughout the body are critical in diabetes.

Unfortunately, your patients might be missing GLP-1, too. Many people with type 2 diabetes may have impaired GLP-1 secretion and impaired beta-cell response to GLP-1.^{2,3} This could contribute to the pathogenesis of the disease.¹

Looking at the whole problem is the most important part of understanding it. That's why Novo Nordisk is dedicated to ongoing research.

References: 1. Zander M, Madsbad S, Madsen JL, Holst JJ. Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and β -cell function in type 2 diabetes: a parallel-group study. *Lancet*. 2002;359(9309):824-830. 2. Toft-Nielsen M-B, Damholt MB, Madsbad S, et al. Determinants of the impaired secretion of glucagon-like peptide-1 in type 2 diabetic patients. *J Clin Endocrinol Metab*. 2001;86(8):3717-3723. 3. Kjems LL, Holst JJ, Volund A, Madsbad S. The influence of GLP-1 on glucose-stimulated insulin secretion: effects on β -cell sensitivity in type 2 and nondiabetic subjects. *Diabetes*. 2003;52(2):380-386.