Caldolor®: Old Drug, New Route

By Rebecca Baer, PharmD

Ibuprofen injection (Caldolor®) for intravenous (IV) administration was approved for use in adults by the U.S. Food and Drug Administration (FDA) in June 2009.[1] Caldolor® is manufactured by Cumberland Pharmaceuticals and is FDA-indicated for treatment of fever, mild to moderate pain and as an adjunct to opioids for the treatment of moderate to severe pain.[2] The only other injectable nonsteroidal anti-inflammatory drug (NSAID) FDA-approved for pain management is ketorolac (Toradol®), which is approved for intravenous or intramuscular use in the treatment of moderate to severe acute pain.[3] Injectable NSAIDs may be useful for hospitalized patients when the oral route of administration is impractical or undesirable. There is no other injectable medication approved by the FDA for treatment of fever.

The recommended analgesic dosing for Caldolor® is 400 to 800 mg IV every six hours as needed. The recommended antipyretic dosing is 400 mg IV followed by 400 mg every four to six hours, or 100 to 200 mg every four hours as needed. The total maximum daily dose is 3200 mg, and the dosing regimen should include the lowest effective dose for the shortest effective duration. To minimize renal risks, patients should be sufficiently hydrated before receiving Caldolor®.[2]

Unlike intravenous ketorolac, which can be administered undiluted over as little as 15 seconds,[3] Caldolor® must be diluted and infused over at least 30 minutes. To avoid hemolysis, Caldolor® must be diluted to a final concentration of 4 mg per mL or less with 0.9 percent sodium chloride, 5 percent dextrose or lactated ringers solution. Therefore, an 800 mg dose must be diluted in at least 200 mL of diluent. The solution is stable at room temperature up to 24 hours after diluting. Caldolor® is available in single-dose vials containing either 400 mg per 4 mL or 800 mg per 8 mL of ibuprofen. The vial stoppers are latex-free.[2]

The drug interactions, contraindications, precautions and FDA boxed warnings assigned to Caldolor® are the same as for oral ibuprofen and other NSAIDs. The boxed warnings pertain to cardiovascular risks and gastrointestinal risks and include the contraindication for its use peri-operatively for coronary artery bypass graft surgery. Caldolor® is also contraindicated in patients with a history of hypersensitivity reactions to ibuprofen or history of aspirin- or NSAID-induced asthma, urticaria or other allergic-type reactions. Adverse reactions reported most frequently (> 5 percent) in pain studies with Caldolor® were nausea, vomiting, headache, flatulence, hemorrhage and dizziness. Except for dizziness, these occurred at rates similar to placebo; all patients were also receiving morphine. Pruritus (<1 percent) was the most common cause of discontinuation in clinical trials. Just as with ibuprofen used by the oral route, Caldolor® should be used cautiously in patients with renal impairment, congestive heart failure, risk of thrombosis or history of gastrointestinal ulcers or bleeding.[2] Caldolor® carries the FDA Pregnancy Category C for the first and second trimesters. As with other NSAIDS, it is Pregnancy Category D in the third trimester and should be used only if the benefit to the mother outweighs the risk of premature closure of the ductus arteriosus in the fetus. The medication has not been adequately studied in pregnant women.[4]

Caldolor® was studied in a randomized, double-blind trial that compared 400 or 800 mg of IV ibuprofen to placebo in patients also receiving morphine for pain following elective orthopedic or abdominal surgery. These investigators found a significant reduction in morphine use (by 22 percent compared to placebo) during the first 24 hours after administration of 800 mg IV ibuprofen every six hours (P=0.03). They also found significant reductions compared to placebo in pain at rest and with movement. Dizziness was reported significantly more often for the ibuprofen 800 mg subjects (9 percent) than for the placebo subjects (1 percent), P=0.011. Gastrointestinal adverse effects were reported significantly more often for placebo subjects (84 percent) than for subjects in the 400 mg ibuprofen group (74 percent, P=0.05) and the 800 mg ibuprofen group (71 percent, P=0.009).[5]

Caldolor® was studied in another pain trial, which included 319 patients given 800 mg IV ibuprofen or placebo every 6 hours after abdominal hysterectomy. All patients also had access to morphine, and efficacy was assessed by measuring use of morphine post-operatively for 24 hours. Researchers found that the median morphine requirement was 19 percent less for patients in the ibuprofen group compared to the placebo group (47 mg and 56 mg respectively, P<0.001). Patients in the Caldolor® group (versus placebo group) also reported a 21 percent reduction in pain intensity score at rest (P=0.011), and a 14 percent reduction in pain intensity score with movement (P=0.010) through the 24th hour after surgery. Adverse events were similar in the two treatment arms.[6]

The ability of Caldolor® to reduce fever was tested in a randomized, double-blind comparison (n = 120) of 100 mg, 200 mg, 300 mg or 400 mg of IV ibuprofen to placebo given every four hours for 24 hours to hospitalized patients with temperatures of 101°F or higher. The primary objective was to determine the efficacy of 400 mg Caldolor® by measuring the percentage of patients whose fever was reduced below 101°F four hours after administration. Four hours following administration, 32 percent of subjects in the placebo group had temperatures below 101°F compared to 77 percent in the 400 mg Caldolor® group (P=0.0005), 70 percent in the 200 mg group (P=0.0043) and 61 percent in the 100 mg group (P=0.0264). Adverse events were similar between placebo and treatment groups except for bacteremia, which occurred in 4 patients in the 100 mg Caldolor® group and no patients in the placebo or other Caldolor® groups. This adverse event was felt to be unrelated to Caldolor®.[7] The manufacturer also recently announced results from a clinical trial showing success in fever reduction with 800 mg Caldolor® administered every six hours over the first 24 hours of treatment in adult burn patients.[8]

There are no published clinical trials comparing Caldolor® to other injectable NSAIDs for treatment of pain. There are studies planned or underway for comparisons between Caldolor® and acetaminophen.[9] Caldolor® may prove to be a safer choice than ketorolac, the only other injectable NSAID approved in the U.S. to treat pain. The product labeling for ketorolac includes more warnings than for other NSAIDs, including a boxed warning limiting the use of injectable or oral ketorolac to moderate to severe acute pain, and for duration of no more than five days.[10] The average wholesale price (AWP) for Caldolor® is $9.20 for a 400-mg vial and $13.12 for an 800-mg vial.[11] The AWP for ketoroloc is around $2 or less per dose for the 15-mg or 30-mg injection.[12]

Caldolor® may prove to be a safer option than ketorolac in hospitalized patients for whom the oral route is not desirable, especially those patients at high risk for the adverse events associated with ketorolac. Disadvantages to Caldolor® are the higher acquisition costs, the extra volume of fluid needed for diluting each dose and the need to infuse each dose over at least 30 minutes. Caldolor® is the subject of further clinical trials, including a trial evaluating the pharmacokinetic profile, safety and tolerability of intravenous ibuprofen administered over 5 to 7 minutes.[2] In addition, there could be another injectable NSAID on the horizon. According to a Dec. 2, 2009, press release, Javelin Pharmaceuticals has submitted a New Drug Application for its injectable NSAID product, Dyloject™ (diclofenac sodium), to be used as a single agent to manage acute moderate to severe pain in adults.[13]

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