The Shortened Infusion Time of Intravenous Ibuprofen, Part 2: A Multicenter, Open-label, Surgical Surveillance Trial to Evaluate Safety

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ABSTRACT

Purpose: The literature and clinical data support the use of intravenous (IV) infusions of ibuprofen to control pain and reduce the opioid requirements associated with surgical pain. According to current guidelines, IV ibuprofen can be administered via a slow IV infusion performed during a 30-minute period. Although recent studies indicate that more rapid infusions may yield additional benefits for patients, the safety of such an approach needs further evaluation. The main purpose of this study was to determine the safety of single and multiple doses of IV ibuprofen (800 mg) administered over 5 to 10 minutes at the induction of anesthesia and after the surgical procedure for the treatment of postoperative pain.

Methods: This was a Phase IV, multicenter, open-label, clinical surveillance study. It was conducted at 21 hospitals in the United States, and 300 adult hospitalized patients undergoing surgery were enrolled. The exclusion criteria for the study were: inadequate IV access; hypersensitivity to any component of IV ibuprofen, aspirin, or related products; and any active, clinically significant bleeding. Also excluded were patients who had taken NSAIDs <6 hours before administration of IV ibuprofen; pregnant or breastfeeding female patients; and patients in the perioperative period of coronary artery bypass graft surgery. Patients received 800 mg of IV ibuprofen administered over 5 to 10 minutes preoperatively. Vital signs, adverse events, and pain scores were assessed.

Findings: Approximately 22% (65 of 300) of patients reported adverse events (serious and nonserious). The most common adverse event was infusion site pain (34 of 300 [11%]). No deaths were reported. Nine subjects reported serious adverse events, 8 of which occurred during the first 6 hours. All serious events reported were judged unrelated to ibuprofen. Of the 300 total patients, 2 (0.67%) discontinued the study drug due to an adverse event (1 patient discontinued the study because of infusion site pain, and 1 patient withdrew due to a hypersensitivity reaction after drug administration).

Implications: Our study found that IV ibuprofen infused over 5 to 10 minutes at induction of anesthesia is a safe administration option for surgical patients. ClinicalTrials.gov identifier: NCT01334957. (*Clin Ther.* 2015;37:368–375) © 2015 The Authors. Published by Elsevier HS Journals, Inc.

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INTRODUCTION

Although the importance of controlling postoperative pain is widely accepted, achieving this goal remains a challenge.[1] The 2012 Updated Report by the American Society of Anesthesiologists Task Force on Acute Pain Management recommends a multimodal approach to pain management.[2] The task force agrees that, unless contraindicated, patients should receive an around-the-clock regimen of NSAIDs, cyclooxygenase-2 selective inhibitors, and/or acetaminophen. Following this guidance and using a multimodal approach, numerous randomized, double-blind, placebo-controlled trials were conducted in surgical patients undergoing orthopedic procedures evaluating both pain reduction and the opioid-sparing effects of intravenous (IV) ibuprofen. These studies demonstrated a significant reduction in pain and a morphine-sparing effect when IV ibuprofen therapy (each dose infused over 30 minutes) was initiated, either at induction of anesthesia or perioperatively.[3–5]

Although the 30-minute infusion of IV ibuprofen has been shown to be safe and efficacious, further shortening of the infusion time may provide additional benefits. A 5- to 10-minute infusion of IV ibuprofen would significantly shorten the T_{max} and time of onset of the therapeutic action compared with the 30- to 60-minute infusion protocol or peroral administration. It would then eliminate any variability in ibuprofen's pharmacodynamics associated with the variable absorption rate of the orally administered formulation of the drug.[6] These factors are particularly critical in the perioperative period, during which time and pain are closely related. Emergency medicine is another specialty in which rapid infusion of IV ibuprofen may prove beneficial.

A recent study in healthy subjects found that a shortened infusion time of 5 to 7 minutes for IV ibuprofen is well tolerated and results in a higher C_{max} and shorter T_{max} compared with a 30-minute infusion or oral administration.[7] Subsequently, a Phase IV, multicenter, open-label, surveillance safety study found that a shortened infusion time of IV ibuprofen can be safely administered in hospitalized patients experiencing fever or mild to moderate or moderate to severe pain.[8]

The present trial was designed to further evaluate the safety of a shortened infusion time of IV ibuprofen in surgical patients. We hypothesized that a shortened infusion time in surgical patients would present no additional risks compared with a 30-minute infusion period.

PATIENTS AND METHODS

This Phase IV, multicenter, open-label, clinical surveillance study was designed to assess the safety of IV ibuprofen administered over 5 to 10 minutes to hospitalized adult patients undergoing surgical procedures. The study was approved by site-specific institutional review boards. Adults (ie, aged $\geq$18 years) scheduled for surgery and with an anticipated need for postoperative analgesia were eligible for study inclusion. Exclusion criteria included: inadequate IV access (ie, difficulties in securing reliable IV access by using a $\geq$20-gauge diameter catheter); history of allergy or hypersensitivity to any component of IV ibuprofen or aspirin (or related products); or any active, clinically significant bleeding. Patients were excluded from enrollment if they had taken NSAIDs $<$6 hours before IV ibuprofen administration; also excluded were pregnant or breastfeeding female patients or patients in the perioperative period of coronary artery bypass graft surgery.

Eligible patients received up to 4 doses of 800 mg of IV ibuprofen, administered at 6-hour intervals, depending on patient requirements. The first dose of IV ibuprofen was administered before the surgical procedure, approximately at the time of induction of anesthesia. The drug was diluted in saline and administered at a concentration of $\leq$4 mg/mL over 5 to 10 minutes. The use of the 800-mg preoperative dose of IV ibuprofen was based on the product package insert and previous surgical studies.[3–5,9] All NSAIDs (excluding ibuprofen) were restricted during the treatment and posttreatment periods. There was no formal anesthesia protocol.

Assessments

To evaluate the safety of a single dose of IV ibuprofen administered over 5 to 10 minutes for the treatment of postoperative pain, vital signs were recorded at baseline and 4 hours after the initial IV ibuprofen infusion. The incidence of adverse events