Off-Label Drug Uses

Lidocaine: Cough (Fentanyl Induced)

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This *Hospital Pharmacy* feature is extracted from *Off-Label Drug Facts*, a publication available from Wolters Kluwer Health. *Off-Label Drug Facts* is a practitioner-oriented resource for information about specific drug uses that are unapproved by the US Food and Drug Administration. This new guide to the literature enables the health care professional or clinician to quickly identify published studies on off-label uses and determine if a specific use is rational in a patient care scenario. References direct the reader to the full literature for more comprehensive information before patient care decisions are made. Direct questions or comments regarding *Off-Label Drug Uses* to jgeneral@ku.edu.

BACKGROUND

Although most opioid agonists are known to have antitussive activity, the intravenous (IV) administration of fentanyl, a synthetic opioid, has been reported to induce vigorous reflex cough episodes in as many as 28% to 46% of patients receiving the drug. In a study of 1,311 adult surgical patients undergoing general anesthesia, 120 developed vigorous cough attacks within the first 20 seconds after IV administration of fentanyl.¹ In this study, independent risk factors for fentanyl-induced cough were younger age, being a nonsmoker, premedication with a benzodiazepine, absence of epidural lidocaine, and absence of a priming dose of vecuronium. In contrast, risk decreased with increased age, cigarette smoking, epidural lidocaine, and a priming dose of vecuronium. There was no effect due to gender, prior atropine use, or underlying pulmonary disease (eg, bronchial asthma, chronic obstructive pulmonary disease [COPD]). Despite this information, there is no clear understanding of the mechanism of action related to fentanyl-induced cough. Several pharmacological therapies have been evaluated with varying rates of success, including morphine, inhaled terbutaline or salmeterol, cromolyn, and, most recently, IV lidocaine. Lidocaine has been shown to reduce airway reactivity, possibly via mechanically and chemically induced airway reflexes.

PATIENT POPULATION

Adult surgical patients with American Society of Anesthesiologists (ASA) physical status I or II, scheduled

for elective surgery, and receiving fentanyl as an induction agent (2.5 to 3 mcg/kg).

DOSAGE AND DURATION

The IV dose of lidocaine in the prevention of fentanyl-induced cough has ranged from 0.5 to 2 mg/kg, administered over 5 seconds, 1 minute prior to the administration of fentanyl. One controlled study, which evaluated 3 different dosages (0.5, 1, or 1.5 mg/kg), suggested that there were no significant differences among the dosages and that 0.5 mg/kg may be the minimal dose required to suppress fentanyl-induced cough.²

RESULTS

Lidocaine for the prevention of fentanyl-induced cough has been evaluated primarily in controlled trials enrolling over 500 surgical patients, demonstrating significantly greater efficacy than placebo.²⁻⁴

Controlled Trials

In a double-blinded, placebo-controlled, prospective trial, 502 adult patients (age range, 18-60 years) with ASA physical status I or II scheduled for elective surgery were randomized to receive either intravenous lidocaine (1.5 mg/kg) or placebo administered over a 5-second period 1 minute prior to peripheral intravenous fentanyl (3 mcg/kg) administration. The assumption was that the incidence of coughing after intravenous fentanyl administration would be 25% and that a reduction of 10% after

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lidocaine treatment for an 80% power of test would require a minimum of 250 patients in each group. A total of 251 patients were assigned to each group and all completed the trial. Coughing severity was based on the number of episodes (mild, 1 to 2; moderate, 3 to 4; and severe, ≥ 5). The mean age was 41.67 years and 42.26 years in the lidocaine and placebo groups, respectively. Coughing occurred in 13.1% of the lidocaine group and in 34.2% of the placebo group. The absolute risk reduction with lidocaine pretreatment was 21.12%, and the relative risk reduction was 62%. There was no significant difference in severity of cough between the 2 groups. The authors concluded that IV lidocaine pretreatment given 1 minute prior to fentanyl is effective in suppressing fentanyl-induced cough without affecting the severity of cough.³

In another double-blinded, placebo-controlled trial by the same investigative group, 3 different dosages of lidocaine (0.5, 1, or 1.5 mg/kg) pretreatment were evaluated in suppressing fentanyl-induced cough in adult patients scheduled for elective surgery. The administration of lidocaine and fentanyl and the assessment of cough were the same as the previous study. In contrast, the incidence of fentanyl-induced cough was assumed to be 30%, with a 20% reduction assigned to lidocaine treatment. With these considerations, an 80% confidence level of detecting a true difference (at the 5% level of significance) between the groups required a minimum of 79 patients in each group. A total of 320 patients were enrolled and completed the study (80 in each group). Coughing occurred in 35% of the placebo group and in 13.75%, 15%, and 13.75% of the lidocaine group (0.5 mg/kg, 1 mg/kg, or 1.5 mg/kg), respectively ($P < .05$). However, there was no difference in the severity of cough among the groups. The authors concluded that the 0.5 mg/kg lidocaine dose may be the minimal dose to suppress fentanyl-induced cough and that further increases in dose do not reduced the incidence or severity of cough.³

In a double-blind, placebo-controlled trial, 118 adult ASA I or II surgical patients were randomized to receive IV doses of lidocaine (2 mg/kg), propofol (0.6 mg/kg), ephedrine (5 mg), or placebo 1 minute prior to the administration of fentanyl (2.5 mcg/kg). Cough was assessed within 2 minutes after the fentanyl injection. The intensity of the cough was graded as no cough (grade 0), cough less than 3 seconds (grade 1), and cough more than 3 seconds (grade 2). A total of 65% (20/31) of placebo patients developed coughing. In contrast, coughing was significantly less frequent in

the lidocaine and ephedrine pretreatment groups (14% [4/29] and 21% [6/28], respectively; $P < .05$). The frequency of cough in the propofol group was not significantly different than that of the placebo group (37%). In the placebo group, an age-related incidence of fentanyl-induced cough was observed (92%, < 35 years; 54%, 36-50 years; 20%, > 51 years; $P < .05$). The authors concluded that intravenous lidocaine or ephedrine, but not propofol, was effective in preventing fentanyl-induced cough.⁴

SAFETY

Adverse reactions were reported in only 1 controlled trial evaluating 3 active treatments (ie, ephedrine, lidocaine, propofol) compared with placebo. Systolic blood pressure and heart rates did not differ significantly after treatment from baseline values in the placebo and lidocaine groups. In contrast, a significant decrease in systolic blood pressure and heart rate was observed in the propofol group and a significant increase was observed in the same parameters in the ephedrine group. All groups showed a decrease in oxygen saturation, but the decrease was only significant in the propofol group when compared with placebo. Adverse reactions noted in the lidocaine group included dizziness (1), injection pain (1), and nausea/vomiting (1). In the propofol group, adverse reactions included dizziness (2) and injection pain (25). No arrhythmias were observed in any of the patients.⁴

Some clinicians have raised concerns regarding the need for another drug during the induction of anesthesia.⁵ Based on clinical scenarios, they suggest that slow IV administration of fentanyl may be effective in preventing fentanyl-induced cough and that administering IV lidocaine 150 mg may be associated with other risks. They note that IV lidocaine 2 mg/kg exceeds the recommended dose (1 to 1.5 mg/kg) for resuscitation of ventricular fibrillation; as with any antiarrhythmic drug, it may possess some arrhythmogenic effects. In addition, these clinicians suggest that the vasodilatory effects of lidocaine may potentially augment the cardiovascular depression observed with some induction agents.

THERAPY CONSIDERATIONS

Initial data from large controlled trials suggest that pretreatment with lidocaine, in varying doses, is effective in reducing fentanyl-induced cough. The lowest effective dose studied to date was 0.5 mg/kg. Some clinicians have raised concerns regarding the need for another drug during the induction of anesthesia that might carry an increased risk of adverse reactions.

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