ORIGINAL ARTICLE

Diphenhydramine as an adjunct to sedation for colonoscopy: a double-blind randomized, placebo-controlled study CME

Raymond H. Tu, MD, Pam Grewall, MD, Joseph W. Leung, MD, FRCP, FACP, FACG, Arun G. Suryaprasad, MD, Paul I. Sheykhzadeh, DO, Caitlin Doan, MD, Juan Carlos Garcia, MD, Nan Zhang, MS, Thomas Prindiville, MD, Surinder Mann, MD, Walter Trudeau, MD

Sacramento, California, USA

Background: Intravenous benzodiazepines in combination with opiates are used to achieve moderate sedation for colonoscopy. Although effective, these agents have potential adverse effects, such as respiratory depression and hypotension. Diphenhydramine hydrochloride possesses central nervous system depressant effects that theoretically could provide a synergistic effect for sedating patients.

Objective: The objective was to assess the efficacy of adding diphenhydramine hydrochloride as an adjunct to improve sedation and to reduce the amount of standard sedatives used during colonoscopy.

Design: We conducted a prospective, randomized, double-blind, placebo-controlled study.

Setting: The study was conducted in a university hospital with an active GI fellowship training program.

Patients: The study group comprised 270 patients undergoing screening/diagnostic/therapeutic colonoscopy were enrolled.

Interventions: Patients were randomized to receive either 50 mg of diphenhydramine or placebo, given intravenously 3 minutes before starting conscious sedation with intravenous midazolam and meperidine.

Main Outcome Measurements: The main outcome measure was anesthetic effect as assessed by the endoscopy team and by the patient; quantity of adjunctive sedatives to achieve adequate sedation.

Results: Of 270 patients, data were analyzed for 258 patients, with 130 patients in the diphenhydramine group and 128 patients in the placebo group. There was a 10.1% reduction in meperidine usage and 13.7% reduction in midazolam usage in favor of the diphenhydramine group. The mean evaluation scores as judged by the faculty, the fellows, and the nurses were statistically significant in favor of the diphenhydramine group. In addition, patient scores for overall sedation and pain level favored the group that received diphenhydramine.

Conclusions: Intravenous diphenhydramine given before initiation of standard sedation offers a significant benefit to conscious sedation for patients undergoing colonoscopy. (Gastrointest Endosc 2006;63:87-94.)

Colonoscopy is an effective screening technique for colorectal cancer. Moreover, it can be useful in diagnosing conditions that cause abdominal pain, diarrhea, weight loss, and hematochezia. Despite the advent of newer technologies, colonoscopy remains the only therapeutic modality for removing polyps and for obtaining biopsy specimens of the colon. The inherent risks of colonoscopy include bleeding, perforation, medication reaction, and infection.[1] The cost of individual procedures and patient discomfort also should be considered. Although unsedated colonoscopy remains a feasible option and, indeed, has been reported in selected patients, the majority of patients request and often require the use of sedative medications.

Since the 1980s, intravenous (IV) benzodiazepines, such as diazepam and midazolam, have been used to provide anxiolytic and amnestic effects in combination with IV opiates, such as meperidine and fentanyl, which provide analgesia.[2,3] Although effective, these agents have potential adverse side effects, such as respiratory depression, hypoxia, hypotension, and paradoxical agitation.[4]

Diphenhydramine hydrochloride, an ethanolamine, belongs to the class of histamine 1 (H1) antagonists and commonly is used to treat allergic symptoms. It has central nervous system (CNS) stimulant effects that typically

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occur during poisoning, as well as CNS depressant effects that more commonly occur in therapeutic doses.[5] Its sedative properties have been exploited for premedication in dental, ophthalmologic, and endoscopic procedures.[6-11]

The primary end points of this study are to determine if the addition of diphenhydramine to midazolam and meperidine before colonoscopy would (1) improve sedation and (2) decrease the usage of benzodiazepines and opiates without compromising the success of colonoscopy, procedure length, or recovery time. Cost analysis also will be performed and compared between the two groups.

Capsule Summary

What is already known on this topic

- Intravenous benzodiazepines and opiates are used for sedation during colonoscopy, despite their potential adverse effects, such as respiratory depression, hypotension, and paradoxical agitation.
- Diphenhydramine hydrochloride, a histamine-1 antagonist and CNS depressant, may provide a synergistic sedative effect.

What this study adds to our knowledge

- In a prospective, randomized, double-blind, placebo-controlled study, intravenous diphenhydramine, given before standard sedation, offered a significant benefit to conscious sedation in patients undergoing colonoscopy.

PATIENTS AND METHODS

Patients

Consecutive patients over the age of 18 years who were undergoing elective screening/surveillance, diagnostic, and/or therapeutic colonoscopy from November 2002 to May 2004 at the University of California at Davis Medical Center (UCDMC) were eligible for participation. Exclusion criteria included patients with a history of sensitivity to diphenhydramine, closed-angle glaucoma, severe cardiopulmonary disease, pregnancy, and an inability to understand and execute the informed consent process. The study was approved by the institutional review board at UCDMC, and informed consent was obtained from all participants.

Study design

Participants were randomly assigned to receive either 1 mL (50 mg/mL) diphenhydramine hydrochloride or 1 mL 0.9% sodium chloride IV. The standard IV dose of diphenhydramine is 25 to 50 mg. To optimize its sedative properties, 50 mg diphenhydramine was used. Randomization was carried out by the University of California, Davis Investigational Drug Pharmacy, who also prepared and dispensed the study medication as a clear solution in numerically labeled vials.

Four gastroenterology fellows with at least 12 months' experience performed the colonoscopies using either a standard 168-cm video colonoscope (CF-Q160L; Olympus Optical Co, Ltd, Tokyo, Japan) or a 168-cm variable-stiffness pediatric video colonoscope (PCF-160AL; Olympus). Each procedure was supervised by one of 5 attending physicians. Eight endoscopy nurses participated in this study by administering the sedative medications during the colonoscopy.

At the time of the procedure, baseline vital signs, including oxygen saturation, were recorded. Each patient routinely received 2 L of supplemental oxygen by nasal cannula. For each procedure, the contents of the assigned vial were administered intravenously 3 minutes before administration of other medications. The patient, the endoscopists, and the endoscopy nurse were unaware of the contents of each vial. Conscious sedation was achieved and maintained with IV administration of meperidine in 25-mg increments and midazolam in 1-mg increments at the discretion of the endoscopist and the nurse.

The procedure began once adequate sedation had been achieved (as judged by the endoscopist). Continuous monitoring of pulse rate, electrocardiogram, and pulse oximetry was performed. Blood pressure was monitored at 5-minute intervals during the procedure and at 15-minute intervals during recovery by using Datascope Passport monitors (Datascope Corp, Paramus, NJ). Procedure-related complications, including oxygen desaturation, hypotension, and cardiac arrhythmias, were managed according to standard endoscopy laboratory procedures under the supervision of the attending physician.

The following times were recorded: (1) time of study medication administration, (2) times of each incremental sedative dose given, (3) colonoscope insertion, (4) intubation of cecum, (5) removal of colonoscope, and (6) end of postprocedure recovery. The following procedural events were recorded: (1) procedure interruption, defined as any occasion when the patient became sufficiently agitated or uncomfortable to require the endoscopist to temporarily stop the procedure or administer additional medication; (2) oxygen desaturation, $<89\%$ persisting for >30 seconds; (3) hypotensive episodes, defined as a >20 mm Hg decrease in systolic blood pressure or a value of <90 mm Hg systolic persisting for 60 seconds; (4) use of naloxone (Narcan; Endo Pharmaceuticals Inc, Chadds Ford, Pa) or flumazenil (Romazicon; Roche Laboratories, Nutley, NJ) to reverse sedation.

Endoscopists' assessments

Immediately after the procedure, the endoscopy nurse, the staff gastroenterologist, and the gastroenterology fellow each rated the quality of sedation on a standard 10-point scale: 1 (poor) to 10 (excellent). Qualitative