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## Original Contributions

### THE GI COCKTAIL IS NO MORE EFFECTIVE THAN PLAIN LIQUID ANTACID: A RANDOMIZED, DOUBLE BLIND CLINICAL TRIAL

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□ **Abstract**—The “GI Cocktail” is a mixture of medications often given in the Emergency Department (ED) for dyspepsia symptoms. Several combinations are used, but the most effective has not yet been determined. This study compared three combinations commonly given for dyspepsia. The study was a prospective, randomized, double-blinded trial comparing antacid (group 1); antacid + Donnatal® (group 2); antacid + Donnatal® + viscous lidocaine (group 3) for acute treatment of dyspepsia in the ED. Patients were randomly assigned to receive one of the three medication combinations. Patients rated their discomfort on a Visual Analog Scale (VAS) immediately before receiving the medication and 30 min later. Change in VAS was the primary study endpoint. A 13-mm difference in VAS was considered clinically significant. VAS change in the three groups was compared using multivariable regression, controlling for pretreatment VAS, study drug, previous antacid use, and gastrointestinal (GI) history. One hundred twenty patients were enrolled between July and December 2000. One hundred thirteen subjects (113) completed the protocol: Group 1 (N = 38); Group 2 (N = 37); Group 3 (N = 38). There was no statistically significant difference between the groups in terms of age, gender, GI history, previous antacid use, or initial degree of pain. Group 1 had a  $25 \pm 27$  mm mean ( $\pm$  SD), decrease in pain; Group 2,  $23 \pm 22$  mm decrease; and Group 3,  $24 \pm 26$  mm decrease. There was no statistically significant difference in pain relief between the three groups on univariate analysis or multivariable regression. In conclusion, the addition of Donnatal® or Donnatal® + lidocaine to an antacid did not relieve

dyspepsia better than plain antacid. The “GI Cocktail” concoction may not be necessary. © 2003 Elsevier Inc.

□ **Keywords**—GI Cocktail; dyspepsia; liquid antacid; Donnatal; viscous lidocaine

#### INTRODUCTION

Liquid antacids (Maalox®, Mylanta®, etc) have long been used for symptoms of stomach discomfort, and are widely available without prescription. Hospitals and Emergency Departments (EDs) have for many years mixed additional medication with these antacids in an attempt to improve their efficacy. This combination is often referred to as a “GI Cocktail.” The most common of these additional medications are Donnatal®, an antispasmodic, and viscous lidocaine, a topical anesthetic.

Although this practice is widespread, there has been little research to demonstrate that the addition of these medications provides a benefit over the antacid alone. Antispasmodic agents have been evaluated only in a few studies of patients with dyspepsia and have had mixed results. Kagan and Rose suggested that the addition of dicyclomine to an antacid preparation improves efficacy (1,2). In a later study, Stephens et al. suggested that an antacid alone is as effective as a dicyclomine and antacid combination (3).

This relative lack of research may be due to the fact

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that both Donnatal<sup>®</sup> and lidocaine in the doses normally used are usually very well tolerated, with minimal or no side effects, and of fairly low cost. However, despite their apparent benign nature, there are costs both to purchase these medications and to measure and mix them. In addition, those patients who have glaucoma or urinary retention may be put at risk by using Donnatal<sup>®</sup> (4). Therefore, if there is no benefit to this mixture, its use should be abandoned.

This study was conducted to compare the efficacy of Donnatal<sup>®</sup>-viscous lidocaine-antacid (GI Cocktail), Donnatal<sup>®</sup>-antacid, and antacid alone in the treatment of dyspepsia in the ED.

## METHODS

### *Study Design*

This was a double blind, randomized study comparing three different medication regimens for the treatment of dyspepsia in adult patients in the ED. We did not include a placebo control group. All participants gave informed consent. The Institutional Review Board of the study institution approved this study.

### *Study Group*

The trial was conducted in the ED of an urban, tertiary care center with an annual visit census of 55,000. The study group was a convenience sample of adult patients for whom the treating Emergency Physician ordered a "GI Cocktail." Medication was ordered at the discretion of the treating physician, and patients were approached for enrollment only after the treating physician placed this order. No attempt was made to standardize criteria for receiving a "GI Cocktail," but these typically included patients complaining of heartburn, acid reflux, bloating, or epigastric pain or burning. Patients with suspected cardiac or pulmonary etiology of discomfort (including patients receiving any cardiovascular medications in the ED), pregnancy, oral warfarin therapy, active gastrointestinal (GI) bleeding (other than heme-positive stool), incompetence to consent to study or comprehend rating scale, and self-administration of antacid within 1 h before arrival were excluded from the study population. Specific inclusion and exclusion criteria are shown in Table 1.

### *Study Protocol*

Patients in whom the Emergency Medicine residents or faculty ordered a "GI Cocktail" were screened for entry

**Table 1. Inclusion and Exclusion Criteria**

Inclusion criteria	
Patient at least 18 years old	
Dyspepsia symptoms	
Epigastric pain	
Bloating	
Acid reflux	
Epigastric fullness	
Heartburn	
Easy satiety	
Exclusion criteria	
Suspected cardiac or pulmonary etiology	
Patients receiving cardiac medications in the ED	
Pregnancy	
Oral warfarin therapy	
Active GI bleeding (other than heme-positive stool)	
Unable to consent to study	
Inability to read or comprehend rating scale	
Self-administration of an antacid within (one) hour prior to arrival in ED	

criteria. Patients meeting all eligibility requirements and consenting for participation were randomized to treatment with either 30 cc of Mylanta<sup>®</sup> (Group 1); 30 cc of Mylanta<sup>®</sup> and 10 cc of Donnatal<sup>®</sup> (Group 2); or 30 cc of Mylanta<sup>®</sup>, 10 cc of Donnatal<sup>®</sup>, and 10 cc of 2% viscous lidocaine (Group 3). Patients were not to receive any additional medications during the study period. All study medications were prepared in advance by the study institution's pharmacy in identical containers with water and artificial color used to make identical volumes and color. This was done to blind subjects, caregivers, and researchers to the identity of the study drug. The containers of study drug were placed in sequentially numbered study packets in a random order as determined by the pharmacy using a computer random number generator. These packets also contained a written consent form, subject information, and demographics form, two visual analog scales (VAS #1 and #2), and a unit dose sample of study drug. Packets were kept in the ED.

After obtaining written informed consent from the patients, baseline data were obtained. These included name, age, gender, ethnicity, GI history (defined as previously diagnosed peptic ulcer, gastritis, acid reflux, or dyspepsia), current medications, previous antacid use, and current symptoms. Just before the administration of the study medication, patients were asked to indicate their current pain severity with a single mark through a standard 100 mm linear visual analog scale marked "unbearable pain" at the highest end and "no pain" at the lowest end. A research study assistant, Emergency Medicine resident, or a research nurse, who were all blinded to the study medication assignment, performed administration of the VAS. The time of the VAS #1 was documented on the research record. Immediately after VAS #1 was administered, the study medication was given to

the patient. After 30 min, the patients reassessed their pain on a second 100-mm visual analog scale (VAS #2). Patients were not allowed to look at their baseline (VAS #1) when performing the posttreatment (VAS #2). Throughout the entire study, including the data analysis phase, double blinding of the study assignment was maintained.

### Outcomes

The primary outcome was the amount of relief of pain and discomfort as measured by the difference in millimeters between the pretreatment and posttreatment visual analog scales. The distance between VAS #1 and VAS #2 was measured to the nearest millimeter. Before the initiation of the study, a clinically significant response to treatment was defined as a 13 mm or greater decrease from baseline (5).

### Data Analysis

Before the study, sample size calculations demonstrated that 40 subjects per group would be necessary to demonstrate a 13 mm difference with confidence interval (C.I. 0.8;  $p = .05$ ). Baseline data were compared using one-way ANOVA. VAS change within each group was compared using Student's *t*-test. VAS change between groups was evaluated using one-way ANOVA and, to control for possible confounders, multivariable regression was performed. The multivariable regression controlled for pretreatment VAS, study drug assignment, and other variables felt to be possible clinical confounders. Potential confounders included previous antacid use and GI history. Any other variables that were associated with the outcome variable at  $p < .10$  in bivariate regressions were also to be included. Using the baseline value (VAS #1) as a covariate in regression analysis controls for each individual's baseline value, allowing the model to compare the amount of improvement between individuals.

## RESULTS

There were 120 patients enrolled between July and December 2000. One hundred thirteen ( $N = 113$ ) completed the protocol. Two subjects were inadvertently enrolled a second time on a subsequent return visit to the ED. The first visit of each subject was included in the study and the second subject visit was removed from the final analysis. Three subjects had no discomfort with an initial VAS score of zero, before study medication was

**Table 2. Group Characteristics**

	Group 1	Group 2	Group 3	<i>p</i> Value univariate
Subject (N = 113)	38	37	38	
Gender (%) female	63.2%	67.6%	57.9%	0.692
Age	41.5 ± 14.1	37.2 ± 16.5	41.3 ± 14.7	0.386
GI history positive (%)	39.5%	35.1%	29.0%	0.631
Antacid use positive (%)	26.3%	18.9%	31.6%	0.459
VAS 1 (mm)	66.6 ± 27.6	63.3 ± 29.5	61.6 ± 25.5	0.714

given and these were eliminated from the final analysis. Two subjects failed to meet study entry criteria and did not complete the study. Thirty-eight ( $N = 38$ ) patients were in Group 1, thirty-seven ( $N = 37$ ) patients in Group 2, and thirty-eight ( $N = 38$ ) in Group 3. There was **no** statistically significant difference between the groups in terms of age, gender, GI history, previous antacid use, or initial degree of pain (VAS #1) (Table 2).

VAS #2 was lower than VAS #1 in each of the study groups. Group 1 had a  $25 \pm 27$  mm (mean ± SD), decrease in pain. Group 2 had a  $23 \pm 22$  mm (mean ± SD) decrease in pain; Group 3 had a  $24 \pm 26$  mm (mean ± SD) decrease in pain (Figure 1).

These within-group differences were statistically significant for each group (Table 3). In multivariable regression, controlling for VAS #1, GI history and antacid use, there was **no** statistically significant difference between the three treatment groups. Pretreatment (VAS #1) was strongly related to the degree of pain relief ( $p = .004$ ), but GI history ( $p = .249$ ) and previous antacid use ( $p = .243$ ) were not. In the univariate analysis, neither age nor gender was related to outcome, ( $p > .3$ ), and they were not included in the multivariable regression.

## DISCUSSION

Dyspepsia, defined as upper abdominal or epigastric discomfort, heartburn, bloating, or other symptoms considered to be referable to the upper alimentary tract, is extremely common (6–9). This vague group of symptoms is thought to have multiple causes. These include irritation of the esophageal or gastric mucosa and intestinal dysmotility (10,11). Although the specific etiology of dyspepsia in patients who present to the ED may not be known, the typical treatment is with a “GI Cocktail” (a mixture of liquid antacid, viscous lidocaine, and often an anticholinergic or antispasmodic agent) (12).

Numerous studies have shown that antacids are ben-

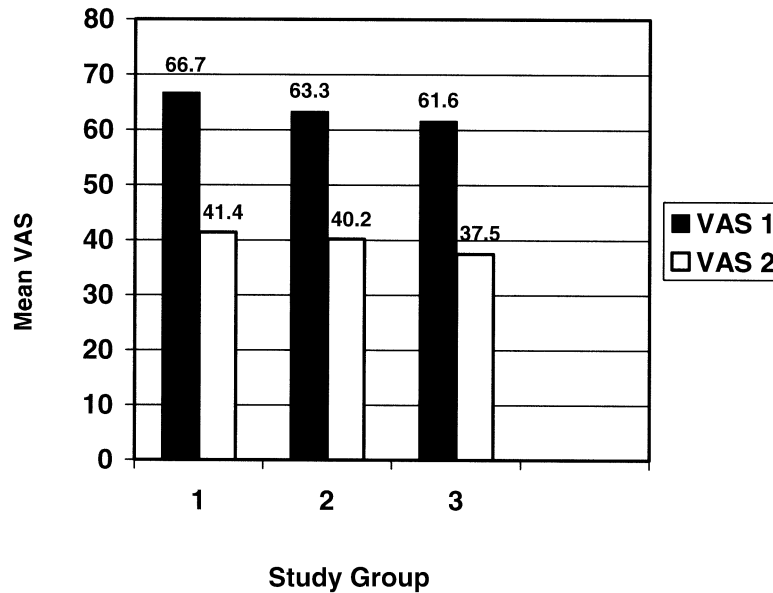


Figure 1. Response to study drug.

eficial in the treatment of dyspepsia (13–17). Because topical lidocaine can produce anesthesia on mucous membranes, and at least some cases of dyspepsia may involve mucosal irritation, it is reasonable to postulate a benefit from viscous lidocaine in patients with dyspepsia. However, only one study, by Welling and Watson in 1990, evaluated the use of antacid combined with viscous lidocaine (10). This was a randomized, patient-blinded study in which 34 subjects with dyspepsia received plain liquid antacid and 39 subjects received antacid plus viscous lidocaine. Symptom severity was measured with a visual analogue scale before and 30 min after medication. The lidocaine/antacid treatment group had a 40 mm improvement on VAS and the plain antacid group had only 9 mm. Although this difference was statistically significant, there was no attempt to blind the interviewers to the agents, raising the question of observer bias. More importantly, this study failed to show

a clinically significant benefit to the plain antacid, which is contrary to both the above-cited studies and most practitioners' experience. This inconsistency raises the possibility that the two treatment groups may not have been evenly matched, falsely allowing an apparent benefit to lidocaine.

Although generally considered nontoxic in small oral doses, lidocaine anesthetizes the posterior pharynx and may blunt a patient's protective airway reflexes (18). This may be a concern if food is consumed shortly after the administration of a "GI Cocktail."

The most commonly used anticholinergic or antispasmodic agent in "GI Cocktails," Donnatal<sup>®</sup> has not been evaluated in any controlled studies. Moreover, the rationale for its inclusion in the "GI Cocktail" is somewhat unclear. Donnatal<sup>®</sup> is a drug combination that provides natural belladonna alkaloids in a specific, fixed ratio combined with phenobarbital to provide peripheral anticholinergic/antispasmodic action and mild sedation (19). Although it has FDA approval for use as adjunctive therapy in the treatment of irritable bowel syndrome, Donnatal<sup>®</sup> is not approved for dyspepsia. Its main mechanism of action is to slow gastrointestinal motility, and previous studies indicate that from 30% to 80% of patients with dyspepsia actually present with delayed gastric emptying or intestinal dysmotility (20,21). We could not find a study combining a prokinetic agent with an antacid, although other studies have suggested that *prokinetic* agents alone, such as Reglan<sup>®</sup>, are effective in the treatment of patients with symptoms of dysmotility-like dyspepsia (22–25). Thus, there is little theoretical reason to expect that Donnatal<sup>®</sup> would aid in the relief of the

Table 3. Outcomes

	Group 1	Group 2	Group 3	<i>p</i> Value* Univariate
Subject (N = 113)	38	37	38	
VAS 1 (mm)	66.6 ± 27.6	63.3 ± 29.5	61.6 ± 25.5	0.714
VAS 2 (mm)	41.4 ± 33.2	40.2 ± 31.6	37.5 ± 33.7	0.873
VAS difference	25.3 ± 27.2	23.1 ± 21.8	24.1 ± 27.8	0.932
<i>p</i> value* VAS (1) vs. VAS (2)	0.001*	0.002*	0.001*	

nonspecific symptoms of dyspepsia. Our study confirmed this lack of benefit.

In addition, although it is generally well tolerated, there are some theoretical concerns about the use of Donnatal®. Donnatal® may produce drowsiness or blurred vision because it contains phenobarbital and atropine sulfate. This could possibly pose a threat to patients who leave the ED and engage in activities requiring mental alertness, such as operating a motor vehicle or other machinery. Also, atropine's mydriatic and anticholinergic properties may exacerbate glaucoma or urinary retention (4,26,27).

A "GI Cocktail" or antacid is inappropriate as a diagnostic tool in the evaluation of chest pain or dyspepsia. The sensitivity and specificity of these agents as a diagnostic test are not known. Dickinson illustrated just how unreliable and potentially dangerous this practice can be. He described a cardiac patient who ruled in for a myocardial infarction, yet got prompt and complete relief of his discomfort from a "GI Cocktail" alone (28). History should be the most important factor in the initial management of patients with these symptoms.

There were no standardized criteria for receiving a "GI Cocktail." However, the inclusion and exclusion criteria of the current study were designed to ensure that patients with a working diagnosis of dyspepsia would be enrolled in the study. There was no attempt to confirm a specific anatomic diagnosis in the ED with endoscopy or any other means. This method of patient identification matches standard Emergency Medicine practice in which treatment of dyspepsia is initiated before a specific etiology has been elucidated. Based on pharmacokinetic data, our study period of 30 min was long enough to include the peak effect of all three study drugs (19). We did not look for the maximum duration of effect, which may have been different.

The current study found that single-dose therapy with a liquid antacid, alone or in combination with either Donnatal® or Donnatal®-viscous lidocaine, demonstrates an improvement in symptoms of dyspepsia, with 25-, 23-, and 24-mm improvements in VAS, respectively. This improvement is both statistically and clinically significant. There is, however, no additional symptom relief when either Donnatal® or Donnatal® plus lidocaine is added to the liquid antacid. Although no significant side effects were produced by the addition of lidocaine or Donnatal®, this study supports the conclusion that more ingredients are no better than less.

## CONCLUSIONS

Liquid antacid provided significant relief of discomfort in a group of patients with typical symptoms of dyspepsia.

The addition of Donnatal® or Donnatal® + viscous lidocaine to the liquid antacid (the "GI Cocktail") did not enhance the degree of relief. Based on these results, we believe that the administration of antacid alone is appropriate for the treatment of dyspepsia in the ED.

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