Diphenidol, A New Antiemetic: A Double-Blind, Placebo-Controlled Study

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Diphenidol is \( \alpha, \alpha \)-diphenyl-1-piperidinebutanol HCl, a nonphenothiazine compound, that has been reported to control apomorphine-induced vomiting in dogs as effectively as chlorpromazine. From reports of clinical studies, it appears to be useful in relieving nausea and vomiting in humans, yet to cause few of the undesirable side effects that can occur with currently marketed antiemetics. This is the first report of a double-blind, placebo-controlled study of diphenidol in patients with nausea and vomiting caused by a wide variety of diseases.

MECHANISM OF ACTION

Although little is known of the mechanism of action of any antiemetic, some assumptions concerning the activity of these drugs have been made from pharmacologic studies. For instance, apomorphine induces vomiting by stimulating the chemoreceptor trigger zone which in turn stimulates the vomiting center in the medulla. Drugs that suppress apomorphine-induced vomiting are said to block stimuli to the chemoreceptor trigger zone. If this mechanism is proposed for the action of diphenidol, it is supported by the fact that diphenidol has also been shown to possess antivertiginous activity. Because the vestibular nuclei, which mediate labyrinthine stimuli, are near the medullary chemoreceptor trigger zone, it is reasonable to assume that diphenidol exerts its antiemetic effect in this general area of the medulla.

MATERIALS AND METHOD

The patients selected had nausea and vomiting from diseases such as uremia, metastatic cancer, afferent loop syndrome following enteroenterostomy, liver diseases, esophagitis, and hiatal hernia. They were rated as having severe, moderate, or mild nausea and vomiting, depending upon the frequency and duration of the vomiting. Each was randomly assigned a code number corresponding to a supply of diphenidol or placebo; each supply consisted of 6 ampules and 1 bottle of 50 capsules. Except in an emergency, the code was not broken until the completed study was submitted to a statistician.

Patients with severe nausea and vomiting who did not respond to treatment

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within 1½–2 days were given known antiemetics such as prochlorperazine or chlorpromazine, trimethobenzamide, or meclizine in place of the medication under study.

Diphenidol was generally given in initial doses of 20–40 mg. (1–2 cc.) I.M. followed by oral doses of 25–100 mg. every 4–6 hr. To balance observations of efficacy against the variable duration of the symptoms, we made 2 ratings. After each dose we rated the medication (drug or placebo) for its effect on nausea and vomiting according to a scale of 0 (no relief) to 3 (complete relief). Then, at the conclusion of the study for each patient, we rated the medication again according to the relief of symptoms and the onset of action. “Excellent” meant that nausea and vomiting had completely subsided after the first 2 doses; “good,” that they had subsided by more than 50% but that the patient vomited once or twice after the first 2 doses; “fair,” that they had subsided somewhat, but not 50%, and that the patient could not retain food; “poor,” that they did not subside appreciably.

RESULTS

Ratings for relief of nausea and vomiting were calculated as averages of the total numerical scores for the 15 patients on diphenidol or placebo. An average greater than “2” indicated more than 50% relief of symptoms; an average lower than “1” indicated less than 50% relief. For the relief of nausea, placebo was rated as 0.8 and diphenidol as 2.3; for the relief of vomiting, placebo rated at 0.9 and diphenidol as 2.3. A chi-square determination of the differences indicates they are statistically significant (P<0.02). In overall performance, placebo was considered excellent, for 2 patients; good, for 2; fair, for 1, and poor, for 10. Diphenidol was considered excellent for 8 patients, good, for 3; fair, for 3; and poor, for 1. The analysis for a chi-square determination indicates that this difference is also statistically significant (P<0.02).

It should be noted that 10 of the 15 patients receiving placebo failed to obtain any relief of nausea and vomiting, whereas only 1 of 15 receiving diphenidol failed to obtain any relief. This patient obtained relief only after nasogastric suction. Of 9 who had received placebo, 4 obtained relief when given prochlorperazine (10–20 mg. I.M. every 4–6 hr), and 1 when given chlorpromazine (100 mg. rectally). Three others obtained no relief with trimethobenzamide, prochlorperazine, or meclizine.

Five patients were bothered by side effects. Two had received placebo: one reported dry mouth and blurred vision; the other, lightheadedness and dizziness on standing. Three had received diphenidol: one reported slight dizziness; another, who had also received an anticholinergic, reported difficulty in reading; the third, a patient with extensive metastases, became extremely drowsy on very high doses (600 mg., or 3 times the maximum recommended dose) and appeared to have a clouded sensorium.

At the end of the study we concluded that diphenidol is a reliable antiemetic.