Antinauseant and Antiemetic Properties of Bismuth Subsalicylate in Dogs and Humans

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Abstract □ Laboratory and clinical investigations were carried out to determine the effectiveness of bismuth subsalicylate in allaying nausea by preventing the physical symptom of emesis. In normal conscious dogs, a bismuth subsalicylate formulation caused a dose-related reduction in the incidence of vomiting in response to an emetic dose of ipecac syrup. In normal human subjects, a bismuth subsalicylate suspension, unlike the placebo formulation, successfully subdued nausea and vomiting in 66.7 and 80% of the subjects, respectively, in response to ipecac syrup. Both findings demonstrate that bismuth subsalicylate can provide antiemetic action and that the decrease in the occurrence of emesis in humans and dogs parallels the decrease in nausea found in humans and the nausea suspected to occur prior to emesis in dogs.

Keyphrases □ Bismuth subsalicylate—antinauseant and antiemetic properties evaluated, dogs and humans □ Antinauseants—bismuth subsalicylate, effect after ipecac dosing, dogs and humans □ Antiemetics—bismuth subsalicylate, effect after ipecac dosing, dogs and humans

Nausea, retching, and vomiting comprise the typical stages relative to emesis in humans (1, 2). The symptoms of nausea and vomiting are associated with many clinical conditions, *e.g.*, acute gastritis or gastroenteritis and dyspepsia induced by alcohol, food intolerances, aspirin, steroids, pregnancy, motion, and other physical and psychological stresses. Antihistamines and phenothiazine derivatives are commonly used in the treatment of nausea and vomiting, but side effects (sedation, hypotension, and drowsiness) limit or preclude their use (3). These unwanted side effects can be avoided by the use of various salts of bismuth, which have been used in the treatment of gastritis and dyspepsia (4).

Various stimuli may induce a chain of events leading to nausea. Clinicians agree that nausea is easily and commonly described for humans (5); this symptom in intact animals, however, is virtually impossible to detect (6). Rarely does an individual vomit without first being nauseated. It follows then that, if the incidence of vomiting is decreased, so also will be the incidence of nausea.

The emetic mechanism in human gastritis parallels that of drugs that induce emesis by gastric irritation (7). The premise that a salt of bismuth, such as bismuth subsalicylate[1], would be effective in allaying nausea induced by an emetic agent (ipecac syrup) was examined in both dogs and humans. For the dog, the physiological event of emesis was used as acceptable, objective evidence of the antinauseant property of bismuth subsalicylate. In humans, both antinauseant and antiemetic activities of bismuth subsalicylate were more definitively evaluated.

EXPERIMENTAL

Dogs—Twelve adult dogs[2] of mixed breed and of either sex, 8.5–24.3 kg, were used. Preliminary screening for an emetic dose of ipecac syrup USP in the dog, representing a dose that was reliably effective but yet not overwhelmingly drastic or potentially toxic, revealed that 0.5 ml/kg orally induced such an effect in 90% of the dogs tested.

A bismuth subsalicylate formulation (an 8.75% suspension in magnesium aluminum silicate[3]–methylcellulose–water vehicle) was administered orally to each dog at doses of 0.5, 1.0, or 2.0 ml/kg 10 min prior to 0.5 ml/kg of ipecac syrup. The dog was observed for emesis for up to 3 hr after the dose of ipecac syrup. Only one dose of bismuth subsalicylate was given to each dog in any given test day, and there was always at least 1 day of rest between tests.

On one occasion, each dog was pretreated with 2 ml/kg of water (a volume equivalent to the highest dose of the bismuth subsalicylate suspension) 10 min before the standard ipecac syrup dose (0.5 ml/kg) to test a potential antiemetic effect through mere dilution of the syrup. A final experiment in which the highest dose of bismuth subsalicylate was administered (not followed by ipecac syrup) was included to rule out conditioned emesis in this group of dogs. The data obtained from these studies were statistically analyzed for significance using the Sign test (8).

Humans—Forty healthy adult men and women, between the ages of 21 and 40 with no history of GI, renal, or cardiac disease, participated in the study. All subjects refrained from food or drink 10 hr before and during the study. The subjects were matched by sex and were randomly assigned to treatment pairs without regard to weight.

One member of each pair received a dose of ipecac syrup followed immediately by 30 ml of the bismuth subsalicylate formulation (a 1.75% suspension in magnesium aluminum silicate–methylcellulose with flavor, coloring, and water); the remaining member received the same dose of ipecac syrup followed immediately by 30 ml of the placebo formulation (containing flavor, coloring, 0.1% titanium dioxide, and water). A second dose of the appropriate liquid formulation was given 30 min after the initial dose. All subjects were observed for at least 3 hr, and each subject wrote a report describing any symptoms which developed.

To minimize human discomfort, a sequential method of statistical analysis was employed. Four groups of 10 subjects were evaluated sequentially and, when a statistically significant conclusion was reached (restricted binomial plan) (9), the study was terminated. Because of the violently disagreeable nature of the response to ipecac syrup in the subjects, it was necessary to adjust the dose as the study progressed; *i.e.*, Group I received 15 ml of ipecac syrup, Group II received 7.5 ml, and Groups III and IV received 5 ml. From the study design, one of three conclusions could be reached: Treatment A (bismuth subsalicylate formulation) was more effective, Treatment B (placebo formulation) was more effective, or no difference between treatments existed.

A four-point scale was developed to evaluate the severity of symptoms described by each subject: 0, subject felt fine throughout study (possible slight gas or queasiness); 1, subject definitely nauseated with or without upset stomach, cramping, or headache; 2, subject vomited at least once (felt well within approximately 1 hr);

[1] Principal active constituent in Pepto-Bismol, Morton-Norwich Products, Inc.

[2] Raised at the Animal Research Center, Norwich Pharmacal Co., Norwich, N.Y.

[3] Veegum, R. T. Vanderbilt Co.

Table I—Effect of Bismuth Subsalicylate Formulation or Water on the Incidence of Emesis Induced by Ipecac Syrup in Dogs[a]

Dog	Weight, kg	Doses of Bismuth Subsalicylate Formulation (8.75%)[b] 0.5 ml/kg	1.0 ml/kg	2.0 ml/kg	Water[b], 2 ml/kg	Bismuth Subsalicylate Formulation (8.75%)[c], 2 ml/kg
1	23.3	+	—	+	—	—
2	20.6	—	—	—	—	—
3	21.3	—	+	—	+	—
4	17.4	+	—	—	+	—
5	23.7	—	—	—	+	—
6	20.1	+	+	—	+	—
7	11.7	—	—	—	+	—
8	12.1	—	—	—	+	—
9	8.5	+	+	—	+	—
10	9.7	+	—	—	—	—
11	10.2	—	+	—	+	—
12	11.6	+	+	+	+	—
Number of dogs vomiting		6/12	5/12	2/12[d]	9/12	0/12
Total number dosed		50	58	87[d]	25	—
Percent protected						

[a] + = emesis, and − = no emesis. [b] Ten minutes prior to 0.5 ml/kg of ipecac syrup USP. [c] Dose of ipecac syrup not administered. [d] Significantly different from water-treatment control group; $p = 0.0195$, Sign test.

Table II—Effect of Bismuth Subsalicylate Formulation and Placebo on the Relief of Symptoms Induced by Various Doses of Ipecac Syrup in Human Subjects

Group[a]	Total Dose of Ipecac Syrup, ml	Relief of Ipecac-Induced Symptoms: Treatment A[b], Average Score[d]	Treatment B[c], Average Score[d]
I	15	1.8	2.4
II	7.5	0.6	2.0
III	5.0	0.6	1.8
IV	5.0	0.8	2.0

[a] Each group consisted of five pairs of subjects. [b] Thirty milliliters of bismuth subsalicylate formulation (1.75%) followed in 0.5 hr by another 30 ml. [c] Thirty milliliters of placebo formulation followed in 0.5 hr by another 30 ml. [d] Mean of the responses obtained on the basis of the response key described under *Experimental.*

and 3, subject experienced severe nausea and vomiting with headache and malaise (symptoms lasted considerably longer than 1 hr).

The data obtained from this clinical study were analyzed statistically for significance employing the χ-square test.

RESULTS

Dogs—As summarized in Table I, the bismuth subsalicylate formulation (8.75% suspension), 0.5 ml/kg in 12 dogs, protected 50% of the animals from the vomiting dose of ipecac syrup. By increasing the doses of the bismuth subsalicylate formulation to 1 and 2 ml/kg, there was a respective dose-related increase (58 and 87%) in protection against the emetic effect of ipecac syrup.

In the control group, 2 ml/kg of water prevented vomiting in 25% of the dogs treated. However, there was still a significant difference found between this control group and the bismuth subsalicylate group (87% protection at 2 ml/kg). None of the dogs vomited with the highest dose of bismuth subsalicylate administered alone.

Humans—In 10 subjects, ipecac syrup, in 15-ml total doses, caused severe and potentially harmful GI symptoms, which were not alleviated by either Treatment A (bismuth subsalicylate formulation) or Treatment B (placebo formulation) (Table II). To avoid such symptoms, the dose of ipecac syrup was lowered to 7.5 ml. At this dose, two patients treated with placebo exhibited grade 3 responses; the average score of these placebo-treated patients was 2 (Table II), indicating relatively little protection. Less severe symptoms were noted following the bismuth subsalicylate formulation (1.75%) administration; the average score was reduced to 0.6, indicating that protection was afforded. In Groups III and IV, when the dose of ipecac syrup administered was 5 ml, treatment with bismuth subsalicylate more effectively relieved the untoward symptoms as opposed to the subjects receiving the placebo.

Table III—Effect of Bismuth Subsalicylate Formulation and Placebo on Symptoms of Nausea and Vomiting in Response to Ipecac Syrup in Human Subjects

Group[a]	Treatment A[b]: Absence of Nausea	Protection from Nausea, %	Absence of Vomiting	Protection from Vomiting, %	Treatment B[c]: Absence of Nausea	Protection from Nausea, %	Absence of Vomiting	Protection from Vomiting, %
I[d]	1/5[e]	20	1/5[f]	20	0/5[e]	0	0/5[e]	0
II	3/5	60	4/5	80	0/5	0	2/5	40
III	3/5	60	4/5	80	1/5	20	1/5	20
IV	4/5	80	4/5	80	0/5	0	0/5	0
Total number in Groups II, III, and IV	10/15		12/15		1/15		3/15	
Mean protection in Groups II, III, and IV		66.7[g]		80[g]		7		20

[a] Each group consisted of five pairs of subjects. [b] Thirty milliliters of bismuth subsalicylate formulation (1.75%) followed in 0.5 hr by another 30 ml. [c] Thirty milliliters of placebo formulation followed in 0.5 hr by another 30 ml. [d] Explanation for not pooling these data was discussed under *Results.* [e] Number without nausea/number treated. [f] Number not vomiting/number treated. [g] Significantly different from Treatment B using χ-square test; $p = 0.05$ or less.

Table III summarizes the results of the study of the two test formulations in preventing nausea and vomiting in subjects receiving ipecac syrup. Because of the small number of subjects, it was necessary to pool the results in Groups II–IV for Treatment A or B. Pooling of the data was determined to be permissible since sequential testing revealed that no differences in response existed among Groups II–IV and, according to the binomial theorem of analysis, these groups were not significantly different. However, Group I was significantly different from each of the other groups and was not pooled with the three groups. The high dose of ipecac syrup in Group I caused severe GI irritation along with other marked side effects.

When the results of Groups II–IV were combined, 66.7% of the subjects failed to experience nausea following bismuth subsalicylate while only 7% were not nauseated by the ipecac syrup after the placebo administration. The act of vomiting in response to ipecac syrup was completely prevented in 80% of the subjects (Groups II–IV) treated with the bismuth subsalicylate formulation, and the placebo formulation afforded 20% protection. χ-Square statistical evaluation for the difference between patients receiving bismuth subsalicylate and those receiving the placebo formulation indicated that bismuth subsalicylate is significantly superior in its ability to control nausea and vomiting compared to the placebo formulation.

DISCUSSION

The mechanism of action of ipecac, or its principal alkaloid emetine, with respect to the induction of vomiting is poorly understood, although standard pharmacology texts generally agree that both a local and a central component are involved. In the present study, ipecac syrup was used to induce vomiting in dogs and nausea and vomiting in humans. After establishing the dose of ipecac syrup necessary to meet the criteria of a reliably effective, but not overwhelmingly drastic, emetic, it was found that bismuth subsalicylate formulation elicited a dose-related protective effect against ipecac syrup-induced emesis in the dog.

The laboratory evidence was corroborated by clinical evidence, in which it was revealed that the bismuth subsalicylate formulation was capable of arresting both nausea and vomiting in response to doses of ipecac syrup capable of inducing mild GI upset in humans. In the clinical study, it was necessary to adjust the dose of ipecac syrup to avoid the severe and harsh symptoms induced by the emetic. When utilizing the doses (5.0 and 7.5 ml) of ipecac syrup that appeared to mimic the symptoms of nonspecific GI upset and irritation in humans, the signs and symptoms of ipecac syrup ingestion were easily reproducible. Bismuth subsalicylate, unlike the placebo suspension, successfully controlled the nausea and vomiting in 66.7 and 80% of the subjects, respectively, in response to ipecac syrup.

Thus, both laboratory and clinical findings concur that bismuth subsalicylate provides antiemetic protection against the effects of ipecac syrup and that the decrease in the incidence of emesis in humans and dogs parallels the decreased incidence of nausea noted in humans and the nausea suspected to occur prior to vomiting in the dog.

REFERENCES

(1) J. S. Fordtran, in "Vomiting in Gastrointestinal Disease," M. H. Sleisenger and J. S. Fordtran, Eds., Saunders, Philadelphia, Pa., 1973, pp. 127–143.

(2) W. H. Resnik, "Principles of Internal Medicine," 5th ed., McGraw-Hill, New York, N.Y., 1966, pp. 107–110.

(3) J. W. Bellville, in "Drugs of Choice 1972–1973," W. Modell, Ed., Mosby, St. Louis, Mo., 1972, pp. 294–305.

(4) L. Jaenicke, "Bismuth—A Survey of the Pharmacology and Medicinal Uses," Mining and Chemical Products, Ltd., London, England, 1950, pp. 1–44.

(5) F. A. Jones, J. W. P. Gummer, and J. E. Lennard-Jones, "Clinical Gastroenterology," 2nd ed., Blackwell Scientific Publications, Oxford, England, 1968, p. 15.

(6) S. Wolf, *Gastroenterology*, **12**, 212(1949).

(7) J. H. Moyer, "Effective Antiemetic Agents," Medical Clinics of North America, Saunders, Philadelphia, Pa., 1957, pp. 405–432.

(8) K. A. Brownlee, "Statistical Theory and Methodology in Science and Engineering," 2nd ed., Wiley, New York, N.Y., 1965, p. 242.

(9) P. Armitage, "Sequential Medical Trials," 1st ed., Blackwell Scientific Publications, Oxford, England, 1960, pp. 25–47.

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Solid-State Anomalies in IR Spectra of Compounds of Pharmaceutical Interest

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Abstract □ Solid-state anomalies in the IR spectra of lysine monohydrochloride, etoxadrol hydrochloride, thiamine hydrochloride, and L-histidine in a potassium bromide matrix were noted. With the first three compounds, the anomalies were due to metathetical exchange of the halide anion between the compound and the matrix. The anomaly seen with L-histidine was related to the crystal structure.

Keyphrases □ IR spectroscopy—solid-state anomalies, lysine monohydrochloride, etoxadrol hydrochloride, thiamine hydrochloride, and L-histidine □ Lysine monohydrochloride—IR spectra, solid-state anomalies □ Etoxadrol hydrochloride—IR spectra, solid-state anomalies □ Thiamine hydrochloride—IR spectra, solid-state anomalies □ L-Histidine—IR spectra, solid-state anomalies

It is well known that IR absorption spectra of solids depend on both structure and crystalline form. Variations between mull and pellet spectra are due either to an induced physical isomerization or to the samples having been rendered amorphous in the alkali halide pellet (1). In addition, the observed spectra from dif-