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Comparison of the Ventilatory Effects of Two Antiemetics, Benzquinamide and Prochlorperazine

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Benzquinamide, an ataractic antiemetic, is also a respiratory stimulant of modest efficacy. In a dose of 0.7 mg/kg intravenously it increases ventilation at constant controlled alveolar CO_2 tension by 12.4 l/min. The curve of the ventilatory response to CO_2 after 0.7 to 1.4 mg/kg is parallel to and 10 torr to the left of the pre-drug response curve. Prochlorperazine, a phenothiazine antiemetic studied in comparison, has little respiratory effect in doses of 0.35 mg/kg or less except as associated with akathisic arousal. After stable morphine-induced respiratory depression, benzquinamide (0.7 mg/kg) gave brief stimulation and little change in ventilation for 3 hours thereafter. Prochlorperazine (0.18 mg/kg), by contrast, potentiated the opioid depression, with some suggestion of waning effect by 3½ hours. (Key words: Ataractic agents: benzquinamide; Vomiting: antiemetics: benzquinamide; Vomiting: antiemetics: prochlorperazine; Interactions: morphine–benzquinamide; Interactions: morphine–prochlorperazine.)

THE ANTIEMETIC, ataractic drugs of the phenothiazine group may have as limiting side effects hypotension and respiratory depression or potentiation of respiratory depression from other drugs. However, an ataractic of the benzquinolizine family, benzquinamide (Emete-con, Roerig), is both antihypotensive and antiemetic. Animal studies have demonstrated mild anticholinergic, antihistaminic, and antiserotonin effects of this compound.[1] The antihypotension action is evident when benzquinamide is given during hypotension which follows administration of apomorphine or during hypotension occurring in the course of halothane anesthesia in man.[2] This action is also seen in animals made hypotensive by bleeding or by histamine infusion. Burstein reported that minute ventilation increased after benzquinamide injection during anesthesia and persisted for more than 2½ minutes.[4] These actions of benzquinamide differ from side effects of other ataractic antiemetics, warranting a careful comparison. In the present study we used prochlorperazine (Compazine), a drug in wide clinical use, for comparison. A study of ventilatory response to carbon dioxide challenge showed that benzquinamide is a mild respiratory stimulant when given alone, whereas prochlorperazine is not, and that morphine induced respiratory depression is not significantly affected by benzquinamide but is potentiated by prochlorperazine.

Methods

Ventilatory response to carbon dioxide was used to evaluate the respiratory effects of benzquinamide and prochlorperazine alone as well as following morphine-induced depression. The experiment consisted of two parts: first, we obtained logarithmically graded cumulative dose–response curves for the antiemetic drugs; second, we followed the time course of ventilatory changes after prior morphine depression.

The simple nonrebreathing respiratory circuit permitted delivery of known gas concentrations to the inspiratory Sadd valve from a bank of rotameters fed with oxygen, carbon dioxide, and air. Carbon dioxide challenges included 3, 5, and 7 per cent CO_2 in 50 per cent O_2 for 10 minutes each. For those portions of the experiment conducted with the isohypercapnic techniques of Lambertsen,[3] inspired carbon dioxide was varied to keep end-tidal carbon dioxide tension at a preselected value. We selected the end-tidal carbon dioxide tensions initially obtained by

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inspiring 5 per cent carbon dioxide in the dose–response curve study and by inspiring 7 per cent carbon dioxide in the morphine-interaction study.

The expiratory limb of the breathing circuit consisted of a Sadd valve, a 3-liter mixing chamber,[7] and a Wedge spirometer and recycler. Minute volume, respiratory frequency, and tidal volume were calculated from the spirometer output recorded on a Texas Servoriter II and converted to body temperature and pressure saturated. A large-bore tap and carbon dioxide absorption canister converted the circuit to a closed circle for measurement of screening pulmonary function tests (inspiratory capacity, expiratory reserve volume, vital capacity, forced vital capacity at one second) and oxygen consumption. EKG was monitored continuously, and pulse and blood pressure measurements were recorded intermittently.

A Godart NV Capnograph, calibrated with several mixtures of carbon dioxide in oxygen and corrected for the known collision-broadening effect of 50 per cent nitrogen, measured carbon dioxide tensions. Gas was continuously sampled within the mouthpiece for detection and measurement of end-tidal tension. Mixed expired gas was intermittently sampled distal to the mixing chamber. Mixed venous (oxygenated, rebreathing) carbon dioxide tension was measured from the plateau value of expired carbon dioxide within 15 seconds after rapid rebreathing of a 1-liter mixture of 8 per cent carbon dioxide had begun. Inspired carbon dioxide was monitored at the intraoral site and, when control of end-tidal carbon dioxide was demanded by the protocol, was varied on a breath-by-breath basis.

Benzquinamide–Prochlorperazine Dose–Response Curves

Six healthy men, awake, supine and fasting, volunteered for the dose–response study. Their ages ranged from 21 to 25 years; weights, from 64.2 to 98.9 kg. Each volunteer was the subject of two studies, a week apart, and received both benzquinamide and prochlorperazine in randomly assigned order. The drugs were prepared and diluted to 50 ml by a nurse or physician not connected with the study, to maintain double-blind conditions. After screening pulmonary function tests and collection of the data for the control steady-state responses to carbon dioxide, the subjects breathed 5 per cent CO_2 for 6 minutes. End-tidal tension was controlled at the level achieved at this time for the next 60 minutes by altering the inspired tension. The drugs were administered via a previously established intravenous infusion of 5 per cent glucose and water, increasing the dose logarithmically at 12-minute intervals during continuous control of $P_{A_{CO_2}}$. This was sufficient time to observe stable drug effects following iv injection. The doses of benzquinamide were given to produce cumulative doses of 0.09, 0.18, 0.35, 0.7, and 1.4 mg/kg (a total of 100 mg/70 kg). The prochlorperazine injections provided cumulative doses of 0.045, 0.09, 0.18, 0.35, and 0.7 mg/kg (a total of 50 mg/70 kg). Because of unpleasant subjective sensations, not all subjects received all of the planned injections. Following the final injections, which were accepted by each subject, ventilatory response to carbon dioxide was redetermined by the steady-state method, using 0, 3, 5 and 7 per cent inspired carbon dioxide. Finally, screening pulmonary function tests were repeated.

Time Course after Prior Morphine Depression

The second part of the study, evaluation of the time courses of prochlorperazine and benzquinamide effects during stable morphine depression, also employed six healthy men ranging in age from 21 to 28 years, and in weight from 70.0 to 84.3 kg, each of whom reported to the laboratory for two studies at least a week apart. After determining the initial steady-state response to carbon dioxide inhalation at 0, 3, 5, and 7 per cent CO_2, 0.21 mg/kg morphine sulfate (15 mg/70 kg) was infused intravenously over a one-minute period while end-tidal carbon dioxide tension was maintained at the level determined by the inspiration of 7 per cent CO_2 during the pre-drug period.

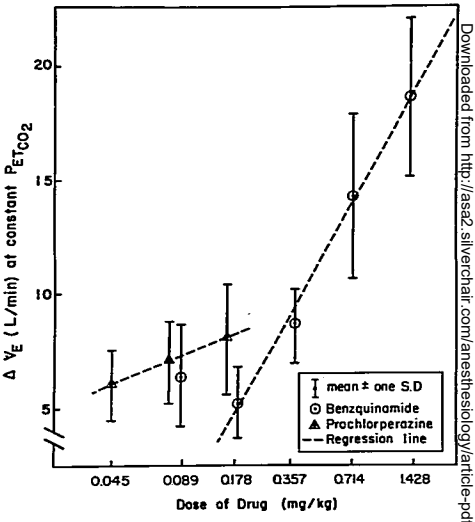

FIG. 1. Dose–response curves for incremental doses of benzquinamide and prochlorperazine. Ventilatory changes from control at isohypercapnia are plotted against logarithmically increased cumulative doses. All points are means of six subjects except the last benzquinamide point, where only three subjects were studied. Regression lines were computed by least-squares fit.

Careful measurements of ventilation at controlled end-tidal carbon dioxide tension were recorded 10, 20, 30, and 45 minutes after the infusion of morphine, anticipating that this would document a steady level of morphine-depressed ventilation. A second steady-state evaluation of the ventilatory response to carbon dioxide at the several inspired carbon dioxide tensions was made 50 to 90 minutes after injection of morphine. After restoration of isohypercapnic control, either benzquinamide in a dose of 50 mg/70 kg or prochlorperazine in a dose of 12.5 mg/70 kg was administered intravenously, maintaining double-blind conditions for the observer and the volunteer. These doses were assumed to be approximately equiantiemetic, based on unpublished data of the manufacturer. Values of isohypercapnic ventilation for prochlorperazine and benzquinamide were recorded at intervals of 10 and 20 minutes after the initial injection. Steady-state ventilatory responses to carbon dioxide were determined one, two, and three hours after injection of the antiemetic, anticipating that this would document the time course of the antiemetic effects on ventilation during a fairly stable morphine effect. Subjects breathed air between these steady-state measurements.

During the isohypercapnic control portions of the experiments, it was possible to maintain end-tidal carbon dioxide tensions within ±0.7 torr of the previously selected value. For purposes of constructing the dose–response curves comparing the time courses, however, the small variations from the exact control value were corrected for using the slopes of the appropriate ventilatory response to carbon dioxide measured in the individual subjects.

The data were calculated and analyzed by appropriate analyses of variance. The probability values in the text refer to either the resultant f ratio or the probability that two treatments are different when analyzed by Student's t test for paired data.

Subjective effects were recorded during the study and 24 and 48 hours after the study by questionnaire and interview.

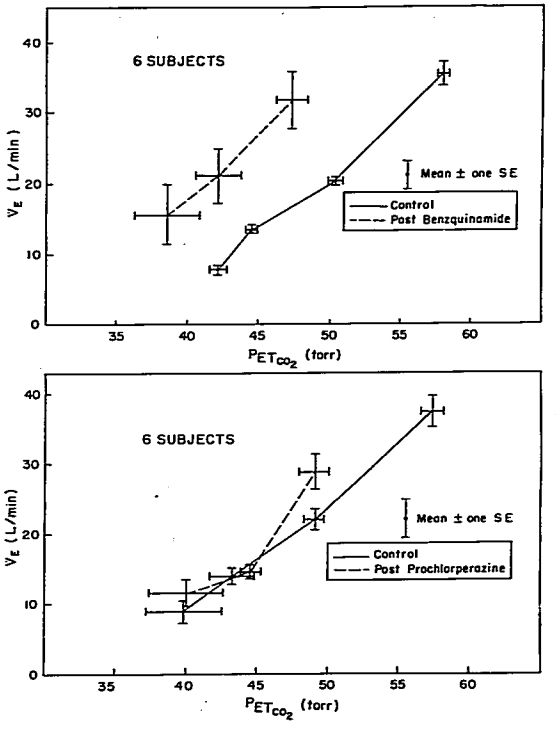

FIG. 2. Ventilatory responses to carbon dioxide before and after benzquinamide and prochlorperazine. *Above*, three subjects received 0.7 and three, 1.4 mg/kg benzquinamide. *Below*, Four subjects received 0.18, one 0.35, and one 0.7 mg/kg prochlorperazine.

Results

VENTILATORY EFFECTS OF BENZQUINAMIDE AND PROCHLORPERAZINE ALONE

The initial dose of either drug caused slight stimulation of ventilation. With further injections, benzquinamide alone was a mild respiratory stimulant, with dose-related effects throughout the ranges studied (three subjects accepted 1.4 mg/kg and three stopped at 0.7 mg/kg). After the initial stimulation, prochlorperazine had no further effect on ventilation until dysphoric side effects caused increases in ventilatory values in some subjects. Four subjects stopped the study after 0.18 mg/kg (third dose), and only one completed the five doses planned.

Figure 1 shows the ventilatory changes at constant PA_{CO_2} as the incremental doses were administered. With logarithmically increasing doses of drugs at 12-minute intervals, the initial change of V_E after 6.25 mg/70 kg (0.09 mg/kg) of benzquinamide represented a significant increase in ventilation ($P < 0.05$). The V_E increase after the fourth dose (50 mg/70 kg or 0.7 mg/kg) was 12.4 l/min (significant, $P < 0.025$). While only three of the subjects received the fifth dose of benz-

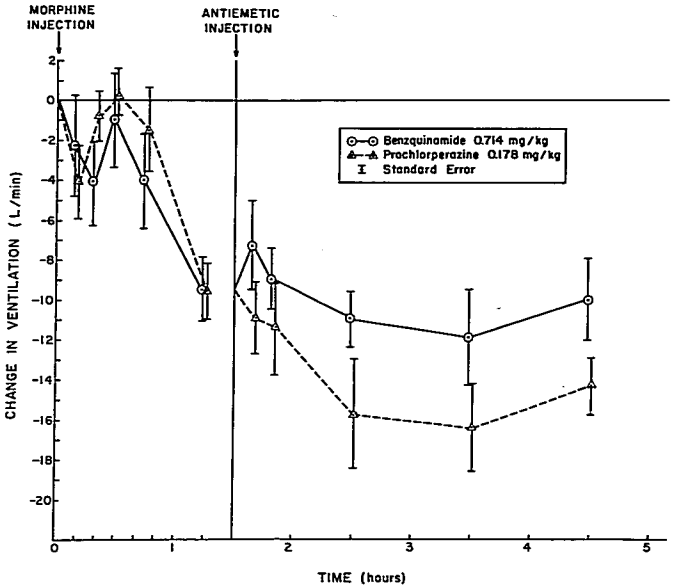

FIG. 3. Time courses of benzquinamide and prochlorperazine interactions with morphine depression of ventilation. Morphine sulfate, 0.21 mg/kg, was given intravenously at time zero. $P_{A_{CO_2}}$ was controlled at the level produced by 7 per cent inspired carbon dioxide except during measurement of steady-state ventilatory responses 75 minutes after morphine, and after two hours.

quinamide, all three had further increases in V_E, averaging 4.4 l/min ± 2.8.

Neither drug had a significant effect on oxygen consumption, CO_2 excretion, or screening pulmonary function tests. Respiratory frequency and deadspace were unchanged. Steady-state ventilatory responses are shown in figure 2. Analysis of the pre-drug and post-drug slopes showed no significant difference. The CO_2 response curves show left parallel displacement of 10.1 torr after benzquinamide and 1.3 torr after prochlorperazine. The difference for benzquinamide was statistically significant ($P < 0.02$).

During the benzquinamide study, agitation, dry mouth, and flushing of the skin were noticed by four subjects, dysphoria and shivering by two of the four, and drowsiness by another. The only symptom persisting for more than an hour after the study was drowsiness, reported by three. In contrast to these brief responses to benzquinamide, reactions to prochlorperazine were more frequent, more bothersome, and longer lasting. Four subjects reported symptoms of akathisia (motor restlessness, urge to move about), dysphoria, and dry mouth. Two reported tremor. These effects lasted 12 to 24 hours in two, and as long as 48 hours in the other two. One subject was treated with 25 mg diphenhydramine after an emergency room visit for complaints of muscle

spasm of the neck and shoulder. No nausea or vomiting was reported.

Ventilatory Effect and Time Course after Morphine Depression

The changes in ventilation at isohypercapnia after morphine and after antiemetics are shown in figure 3. Maximal depression from 15 mg/70 kg (.21 mg/kg) of morphine occurred during the 60–90-minute steady-state measurements, when ventilation was 9.5 l/min less than control at the constant $P_{A_{CO_2}}$ of 61 torr. Analysis of variance of the five CO_2 response curve slopes (control, after morphine, and three times after antiemetic injection) showed no significant difference for either antiemetic, so the time course can properly be described as changes in the isohypercapnic V_E shown in figure 3.

After administration of benzquinamide an initial period of stimulation (insignificant) was followed by insignificant depression for four hours. Administration of prochlorperazine was followed by increasing depression, which because significant ($P = 0.03$) in the one-, two-, and three-hour postemetic periods. There was no significant change in respiratory frequency, deadspace, blood pressure or pulse after either antiemetic.

The agitation and dysphoria seen in subjects given antiemetics alone were less marked after morphine. No subject reported dysphoria after benzquinamide. Four reported dysphoria, lasting 12 to 24 hours, after prochlorperazine. Drowsiness and sleep, lasting much longer after prochlorperazine, were reported by three subjects. Nausea occurred despite the drugs. Four subjects vomited in the 12-hour period after benzquinamide, and two after prochlorperazine.

Discussion

Benzquinamide is a ventilatory stimulant without significant effect on respiratory gas exchange or static lung volume. Steen[8] reported significant ventilatory stimulation one hour, but not 20 minutes, after benzquinamide, 0.7 mg/kg iv. In that study data were reported as the displacement of a rebreathing carbon dioxide response curve, assuming no slope change. This study showed no slope change in steady-state carbon dioxide response curves following the drug and indicated significant ventilatory stimulation by 0.35 mg/kg intravenous benzquinamide. The onset of ventilatory stimulation occurs within 12 minutes both when benzquinamide is given alone and when it is given during morphine-induced depression. This rapid onset is similar to the stimulation noted by Burstein[4] at 20 minutes.

The parallel shift to the left of the curve of the ventilatory response to carbon dioxide after benzquinamide alone suggests that this drug might be a nonspecific physiologic antagonist of respiratory depression. However, the second part of the study demonstrated considerable blunting of the stimulation after established morphine-induced depression. Alone, benzquinamide stimulated isohypercapnic V_E 15 l/min; after morphine, only 2–5 l/min. This is not sufficient stimulation, at doses likely to be used, to recommend its use for reversal of opioid depression. It does differ from the opioid-potentiating effect of other antiemetics. Prochlorperazine alone produced a minor increase in ventilation, not dose-related, while after established morphine-induced depression, it decreased ventilation by 6 l/min, *i.e.*, it clearly potentiated morphine. Similar effects have been found by Hoffman and Smith with meperidine and propiomazine,[9] and by Lambertsen *et al.*[10] with chlorpromazine and meperidine.

The time course of the action of morphine, iv, was surprising. Maximal depression did not occur until 75 to 90 minutes after administration. An initial stable depression is usually seen after 10 to 20 minutes, but after 30 minutes ventilation was restored to near control values in nine of 12 subjects. By 45 minutes, ventilation was again significantly depressed ($P < .05$) and by 90 minutes further depressed ($P < .025$). Respiratory frequency changed little during maximum depression of V_E after morphine. These observations warrant further study of the time course of the effects of morphine on ventilation. Factors such as protein binding and active metabolites of morphine might explain the delayed onset of maximal depression. Alternately, one could hypothesize that arousal resulting from the

"rush" of opioid administered iv, from the enforced immobility on a narrow operating table, from oral discomfort due to mouth breathing of dry gases, and from the encouragements to stay awake, at first partially masked the morphine effect. After one to two hours, accommodation plus morphine sedation overcomes these arousal mechanisms. The latter view is compatible with placebo response reported by Lambertsen, Wendell and Longenhagen.[10] In that study, isohypercapnic ventilation tended to increase several liters per minute, peaking at about half an hour and tending to return toward control values thereafter.

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Obstetrics

ABNORMAL PREGNANCY AND SURFACTANT MATURATION In a random sample of 134 pregnancies, amniotic fluid lecithin/sphingomyelin (L/S) ratios of 2.0 or more were not associated with the development of neonatal respiratory distress syndrome (RDS). With lower ratios, RDS occurred regardless of gestational age and birth weight. The L/S ratio reached 2.0 at approximately 35 weeks' gestation in normal pregnancies. A study of 147 pregnancies with maternal, fetal, or placental disease states revealed alterations in rate of maturation of fetal lungs away from the 35-week norm. Toxemia, hypertensive renal disease, severe diabetes, and retroplacental bleeding cause much earlier achievement of L/S ratios of 2.0 or above, while mild diabetes, chronic nonhypertensive glomerulonephritis and hydrops fetalis delayed pulmonary surfactant maturation beyond 35 weeks' gestation. The authors conclude that chronic intrauterine stress generally causes early maturation of pulmonary surfactant and decreases the risk of neonatal RDS despite the higher incidence of low birth weight and prematurity. *(Gluck, L., and Kulovich, M.: Lecithin/Sphingomyelin Ratios in Amniotic Fluid in Normal and Abnormal Pregnancy. Am J Obstet Gynecol 115: 539, 1973.)*