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Physostigmine: Effectiveness as an Antagonist of Respiratory Depression and Psychomotor Effects Caused by Morphine or Diazepam

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Each of six healthy volunteers was studied on three different occasions to determine the interactions of placebo–physostigmine, diazepam–physostigmine, and morphine–physostigmine with respect to respiration and psychomotor function. Respiratory measurements were made using the steady state and isohypercapnic techniques. Psychomotor function was assessed by the Trieger Dot Test (TDT) and compared with the Continuous Performance Test (CPT). Administration of physostigmine alone (3 mg, iv) did not affect ventilation. Diazepam (0.29 mg/kg, iv) did not cause a significant depression of ventilation in all subjects, although psychomotor function was impaired as measured by the CPT. The latter was unaffected by physostigmine. Administration of morphine (0.21 mg/kg, iv) caused a significant decrease in ventilation that was not antagonized by physostigmine. Morphine did not impair psychomotor function. The authors conclude that physostigmine is an ineffective antagonist of narcotic-induced respiratory depression and that the CPT correlates well with the TDT. (Key words: Analgesics: morphine. Antagonists, miscellaneous: physostigmine. Carbon dioxide: ventilatory response; steady state. Hypnotics: benzodiazepines; diazepam. Psychomotor function: Trieger Dot Test; Continuous Performance Test. Recovery: measurement of.)

PHYSOSTIGMINE HAS RECEIVED considerable attention as an antagonist of various central nervous system depressants.[1–5] Being an uncharged tertiary amine, physostigmine easily penetrates the blood brain barrier and increases acetylcholine levels by inhibiting cholinesterase. It therefore can effectively antagonize drugs such as scopolamine, tricyclic antidepressants, and butyrophrenones, which induce the "central anticholinergic syndrome."[6,7] Physostigmine's antagonistic properties are believed to be due to a nonspecific central arousal.[5] Reports on the effect of physostigmine on diazepam-induced respiratory depression have been contradictory,[8–11] whereas other reports indicate that physostigmine can antagonize morphine-induced respiratory depression.[12–14] We therefore studied the effects of physostigmine on the respiratory changes caused by both diazepam and morphine. Concurrently, we studied the psychomotor effects using the Trieger Dot Tests (TDT,[15] and compared the results with those obtained with the Continuous Performance Test (CPT) (Sunrise Systems, Pembroke, Massachusetts; see Appendix), which has not been used previously in anesthesia-related studies.

Methods

In a study approved by our institutional review committee, we studied six ASA physical status I informed consenting male volunteers ranging in age from 20 to 34 yr. Subjects refrained from all drugs, including caffeine, nicotine, and alcohol, for 24 h prior to the study, and they fasted for 8 h immediately before it. Each subject participated in three sessions, which differed only in the random double-blind administration of an unknown drug. Each subject's study sessions were spaced at least 5 days apart. In an effort to maintain a constant level of stimulation, the laboratory was kept quiet, well lighted, and free of visitors, and subjects were reminded not to close their eyes or to sleep. All subjects returned 1 week after their final session to discuss subjective reactions to the drugs.

For each study session we applied a blood pressure cuff, precordial stethescope, and ECG leads, and inserted an intravenous catheter for infusion of saline and drugs. Subjects then breathed through a rubber mouthpiece into a low-resistance nonrebreathing circuit for a 15-min acclimatization period. Inspired O_2 was between 30% and 35% at all times. The breathing circuit permitted the addition of both O_2 and CO_2 to inspired air and included a spirometer (Med-Science Wedge Spirometer®) and sampling sites for inspired, end-tidal, and mixed expired CO_2. Sampled gas was delivered to an infrared CO_2 analyzer (Gould Godert Capnograph®) and returned to the circuit. The spirometer and CO_2 analyzer were calibrated with appropriate standards before and after each study session. CO_2 and spirometer data were recorded continuously on a two-channel recorder (Hewlett Packard).[16] At various times during the sessions, the TDT and CPT tests of psychomotor function were administered.

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TABLE 1. Continuous Performance Test Data

	Control	Unknown	Physostigmine 1 mg	Physostigmine 2 mg	2 h	4 h
Placebo	63.2 ± 2.3	62.2 ± 2.6	63.2 ± 2.3	67.3 ± 3.5*†	64.3 ± 3.4	63.7 ± 3.2
Diazepam	64.5 ± 3.1	78.2 ± 4.1*	69.5 ± 2.6*	68.0 ± 1.9*†	71.0 ± 1.5*	72.3 ± 3.9*
Morphine	63.8 ± 1.6	61.5 ± 1.5	65.8 ± 1.4	71.5 ± 1.5*	67.2 ± 2.1*†	63.7 ± 2.1

Values are mean time to respond ± 1 SEM in hundredths of a second.

* Significantly different from control value as determined by ANOVA, LSD, and Dunnett's test ($P < 0.05$).

† Not significantly different by Bonferroni's correction ($P < 0.05$).

At the end of the acclimatization period, during unstimulated respiration, we measured the following: minute ventilation ($\dot{V}_E$), tidal volume (TV), respiratory rate (f), inspired CO_2 (PI_{CO_2}), end-tidal CO_2 (PET_{CO_2}), and mixed expired CO_2 (Pm_{CO_2}). We then determined a control CO_2 response by adding 3% and 6% CO_2 to the inspired gases. At each concentration, results were recorded after 8 min. Following determination of the control CO_2–response curve, 3% CO_2 was administered for 10 min, after which psychomotor and respiratory results were recorded. The end-tidal CO_2 observed during that period was maintained throughout the next, isohypercapnic[17] phase of the study by varying the inspired CO_2. After 15 min of isohypercapnia, the unknown drug (either 0.29 mg/kg diazepam, 0.21 mg/kg morphine, or saline) was given iv. Fifteen and 30 min after administering the unknown drug, physostigmine doses of 1 mg iv and 2 mg iv, respectively, were given. End-tidal CO_2 was maintained constant throughout this period, and respiratory and psychomotor observations were made 12 min after each dose was given. Twenty minutes after the second dose of physostigmine, inspired CO_2 was increased to 6% to provide a second point for a CO_2–response curve, after which subjects were allowed to rest. Beginning at 2 and 4 h after administering the unknown drug, CO_2–response curves again were determined, and psychomotor tests were administered during the inspiration of 3% CO_2.

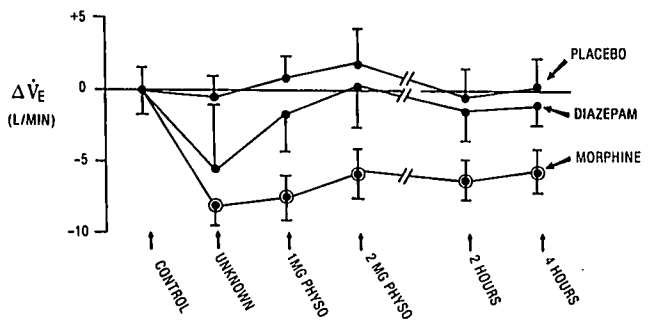

FIG. 1. Isohypercapnic minute ventilation. Values are mean ± 1 SEM. Values at 2 and 4 h were interpolated from CO_2-response curves at P_{ET} = 46 mmHg. Control V_E = 14.2 ± 1.3 l/min. Circled points are different from control ($P < 0.05$).

All respiratory measurements were corrected to BTPS. Respiratory and CPT results first were subjected to analysis of variance (ANOVA). Where indicated, treatment results were compared with control by the method of least significant difference (LSD) and the Bonferroni correction. These data also were analyzed by Dunnett's test.[18] The results are reported as significant, $P < 0.05$, when they met the criteria for ANOVA, LSD, and Dunnett's test. Those results that satisfied the aforementioned tests but not Bonferroni's correction are so indicated (table 1).

TDT scores were analyzed by the Friedman two-way analysis of variance by ranks. The Spearman rank correlation coefficient was used to compare the CPT with the TDT. $P < 0.05$ was interpreted as significant. Results are reported as mean ± SEM unless otherwise noted.[19,20]

Results

PLACEBO

Control respiratory measurements were within normal limits. Neither placebo nor the subsequent administration of physostigmine caused significant changes during the 4-h observation period (fig. 1). Psychomotor function, measured by the CPT 12 min after the second dose of physostigmine, decreased but returned to normal 1 h later (table 1).

DIAZEPAM

Control respiratory measurements were within normal limits. During isohypercapnia, PET_{CO_2} = 46.0 ± 1.30 mmHg, administration of diazepam was followed by a nonsignificant decrease in minute ventilation from 14.20 ± 1.30 l/min to 8.49 ± 5.80 l/min (fig. 1). Fifteen minutes later, *i.e.*, 12 min after administration of 1 mg of physostigmine, minute ventilation was within 2 l/min of control and remained within that range following the second dose of physostigmine and thereafter, as interpolated from the 2- and 4-h CO_2–response curves. CO_2–response curves at 1, 2, and 4 h did not differ from control.

Diazepam caused a deterioration in psychomotor function that was unaffected by physostigmine and per-

sisted throughout the study period as measured by the CPT (table 1). TDT scores did not differ from control at any time (table 2).

MORPHINE

Control respiratory measurements were within normal limits. Morphine caused isohypercapnic $\dot{V}_E$ to decrease by 7.42 l/min to 6.78 ± 1.31 l/min (fig. 1). This decrease in $\dot{V}_E$ was unaltered by physostigmine. $\dot{V}_E$s interpolated from the 2- and 4-h CO_2–response curves at PET_{CO_2} = 46 mmHg also were significantly below control. CO_2–response curves at 1, 2, and 4 h were shifted to the right 8 ± 1 mmHg without change in slope. As measured by the CPT, psychomotor testing revealed a decrease in performance only after the second dose of physostigmine was given and returned to control 1 h later (table 1). TDT results did not differ from control throughout (table 2).

OTHER

Correlation of the CPT with the TDT, using the Spearman rank correlation coefficient, was high, r_s = 0.96 ($P < 0.01$). Throughout the 18 study sessions there were no abnormal ECG events; in no case did the heart rate decrease by more than 10 beats/min after administering physostigmine. Blood pressure stayed near normal in all cases. The 1-mg dose of physostigmine occasionally caused mild nausea unrelated to the unknown drug; after the 2-mg dose of physostigmine, all subjects experienced varying degrees of nausea. Nausea was most apparent during the placebo–physostigmine sequence, during which two subjects had brief episodes of vomiting. When subjects returned for their poststudy interviews approximately 1 week after their last study session, all reported the study as unpleasant, primarily because of the nausea.

Discussion

Our findings, which will be discussed more fully below, are as follows: 1) physostigmine did not antagonize the respiratory depression caused by morphine; 2) in those instances where diazepam caused respiratory depression, physostigmine appeared to be a useful antidote; 3) the CPT may be a valuable tool for assessing psychomotor function as it is affected by anesthetic and adjuvant drugs. The finding that physostigmine alone has little effect on the respiration of normal volunteers is not surprising. Its direct effect on psychomotor function has been documented previously.[21] Psychomotor function also may have been affected by the nausea experienced by the subjects. Tables 1 and 2 show the psychomotor test results. The statistical handling of these data warrants a brief comment in view of the current controversy over multiple comparisons.[22] The use of ANOVA and LSD tends to control the per-comparison error rate, and in theory the per-experiment rate becomes a direct function of the number of comparisons. On the other hand, Bonferroni's correction controls the per-experiment error rate, and the per-comparison error rate then varies inversely as the number of comparisons. Bonferroni's correction is certainly appropriate when data dredging many groups but may be unnecessarily restrictive when making comparisons that flow naturally from the experimental design.[23] In table 1 we have indicated wherever the two approaches have conflicted.

TABLE 2. Treiger Dot Test Median Scores

	Control	Unknown	Physostigmine 1 mg	Physostigmine 2 mg	2 h	4 h
Placebo	3	4	2	8	4	3
Diazepam	3	24	5	7	4	7
Morphine	3	3	3	7	4	3

No values are significantly different from control.

MORPHINE

Snir-Mor *et al.* recently reported that physostigmine antagonizes morphine-induced respiratory depression in humans.[12] However, our results indicate that physostigmine is ineffective in antagonizing such respiratory depression. A closer examination of the methods used in the studies may explain the conflicting results. Our subjects were healthy volunteers who had refrained from all drugs (including caffeine, alcohol, and nicotine) during the 24 h preceding the study sessions. The only drugs administered during the morphine study sessions were morphine and physostigmine. We made continuous hypercapnic observations before, during, and for 45 min after drug administrations. We determined CO_2–response curves using the steady state technique. In contrast, Snir-Mor *et al.* studied preoperative patients who may have received hypnotics the evening before, who were given droperidol before any control observations were made, and who received an anticholinergic shortly before physostigmine. They determined CO_2–response curves using the rebreathing technique. If their patients received hypnotics the evening before, residual effects may have persisted into the study period. Physostigmine has been reported to have antagonistic effects on many commonly used hypnotic agents.[1,2] Moreover, using droperidol before control observations makes interpreting respiratory effect difficult. Droperidol is known to have central anticholinergic effects, and at least three reports have shown that there is a wide

TABLE 3. Minute Ventilation (mean ± SEM) during Isohypercapnic ($P_{ET}CO_2$ = 46 mmHg) Phase of Diazepam Sessions

	Control	After Diazepam 0.29 mg/kg	After Physostigmine 3 mg
Group 1 (N = 3)	14.8 ± 1.2	7.5 ± 0.9	13.2 ± 1.9
Group 2 (N = 3)	13.6 ± 3.2	13.3 ± 3.9	15.8 ± 5.1

variation in respiratory response after administering droperidol.[24-26] Studying the effects of droperidol alone, Prokocimer *et al.* reported that although there was no net effect averaged over eight subjects, seven of the eight had significant variations from control at one time or another during the study.[26] The rebreathing technique frequently is used to determine CO_2–response curves primarily as a matter of time and convenience. Read[27] demonstrated that under normal conditions the steady state and rebreathing techniques are comparable; however, comparability has not been demonstrated during all nonstandard conditions. In fact, after administration of narcotics, CO_2–response curves often show a decrease in slope when the rebreathing technique is used, although there is no change in slope with the steady state technique. At least one study clearly demonstrates differences between the two techniques under nonstandard conditions.[28]

While the results of Snir-Mor *et al.* may be obscured by the above points, the primary basis for their conclusions is a comparison of two groups similarly treated except for the replacement of morphine by saline in the control group. However, with respect to the position of the initial CO_2–response curves, the control and experimental groups may not be comparable. We believe that our findings using unmedicated, healthy volunteers are clear: physostigmine did not antagonize the respiratory depression caused by morphine.

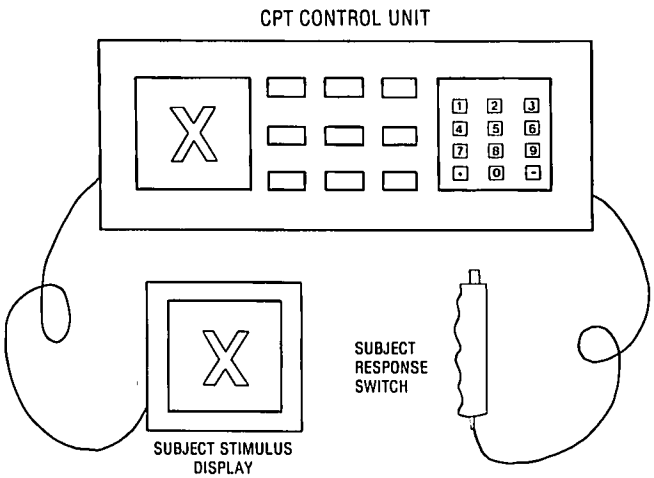

FIG. 2. Continuous Performance Test apparatus, schematic. *Top:* investigator's control unit with, left to right, stimulus monitor, results display, and input keyboard. *Lower left:* subject's stimulus display screen. *Lower right:* subject's critical stimulus response switch. See text for further explanation.

DIAZEPAM

We were unable to draw uniform conclusions regarding the interaction of diazepam and physostigmine with respect to CO_2-mediated respiratory control, probably because of the wide variation in respiratory responses to diazepam, which has been documented previously.[29-31] However, our subjects' individual responses to diazepam during hypercapnia easily can be divided into two distinct groups (table 3). In Group 1 all three subjects had decreases in $\dot{V}_E$ of at least 30%, and in each case respiration returned to prediazepam levels after 3 mg physostigmine. Respiratory depression due to diazepam alone usually persists for a much longer period.[32,33] In Group 2 there were no changes in $\dot{V}_E$ after diazepam or physostigmine. There was a similar division of the subjects' responses to diazepam but not to physostigmine in the tests of psychomotor function. These results are consistent with Gross's observation that after administration of diazepam, there is a high correlation between respiratory depression and decreasing levels of consciousness.[33] Although further study of diazepam–physostigmine interaction would be valuable, we believe that treatment of diazepam-related respiratory depression with physostigmine seems reasonable based on our results. Nevertheless, our results also indicate that successful treatment of respiratory depression does not ensure restoration of normal psychomotor function.[11]

Our conclusions that physostigmine is ineffective as an antagonist for morphine-related respiratory depression, yet may be effective in antagonizing diazepam-related respiratory depression, are in concert if one considers that neither morphine nor diazepam is known to have a central anticholinergic effect; however, in the dose used (15 mg/70 kg), morphine seldom is associated with changes in the level of consciousness, whereas diazepam (20 mg/70 kg) may have considerable effect on the level of consciousness.[33] In this context, physostigmine's action would be due primarily to a generalized central cholinergic arousal as opposed to a specific agonist–antagonist mechanism, and one would expect little interaction between morphine and physostigmine. On the other hand, when diazepam does cause respiratory depression, the generalized arousal produced by

physostigmine may result in increased respiration and apparent antagonism.

Psychomotor Tests

The results from the two tests of psychomotor function appear to be at variance. The TDT, which is widely accepted among anesthesiologists as a test of psychomotor function,[11,15,34-36] provided no significant results, although the CPT did. However, the data from tables 1 and 2 sugggest that the results are similar. In fact, as indicated in the "Results" section, the correlation was strong. However, the TDT generates ordinal type data, which must be analyzed by less-powerful nonparametric tests. We believe that the CPT has several advantages: The CPT measures both speed and accuracy, is simple to administer, does not require interpretation, and generates interval type data that are appropriate to more powerful statistical techniques.

Summary

Physostigmine did not antagonize the respiratory depression caused by morphine. It may, however, be effective as an antagonist when respiratory depression is caused by diazepam, but it does not seem to equally restore psychomotor function. The CPT test correlates well with the TDT and appears to be more sensitive.

Appendix

The Continuous Performance Test (CPT) is administered using a device such as the one shown in Figure 2.[37,38] The subject holds the response switch in one hand while viewing the stimulus screen. A series of letters appear on the screen in random sequence. The subject is instructed to depress the switch as quickly as possible each time an "X" (critical stimulus) appears on the screen. The investigator monitors the letter sequence on a control box that allows him to predetermine the following: 1) stimulus period (SP): the duration of the testing period; 2) interstimulus duration (ISD): the time period between successive stimulus presentations; 3) stimulus duration (SD): the period of time each stimulus is displayed; 4) allowed response time (ART): the time allowed after initial presentation of a critical stimulus before a response is considered to be late.

At the end of the testing period, the control box displays the following: 1) the total number of stimuli presented; 2) the number of critical stimuli presented; 3) the number of correct responses; 4) the mean time to respond (MTTR) correctly to critical stimuli; 5) the number of late responses; 6) the number of missed responses.

Based on others' experience and our own pilot study, we used the following values for the CPT: 1) SP = 300 s; 2) ISD = 1.1 s; 3) SD = 0.1 s; 4) ART = 0.65 s.

We used the mean time to respond (MTTR) as the response variable, since it is a measure of sustained attention as well as motor response.[38]

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