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Biphasic Respiratory Depression after Fentanyl–Droperidol or Fentanyl Alone Used to Supplement Nitrous Oxide Anesthesia

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Either fentanyl or Innovar (fentanyl, 0.05 mg/ml, and droperidol 2.5 mg/ml) was administered to supplement nitrous oxide anesthesia for operations on 29 patients. Both fentanyl and Innovar depressed the slope of the rebreathing CO_2 response curve during operation to 42 per cent ± 6 (mean of all intraoperative values, ± SE) of the awake control value. Following the last injection of drug but with continuation of operation, the slope increased such that it was 77 per cent ± 8 of control on the patients' arrival in the recovery room. The slope continued to increase to a peak of 103 per cent ± 9 of control. Soon thereafter respiratory depression recurred, as indicated by a decline in the slope to 55 per cent ± 5 of control, with a subsequent gradual return to 85 per cent ± 8 of control 230 minutes after the last injection. This biphasic response occurred in 90 per cent (26 of 29) of the patients treated either with fentanyl alone or with Innovar. Full recovery appeared to be more rapid with Innovar than with fentanyl alone. Droperidol did not augment and may have attenuated fentanyl-induced respiratory depression. (Key words: Anesthetics, intravenous, fentanyl–droperidol; Carbon dioxide, ventilatory response; Ventilation, fentanyl–droperidol.)

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THE DURATION of respiratory depression induced by Innovar¶ (fentanyl, 0.05 mg/ml; droperidol, 2.5 mg/ml) when used for general anesthesia in man has not been quantified. Accordingly, we designed a study to determine 1) the magnitude and duration of Innovar-induced respiratory depression when Innovar is used for several hours to supplement general anesthesia with nitrous oxide (N_2O); and 2) whether addition of droperidol enhances the respiratory depression induced by fentanyl.

Methods

Twenty-nine patients, aged 25–83 years, ASA classes I–II, were studied. After informed consent had been obtained, the patients were divided into three groups (table 1). Patients received fentanyl (alone or as Innovar), 1.5 μg/kg, intramuscularly, for premedication, 4.5 μg/kg, intravenously, for induction of anesthesia, and in supplementary injections of 0.75 μg/kg for maintenance. Maintenance doses of fentanyl or Innovar were given only in response to patient movement. Four patients received thiopental (mean 156 mg; range 50–275) for induction of anesthesia. The patients received succinylcholine intravenously for endotracheal intubation and N_2O (60 per cent) or maintenance of anesthesia. Vital signs were monitored by conventional noninvasive techniques.

On the evening (one reading) and morning before operation (two readings), resting end-tidal P_{CO_2} and modified Read rebreathing CO_2 response curves were obtained.[1,2] Control

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TABLE 1. Patients Divided on the Basis of Fentanyl or Innovar for Premedication, Induction, and Maintenance

	Number of Patients	Premedication (2.1 ml/70 kg, im)*	Induction (6.3 ml/70 kg, iv)*	Maintenance (1.05 ml/70 kg, iv, multiple)*
Group I	10	Fentanyl	Fentanyl	Fentanyl
Group II	14	Innovar	Innovar	Innovar
Group III	5	Innovar	Innovar	Fentanyl

* Each ml contains 0.05 mg fentanyl (Innovar contains 2.5 mg droperidol in addition).

slope was arbitrarily chosen as that slope which was numerically between the other two (for example, if the three slopes for one patient were 1.0, 1.2, and .9, 1.0 would be designated "control"). These tests were repeated 15 minutes after premedication and then every 30 minutes before, during and after operation either until return to control values occurred or until patients were unable to continue with the study. All measurements were obtained with the patients in the supine position. Prior to rebreathing, the 5-liter rebreathing bag was filled with either 1) 7.5 per cent CO_2 plus oxygen, or 2) 7.5 per cent CO_2 plus 50 per cent N_2O plus oxygen. Breath-to-breath minute ventilation and end-tidal P_{CO_2} were continuously monitored with a Fleisch pneumotachograph–Validyne/analog computer combination and an LB-1 infrared CO_2 analyzer. During any rebreathing test the interval from equilibration of bag and end-tidal P_{CO_2} (usually within 30 sec of initiating rebreathing) to the end of rebreathing CO_2 was divided into five to ten equal periods. The values of minute ventilation and P_{CO_2} for each of these periods were used to calculate linear regression (*i.e.*, the slope and position of the CO_2 response curve). During operation corrected values for carbon dioxide were obtained by using a nitrous oxide calibration curve.[2] Data from the three groups were compared by analysis of variance or covariance.[3]

Results

The 29 patients underwent surgical anesthesia lasting 2.3 ± 0.2 hours and were each given 650 ± 50 μg fentanyl. The CO_2 slope during operation declined to 22 per cent of control at its lowest point, and Pa_{CO_2} rose from a mean of 34 (control) to a peak of 48 torr (during operation) (tables 2 and 3). With the induction dose of fentanyl or Innovar, transient apnea invariably occurred, and end-tidal P_{CO_2} transiently rose from 50 to 65 torr on resumption of respiration.

The three groups did not differ significantly in weight, age, surgical time, slope of the control CO_2 response curve, control end-tidal P_{CO_2}, or dose of fentanyl (tables 2, 3, and 4). The groups also did not differ in: 1) amount of narcotic administered per body surface area per surgical time (period of time from induction to skin closure) (table 4); 2) mean time from the last dose to the flattest postoperative CO_2 response slope; 3) the magnitude of this slope (table 2) or the mean time to and magnitude of the highest postoperative resting end-tidal P_{CO_2} (table 3).

Respiratory depression diminished on cessation of fentanyl or Innovar administration (tables 2 and 3, figs. 1 and 2). By the time the patients entered the recovery room, the CO_2 response slopes and end-tidal P_{CO_2} values for all groups were 77 ± 8 per cent of control and 38 ± 1 torr, respectively. Thirty minutes after entering the recovery room, the slope values for the patients treated with Innovar (Groups II and III) exceeded normal (127 ± 15 per cent and 119 ± 16 per cent, respectively, of control) and were significantly greater ($P < 0.02$ by Wilcoxin rank test) than values for the fentanyl group (84 ± 8 per cent).

Recovery from respiratory depression was not sustained (tables 2 and 3, figs. 1 and 2). Twenty-six of the 29 patients manifested the biphasic response. After reaching an average peak value of 103 ± 9 per cent of control, the slope of the CO_2 response curve progressively diminished to a low of 55 ± 5 per cent of control, and from this point gradually rose again to

TABLE 2. CO_2 Response Slopes (Mean ± SE) in Percentages of Control before, during and after Operation

	Control (l/min/torr)	Percentage of Control								
		Premedication Low	During operation				In Recovery Room			
			Mean	Low	Immediately after Last Dose	Last	First	High	Low	Last
Group I (n = 10)	1.04 ± .25	63 ± 8	26 ± 4	10 ± 5	28 ± 7	37 ± 7	67 ± 11	77 ± 11	41 ± 5	65 ± 9
Group II (n = 14)	1.46 ± .37	73 ± 7	59 ± 11	34 ± 8	48 ± 12	81 ± 19	83 ± 15	120 ± 14	62 ± 7	93 ± 13
Group III (n = 5)	1.54 ± .35	60 ± 19	25 ± 5	13 ± 6	26 ± 10	32 ± 11	81 ± 16	110 ± 14	68 ± 12	99 ± 13
GRAND MEANS	1.27 ± .20	69 ± 5	42 ± 6	22 ± 5	37 ± 7	59 ± 10	77 ± 8	103 ± 9	55 ± 5	85 ± 8

TABLE 3. Resting End-tidal P_{CO_2} (torr) Values (Mean ± SE) before, during, and after Operation

	Control	Premedication High	During Operation				Recovery Room			
			Mean	High	Immediately after Last Dose	Last	First	Low	High	Last
Group I (n = 9)	34 ± 1	35 ± 2	42 ± 2	49 ± 4	42 ± 5	36 ± 2	36 ± 2	37 ± 1	40 ± 1	35 ± 2
Group II (n = 9)	35 ± 1	36 ± 1	41 ± 3	49 ± 2	41 ± 3	37 ± 3	39 ± 1	32 ± 2	39 ± 2	37 ± 1
Group III (n = 3)	33 ± 3	35 ± 1	34 ± 3	42 ± 6	36 ± 4	33 ± 2	39 ± 3	37 ± 2	42 ± 1	36 ± 1
GRAND MEANS 21	34 ± 1	35 ± 1	40 ± 2	48 ± 2	41 ± 2	36 ± 1	38 ± 1	35 ± 1	39 ± 1	36 ± 1

TABLE 4. Mean Values (± SEM) for Groups I, II, and III

	Weight (kg)	BSA (m^2)	Age (Years)	Fentanyl (ml)	Surgical Time (Hours)	Dose Fentanyl per Surgical Time (ml/Hr)	Dose Fentanyl per BSA per Surgical Time (ml/m^2/Hr)
Group I	75 ± 7	1.81 ± .09	49 ± 6	15 ± 1	2.47 ± .25	6.78 ± 1.08	3.67 ± .51
Group II	71 ± 3	1.78 ± .05	51 ± 5	12 ± 2	2.05 ± 22	6.72 ± 1.08	3.80 ± .62
Group III	58 ± 6	1.65 ± .11	61 ± 6	13 ± 3	2.77 ± .43	6.54 ± 1.20	3.28 ± .84

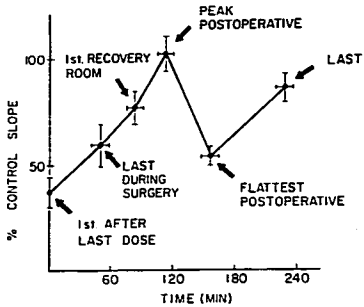

FIG. 1. CO_2 response slopes as percentages of control slope (± SEM) at the time (± SEM) of the last dose of fentanyl or Innovar (time = 0), at the end of operation, at the time when they were steepest, at the time when they were flattest, and at the end of the study (n = 29, except for "flattest postoperative," where n = 26).

86 ± 7 per cent of control 230 minutes after the last injection of narcotic.

Mean systolic blood pressure and pulse rate before operation were 126 ± 5 torr and 74 ± 2/min, respectively, and during operation, 133 ± 5 torr and 82 ± 2/min. The immediate mean postoperative systolic blood pressure, pulse rate, and temperature were 135 ± 3 torr, 88 ± 2/min, and 35.9 C ± 1. Systolic blood pressure and pulse rate decreased postoperatively to 124 ± 4 torr and 80 ± 3/min.

Discussion

Our results agree with those of others[4-8] in that Innovar and fentanyl can cause significant respiratory depression. In particular, we found, as did Dunbar *et al.*[4] and Harper *et al.*,[5] consistent decreases in the slope of the CO_2 response curve. That Innovar and fentanyl both depress the slope of the CO_2 response curve when given in amounts necessary for general anesthesia with N_2O is not surprising. However, the recurrence of respiratory depression in the recovery room, as indicated by the decreased slope after normality had apparently been achieved, was unexpected, and may be of considerable clinical concern. Although the average "low" slope in the postoperative period was 55 per cent of control, in two patients this minimum slope was less than 10 per cent of control. The absence of a normal response to hypercapnia may increase the risk imposed by otherwise minor respiratory obstruction. Thus, an apparent return to normalcy in the immediate postoperative period may not be sustained, and patients may remain at risk of respiratory depression for one to three hours following anesthesia with Innovar or fentanyl.

The potential risk suggested above also is camouflaged by the normalcy of the end-tidal P_{CO_2}. Our observation of P_{CO_2}'s of 30–40 torr at times when marked slope depression was present suggests that a normal resting end-tidal P_{CO_2} or Pa_{CO_2} may not imply the presence of a normal increase in ventilatory effort in response to airway obstruction.

That droperidol did not enhance the respiratory depression produced by fentanyl, but may have actually decreased it, also was unexpected. This finding correlates with our observation that the addition of droperidol to fentanyl did not reduce the amount of fentanyl needed per unit time of operation (table 2). There appear to be both advantages (less nausea, vomiting, and possibly respiratory depression) and disadvantages (dysphoria, alpha-adrenergic sympathetic blockade) associated with the use of droperidol. These (with the exception of respiratory effects) were not studied in the present investigation. We conclude that droperidol adds to neither the anesthetic nor the respiratory depressant effects of fentanyl.

Several factors influence the CO_2 response. They include 1) temperature,[9,10] 2) acid–base balance,[11-13] 3) sympathetic activity,[12,14] 4) vagal activity,[15] 5) state of consciousness,[16] 6) Pa_{O_2},[17] and 7) surgery.[18] Clearly, any one or a combination of these factors might influence the CO_2 response before, during and after operation. Although none of these factors (with the exception of temperature) was systematically examined during the study, we can assume they had little impact on our results in the absence of any significant change in blood pressure or pulse rate.

Hypothermia progressively decreases the slope of the CO_2 response curve of the dog.[10] If this relationship applies to man, we would predict a 15 per cent depression of control slope for a mean temperature reduction of 1.1 degree C, and thus, temperature reduction

may have contributed to the intraoperative depression seen. However, since temperature progressively increases towards normal in the postoperative period, this would oppose and thereby minimize the biphasic depression seen in the recovery room. If the decreases in blood pressure and pulse rate seen postoperatively reflect a lowered level of sympathetic activity, then the lowered sympathetic activity (which depresses the CO_2 response slope) might account for part of the biphasic postoperative depression. It would also tend to prolong the return to control.

Also, nitrous oxide will falsely elevate the P_{CO_2} reading of a gas measured by an infrared analyzer.[3] Although we corrected for this during operation, no correction was applied during recovery. Of concern is that expired nitrous oxide will accumulate in the rebreathing bag, resulting in a falsely large increase in end-tidal P_{CO_2}. This would tend to make CO_2 response slopes less than the actual slopes. This error should be greatest in the beginning of recovery from general anesthesia and subsequently decrease. Actually, the slopes increased during the beginning of recovery, which suggests that this potential error is relatively unimportant. Nitrous oxide alone has been shown to shift the CO_2 response curve slightly to the left, but not to change the slope.[19]

The biphasic response may be explained by the varying intensity of stimulation during the recovery period.[18] When entering the recovery room, the patient may be stimulated by the initial evaluation by the nurses and the rapid elimination of nitrous oxide. This initial stimulation often is followed by relative inactivity. Perhaps then residual respiratory depression by narcotic is seen. Second, perhaps fentanyl, like meperidine, is sequestered in the stomach during operation.** Then, with passage into the alkaline milieu of the small intestine, an increase in serum concentration and the reappearance of narcotic-induced respiratory depression may occur. We did not measure serum or gastric concentrations of fentanyl,

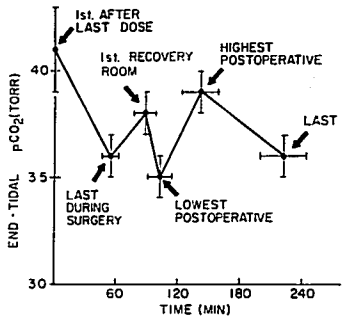

FIG. 2. Mean resting end-tidal P_{CO_2}'s (± SEM) at the time (± SEM) of the last dose of fentanyl or Innovar (time = 0), at the end of operation, at the time when they were lowest, at the time when they were highest, and at the end of the study (n = 21).

and therefore cannot distinguish between these possibilities.

In summary, recovery from respiratory depression associated with Innovar- or fentanyl-supplemented N_2O anesthesia appears to follow a biphasic course. Patients may appear to have no respiratory depression shortly after arriving in the recovery room and subsequently have marked decreases in CO_2 sensitivity. The recurrence of depression probably is not an effect unique to fentanyl (or Innovar), but may occur following any narcotic. Finally, droperidol does not appear to increase the respiratory depression associated with fentanyl, and may actually decrease it.

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Monitoring

ENDOCARDITIS AND PULMONARY-ARTERY CATHETERIZATION Although information obtained through the use of pulmonary-artery catheters may be extremely useful in patient care, there is a concern that endocarditis might result. The authors have reviewed autopsy records over a five-year period (1969–1974) before and after the introduction of pulmonary-artery (PA) catheterization. During a 30-month period preceding the use of PA catheterization, 493 autopsies were performed. Nine cases of left-sided endocarditis and one case of right-sided endocarditis were found. PA catheterization was performed in some patients during the next 30 months. Investigation of 438 autopsies during this period revealed 14 cases of left-sided endocarditis. Twelve were unassociated with catheterization. Two (one aseptic and one septic) were associated with PA catheterization. On the other hand, ten cases of right-sided endocarditis were found. One of these (aseptic) was not associated with catheterization. Four (two septic and two aseptic) were associated with CVP measurement, and five (four aseptic and one septic) with PA catheterization. These five patients represented 9.3 per cent of the cases in which such monitoring was performed during their terminal hospital course. It is concluded that indwelling catheterization of the pulmonary artery does not pose a risk of left-sided endocarditis, although there is an increased risk of aseptic right-sided endocarditis. *(Greene JF, Fitzwater JE, Clemmer TP: Septic endocarditis and indwelling pulmonary artery catheters. JAMA 233: 891–892, 1975.)*