Droperidol and Fentanyl Combination:

Effect on the Human Labyrinth

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The effect of a mixture of droperidol and fentanyl citrate in a ratio of 50:1 (Innovar) on the vestibular systems of young, healthy men was examined. Droperidol (5 mg) with fentanyl (0.1 mg) suppressed the vestibular reaction of the inner ear to caloric stimulation but not the vestibular reaction to galvanic stimulation, suggesting that the site of action was within the labyrinthine part of the vestibular system. The mean time from completion of drug administration to maximal labyrinthine suppression was nine minutes and the mean duration of suppression 198 minutes.

De Castro and Mundeleer (1962) induced an analgesic and sedative state called neuroleptanalgeia [1] for surgical procedures without using barbiturates or volatile anesthetic agents, employing a combination of drugs developed by Janssen. Of several new analgesics and sedatives developed by Janssen,[2] the combination of droperidol [1-{1-[3-(p-flurobenzoyl) propyl]-1,2,3,6-tetrahyrdro-4 pyridyl}-2-benzimidazolinone] and fentanyl [n-(1-phenethyl-4-piperidinyl) propionanilide dihydrogen citrate] (Innovar) provided the most satisfactory anesthetic conditions in animals and man. Recently this combination was found to terminate acute attacks of Meniere's disease [3]; therefore, an investigation of its pharmacologic effects on the vestibular system was undertaken. The present communication presents the results of a preliminary study of the responses of the normal human vestibular system to the mixture of droperidol (5 mg) and fentanyl (0.1 mg).

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Methods

Group A—Comparison of Effects of Innovar on Galvanic an Caloric Reactions of the Vestibular System

Each subject served as his own control. Normal labyrinthine reactions to calorization were established in five young normal men by calorizing both labyrinths with a modified Hallpike technique and using the Hallpike constant-temperature calorimeter.[4] Latency of onset, degree and duration of caloric nystagmus were observed with Frenzel goggles. Between tests recovery periods of 15 minutes were allowed for disappearance of all vestibular reactions. After a further recovery of 30 minutes, baseline galvanic response was recorded by utilizing two to four milliamperes of galvanic current through electrodes mounted on a headset and placed in each external auditory canal, with the falling reaction examined from a sitting position.

One hour after control testing the combination of droperidol (5 mg) and fentanyl (0.1 mg) was administered intravenously over a two-minute period. Caloric and galvanic reactions were tested at 10 and 20 minutes, respectively, after completion of administration of the drugs and again at 30 and 40 minutes, respectively. The galvanic tests were repeated at 180 minutes, and the caloric tests were repeated at 30-minute intervals until normal vestibular reaction to calorization had returned.

TABLE 1. Results of Caloric and Galvanic Falling Tests after Droperidol and Fentanyl Mixture*

Subject	Age	Weight (lb)	Height (in.)	Before Droperidol (5 mg) and Fentanyl (0.1 mg)		After Droperidol (5 mg) and Fentanyl (0.1 mg)		Time to Return of Normal Caloric Reaction (min)
				Caloric Reaction	Galvanic Falling Reaction 2 mA	10-min Caloric Reaction	20-min Galvanic Reaction 2 mA	
1	23	225	77	N	+	O	+	120
2	22	166	72	N	+	O	+	300
3	24	130	67	N	+	O	+	180
4	24	210	70	N	+	S	+	180
5	29	157	67	N	+	O	+	360
Mean†	24.4 (± 1.2)	177.6 (± 19.2)						228 (± 44)

* O = Total suppression of caloric response; no nystagmus, no vertigo. S = Slight to moderate reduction of nystagmus qualities: latency, amplitude, duration. N = Normal result of caloric test without significant deviation from first test.

† Each mean followed by SE.

GROUP B—ELECTRONYSTAGMOGRAPHIC STUDIES OF ONSET AND DURATION OF SUPPRESSION OF LABYRINTHINE ACTIVITY

Suppression of normal labyrinthine function by the combination of droperidol and fentanyl was studied quantitatively in seven young, normal men by the electronystagmographic technique.[5, 6] Horizontal nystagmus was recorded utilizing skin electrodes and a Beckman type R dynograph with a type 482 DC amplifier, a type 481-B preamplifier, and a paper speed of 1 cm/sec.

The subjects were placed in a supine position with the upper portion of the body elevated to 30 degrees from the horizontal to place the horizontal canal into a vertical position. The presence or absence of supine positional nystagmus was determined prior to calorization. The caloric tests were performed utilizing a modified Hallpike technique and a Hallpike constant-temperature calorimeter. The recording machine was calibrated prior to each irrigation. Right or left labyrinthine preponderance and directional preponderance were determined. Labyrinthine preponderance was absent in all of the normal subjects. One subject had a directional preponderance to the right of 35.8 per cent.

After the control studies were performed the drug mixture was administered intravenously over a period of two minutes. Labyrinthine excitability to caloric stimulation was determined at four-minute intervals from the beginning of the administration until 14 minutes after completion. Calorization of the labyrinth was again performed 20 minutes following completion of the administration of the drug and at subsequent 30-minute intervals until the labyrinthine response equalled the preinjection response.

Results

GROUP A

The data from this series of experiments are presented in table 1. When the vestibular response to caloric stimulation was tested ten minutes after administration of the drug mixture, four subjects had total suppression of response and one a moderate reduction of response. Twenty minutes after administration all subjects retained positive falling reactions to galvanic stimulation. All subsequent galvanic tests were positive. The mean time of return of normal caloric reaction was 228 minutes, range 120 to 360 minutes.

GROUP B

A typical electronystagmographic tracing demonstrating the effect of the drug mixture on labyrinthine function is shown in figure 1. Data from this series of experiments are given in table 2.

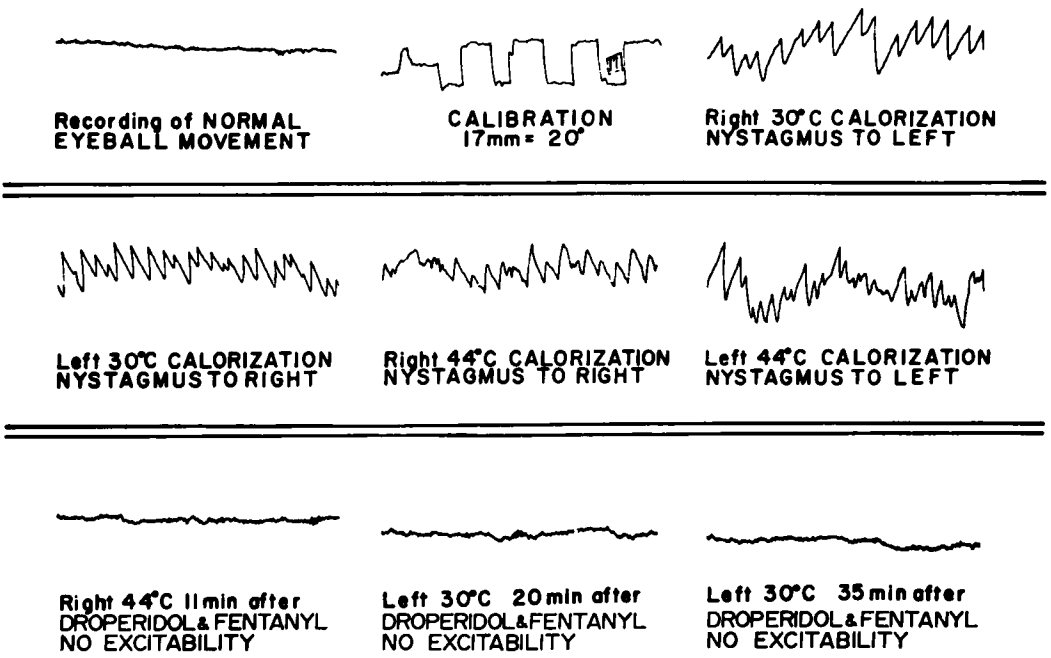

FIG. 1. Representative electronystagmographic tracing of the effect of the mixture of droperidol (5 mg) and fentanyl (0.1 mg) on labyrinthine function.

The mean interval until maximal suppression of labyrinthine function after administration of the drug combination was 9 ± 1.7 minutes. Six subjects responded with total suppression. One responded with only partial suppression, but nine minutes after administration his labyrinth had reached maximal suppression, at which time 87 per cent of normal labyrinthine activity was abolished.

The mean interval until complete recovery in five subjects was 198 ± 20.5 minutes. Subjects 6 and 9 were not tested until complete

TABLE 2. Time to Suppression and Time to Recovery of Labyrinthine Reaction to Caloric Stimulation after Droperidol (5 mg) and Fentanyl (1 mg)

Subject	Age	Weight (lb.)	Height (in.)	Time to Complete Suppression (min)	Time to Complete Recovery (min)
6	25	195	71	5	*
7	25	210	76	8	231
8	24	170	71	5	205
9	23	162	72	**	***
10	23	150	71	15	138
11	24	170	76	13	166
12	19	140	67	8	205
Mean†	23.3 (± .8)	171.1 ± (9.2)		9 ± (1.7)	198 ± (20.5)

* Subject 6 returned to ¾ normal labyrinthine activity to caloric stimulation after 266 minutes (unable to complete until later date).

** Subject 9 had maximal suppression of only 87%, which occurred after 9 minutes.

*** Subject 9 returned to ⅞ normal activity after 370 minutes (unable to complete until later date).

† Each mean followed by SE. Subject 9 was excluded in calculating mean suppression time, and Subjects 6 and 9 were excluded in calculating mean recovery time.

recovery. Their recovery periods were more prolonged than the others, and they refused further testing at that time due to prior commitments. Subject 6, when last tested at 266 minutes, responded with 75 per cent of normal activity. Subject 9, who did not have complete suppression of labyrinthine activity, also had a prolonged recovery. When tested at 370 minutes, he demonstrated a return of 86 per cent of normal activity. When tested at a later date both subjects demonstrated labyrinthine activity within 2.5 per cent of the initial value. This was considered a return to normal activity.

In all subjects return of labyrinthine function was a progressive phenomenon.

Side Effects

Significant respiratory depression occurred in three subjects. The onset was abrupt; it usually occurred within four minutes and abruptly terminated about 15 minutes after administration of the drug combination. This was corrected easily by instructing the subjects to breathe. All were slightly drowsy but were able to converse intelligently and to work mathematical equations; they were not aware of having respiratory depression. Three spontaneously complained of having "tight muscles of the throat"; however, at that time, there was no significant diminution of ventilation. Four subjects had significant irritability and restlessness. The onset was approximately one to one and a half hours after the administration of the drug combination and lasted five to six hours; then, benztropine mesylate was administered intramuscularly after the testing was completed, and the symptoms subsided shortly thereafter. Subject 8 complained of these symptoms; five and a half hours after the administration of the fentanyl and droperidol mixtures a severe oculogyric crisis with opisthotonos occurred. Benztropine mesylate was administered and the crisis immediately terminated.

Discussion

The side effects of respiratory depression and extrapyramidal stimulation that occurred in this study have been adequately described elsewhere.[1, 7-9] When the respiratory depression occurred, onset and termination were abrupt and easily managed by instructing the subjects to breathe. The extrapyramidal stimulation may be prevented by the intravenous administration of benztropine mesylate, 2 mg, five minutes prior to the administration of fentanyl and droperidol. However, in order to eliminate multiple drug effect, this was not done in these experiments.

These findings of the vestibular response confirm one of our original observations that the combination of droperidol and fentanyl suppresses the human labyrinthine response to caloric stimulation in a reversible manner.[3] Study of Group B revealed that the mean interval from completion of the administration of the drugs until maximal suppression was nine minutes and the mean duration of suppression 198 minutes.

The data on duration of suppression of Group A are in accord with those of Group B, even though the data obtained in Group B by electronystagmography should be much more accurate than the gross observations of nystagmus utilized in Group A.

That part of the vestibular system which responded to the drug combination with suppression of the caloric reaction could have been within any of the following: the labyrinth, the vestibular portion of the eighth cranial nerve, the vestibular ganglion; or within the central nervous system.

It is accepted that the nystagmus produced by calorization occurs secondary to changes in the labyrinthine part of the vestibular system.[10] The mechanism of the galvanic reaction has not yet been described, but it has long been known that this reaction still occurs after bilateral resection of the labyrinth.[11] It is thought by some otophysiologists that the nystagmus and falling reaction elicited by galvanic current arise from stimulation of parts of the vestibular system other than the labyrinth.[12] Based on these concepts, we interpret the findings that the mixture of droperidol and fentanyl suppresses the labyrinthine response to calorization but does not alter the galvanic falling reaction to mean that the effective site of the drug combination on the vestibular system was within the labyrinthine part of the vestibular system.

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Obstetrical Anesthesia

EARLY VS. LATE CORD CLAMPING The effects of early and late clamping of the umbilical cord on postpartum bleeding, duration of the third stage of labor, and the incidence of placental retention were studied in 117 mothers. Postpartum bleeding and retained placentae occurred with significantly greater frequency in mothers of infants whose umbilical cords were clamped early. These findings were not related to over-distention of the uterus, medications, or soft-tissue injury. No differences were found in the third stage of labor. (*Walsh, S. Z.: Maternal Effects of Early and Late Clamping of the Umbilical Cord, Lancet 1: 996 (May) 1968.*)

FETAL DEPRESSION Simultaneous monitoring of maternal and fetal EEG in the guinea pig allows one to study placental drug transfer. EEG changes in the fetus appeared within 60 sec of the appearance of similar changes in the maternal EEG following maternal intravenous, intramuscular or intraperitoneal injection of meperidine. Following fetal intramuscular or intraperitoneal injection, rapid transfer to the maternal brain was also documented. This study has special interest because it demonstrates that meperidine, administered to a pregnant patient, has *fetal* as well as neonatal depressant effects. (*Rosen, M. G., and Bleyer, W. A.: Bidirectional Transfer of Meperidine Across the Guinea Pig Placenta, Amer. J. Obstet. Gynec. 101: 918 (Aug.) 1968.*)