Effects of Morphine, Levallorphan, and Respiratory Gases on Increased Intracranial Pressure

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It would be advantageous to predict the response of the patient with increased intracranial pressure to depressant agents (*e.g.*, narcotics, anesthetics) and ventilatory insufficiency or both. There is indirect evidence that the rise in intracranial pressure following administration of narcotics is a function of CO_2 retention consequent to the narcotic-induced respiratory depression. Kepes [1] reported that meperidine and morphine increased cerebrospinal fluid pressure (CSFP) significantly in normal human beings, but no attempt was made to correlate this finding with the ventilatory effects of these drugs. Keats and Mithoefer [2] presented findings in patients postoperatively which indicated that the rise in CSFP produced by morphine was concomitant with a decrease in alveolar ventilation and that this rise may be reversed by nalorphine or hyperventilation. They concluded that the elevation in intracranial pressure produced by morphine is the result of a rise in arterial CO_2 tension, with its consequent increase in cerebral blood flow. However, this conclusion was based on a study in which simultaneous measurements of CSFP, alveolar ventilation, and alveolar gas composition were done in only two subjects. Wilson and associates [3] also believe the rise in intracranial pressure associated with increased arterial P_{CO_2} during anesthesia reflects cerebral vasodilation and augmentation of blood flow. These hypotheses were supported by Sokoloff,[4] who in a review of the literature stated that the effects of narcotics on cerebral circulation are secondary to their actions on other functions such as pulmonary ventilation.

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The effect of hypercapnia and hypoxia on the CSFP measured at the cisterna magna (which we believe to be identical with the intracranial pressure) has been reported for the normal anesthetized dog.[5] This study demonstrated that CSFP increased with apneic oxygenation, and with artificial ventilation with 5 per cent CO_2 or 8 per cent O_2, and directly confirmed the findings in the studies on normal human beings previously mentioned. It is uncertain, however, whether the same results would obtain in the presence of a pre-existing elevation in intracranial pressure. If dogs with increased intracranial tension respond as do normal dogs and man to hypercarbia and narcotics, it may be presumed that patients with increased intracranial pressure may be treated with narcotic analgesics, provided respiratory depression is prevented. The present study was undertaken to evaluate this possibility.

Material and Methods

Mongrel dogs, weighing between 10–20 kg., were anesthetized with intravenous pentobarbital, 25 mg./kg. Their tracheas were immediately intubated, the cuff inflated, and the endotracheal tube connected to a supply of 100 per cent O_2 (fig. 1). The animals either breathed spontaneously or were paralyzed by succinylcholine and their lungs ventilated. Artificial ventilation was maintained constant by an electronically-timed, pressure-limited, intermittent-positive-pressure ventilator. Carinal gases were sampled continuously and measured with a Beckman LB-1 CO_2 analyzer. In all animals, a femoral arterial-venous polyethylene shunt, which incorporated a *p*H electrode,[6] was inserted. The *p*H was measured with a radiometer TTT1 *p*H meter and recorded continuously, with all other measured parameters, on a Sanborn Model 156 direct-writing oscillograph. Carotid artery and external jugular vein cutdowns were performed, and polyethylene catheters inserted for meas-

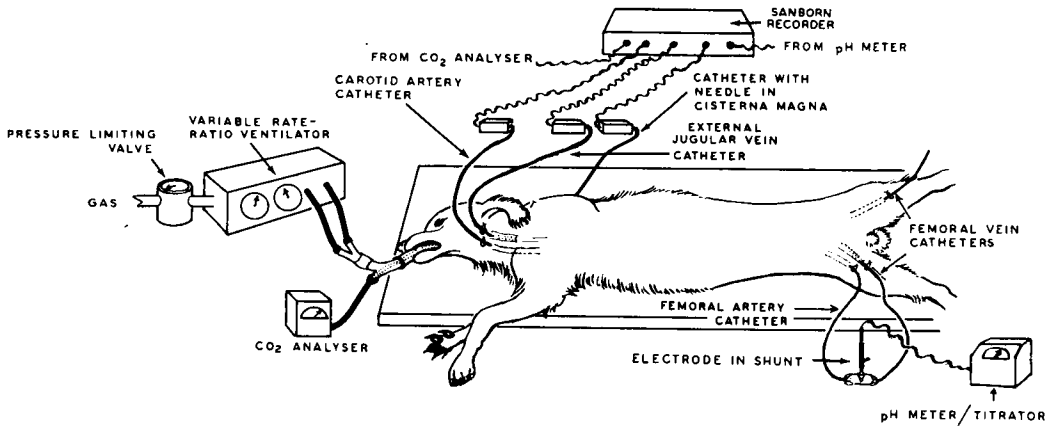

FIG. 1. Schematic design of experiments.

urement of intra-aortic and intrathoracic venous pressures, respectively. The cisterna magna was punctured using a styletted 20-gauge needle connected to a polyethylene catheter via a three-way stopcock. All pressures were transduced by Statham strain gauges.

At this point, when an elevated CSFP was desired, Cytal concentrate * was injected into the cistern. Immediately, CSFP rose precipitously, but then fell steeply within the next two minutes. A gradual rise followed, resulting, usually within 20 minutes, in a stable pressure greater than 300 mm. of water. After a variable period (20–60 minutes) CSFP gradually declined. The pressure throughout remained well above normal. Five minutes after Cytal injection the animal was heparinized, and the femoral A-V shunt was opened. If Cytal was not to be used, the heparin was given after all catheters had been placed and the cisternal tap done. These preparations were completed about 45 to 60 minutes after induction of anesthesia.

In the first series of experiments (CSFP elevated with Cytal), the response was measured to apneic oxygenation (five dogs), to ventilation with 5 per cent CO_2 in 95 per cent O_2 (four dogs), and to ventilation with 8 per cent O_2 in 92 per cent N_2 (four dogs). All the dogs in this group were paralyzed and their lungs ventilated with 100 per cent O_2 immediately after intubation to effect denitrogenation. The test period was terminated after a peak CSFP response had been noted.

The second series (narcotic experiments) was designed in four parts, each having one of the drug combinations shown in table 1.

For drug combination *1* (morphine, then levallorphan) CSFP was observed for 30 minutes after administration of morphine. If a peak CSFP were observed within the 30-minute interval, levallorphan was given immediately after the peak was noted; otherwise it was given after 30 minutes. Observations were continued for about ten minutes. The dose of morphine, which was always administered subcutaneously, usually varied between 2–4 mg./kg. and was always 50 times the dose of levallorphan. Levallorphan was administered intravenously except when given in a morphine mixture.

In drug combination *2* (levallorphan, then morphine) morphine was given 6 to 11 minutes after levallorphan, and observations were continued for 20 to 30 minutes. A similar observation period followed the injection of the morphine-levallorphan mixture (drug combination *3*).

For each experiment, the CO_2 analyzer was calibrated using 4, 5, 8 and 10 per cent CO_2 in O_2 mixtures. At appropriate times, arterial blood samples were obtained and analyzed for *p*H and P_{CO_2} using an Astrup apparatus [7] at

* Cytal is a commercially-available, hyperosmolar, urologic, irrigating fluid, containing 27.0 g. of sorbital and 5.4 g. of mannitol per 100 ml. water. In normal clinical use it is diluted with nine parts of sterile water to provide an approximately-isotonic solution.

TABLE 1. Scheme of Narcotic Experiments

	Spontaneous Ventilation	Artificial Ventilation
Normal intracranial pressure	A. (1) Morphine, then Levallorphan (2) Levallorphan, then Morphine (3) M.S.-Levallorphan Mixture	B. (1) Morphine, then Levallorphan (2) Levallorphan, then Morphine
Increased intracranial pressure	C. (1) Morphine, then Levallorphan (2) Levallorphan, then Morphine (3) M.S.-Levallorphan Mixture	D. (1) Morphine, then Levallorphan (2) Levallorphan, then Morphine

38° C. and a second Radiometer *p*H meter. Standard bicarbonate was then derived from an Astrup nomogram.[8]

Results

Apneic Oxygenation (Table 2). The mean of CSF pressures rose from 433 mm. of water to a peak of 581 mm. of water after an average 14 minutes of apneic oxygenation. Arterial and venous pressures varied widely but without consistent patterns. Arterial P_{CO_2} increased an average of 65 mm. of mercury, while standard bicarbonate showed a small but consistent increase.

Ventilation with 5 Per Cent CO_2 (Table 2). This resulted, after 5.3 minutes, in an average increase of CSFP of 162 mm. of water from 372 to 534 mm. of water. Arterial and venous pressures changed minimally. Standard bicarbonate remained unchanged while P_{CO_2} increased an average of 16 mm. of mercury.

Ventilation with 8 Per Cent O_2 (Table 2). The average CSFP rose from 399 to 567 mm. of water in 8.4 minutes, although in one dog CSFP fell slightly. No correlation was made between changes in arterial, venous and CSF pressures. Acid-base determinations were not done for this group.

Morphine, Then Levallorphan, in Normal Dogs Breathing Spontaneously (Table 3, Fig. 2). In eight dogs, during an average observation period of 22 minutes following the morphine injection average CSFP rose from 96 to 144 mm. of water. Mean blood pressure always fell (average 21 mm. of mercury); intrathoracic venous pressure changes were inconsistent. During this time, average arterial P_{CO_2} rose 25 mm. of mercury. Ventilation

TABLE 2. Average Data From the First Series of Experiments (CSFP Elevated with Cytal)

	CSFP		BP		IVP		P_{CO_2}		Standard HCO_3^-		Time
	Control	Change	Control	Change	Control	Change	Control	Change	Control	Change	
Apneic oxygenation	433	+148‡	108	+47	13	+58	43	+65	28	+2	14
5 per cent CO_2	372	+162‡	126	+ 3	10	− 3.5	39	+16	24	0	5.3
8 per cent O_2	399	+168	96	− 8	1	+ 6	—	—	—	—	8.4

CSFP = cerebrospinal fluid pressure in mm. H_2O.
BP = mean arterial blood pressure in mm. Hg.
IVP = intrathoracic venous pressure in mm. H_2O.
P_{CO_2} = arterial CO_2 tension in mm. Hg.
Standard HCO_3^- = bicarbonate concentration of blood in mmoles/liter, when it is fully saturated with O_2 and has a CO_2 tension of 40 mm. Hg.
Time = time in minutes.
‡ = change significant at 99 per cent confidence limit (Student's *t* test).

TABLE 3. Average Data From the Second Series of Experiments (Narcotic Administration)

	CSFP*		BP*		IVP*		P_{CO_2}*		Standard* HCO_3^-	Time*
	Control	Change	Control	Change	Control	Change	Control	Change		
	Normal Intracranial Pressure									
Spontaneous Ventilation										
Morphine	96	+48‡	104	−21	− 8	+20	52	+25	29	22
Levallorphan after Morphine	133	−66‡	78	+ 4	7	−19	71	−25	29	8.5
Artificial Ventilation										
Morphine	64	+13	103	−19	−26	−13	46	+ 3	26.7	31.3
Levallorphan after Morphine	78	+ 8	84	− 1	−39	+ 4	49	− 1	25.2	7.7
	Increased Intracranial Pressure									
Spontaneous Ventilation										
Morphine	383	−36	119	−22	30	+ 7	35	+17	28.5	19.8
Levallorphan after Morphine	341	−70‡	95	+ 5	38	−17	52	−12	26.8	8.2
Artificial Ventilation										
Morphine	371	−75	101	−16	26	− 4	41	0	23.1	34.3
Levallorphan after Morphine	293	+10	86	+ 8	22	− 3	41	+ 0.5	23.1	6.0

* For explanation, see legend beneath table 2.

improved immediately after levallorphan was given, and P_{CO_2} returned quickly toward, and in some cases, below, its control value (average fall of 25 mm. of mercury in 8.5 minutes). CSFP fell to below its pre-morphine value.

Morphine, Then Levallorphan, in Normal Dogs Artificially Ventilated (*Table* 3). After morphine, during an average observation period in three dogs of 31.3 minutes, the average P_{CO_2} rose only 3 mm. of mercury, while after levallorphan it fell only 1 mm. of mercury. After morphine average CSFP rose 13 mm. of water; it increased an additional 8 mm. of water after levallorphan. Average mean blood pressure fell 19 mm. of mercury after morphine and showed little change after levallorphan.

Morphine, Then Levallorphan, in Dogs with Increased Intracranial Pressure, Breathing Spontaneously (*Table 3 and Fig.* 3). *Average* CSFP of the six dogs in this group was increased by Cytal to 383 mm. of water. They were followed for an average of 19.8 minutes after morphine administration. During this interval CSFP fell an average of 36 mm. of water; mean blood pressure decreased 22 mm. of mercury; intrathoracic venous pressure varied inconsistently, but rose an average of 7 mm. of water; and arterial P_{CO_2} rose 17 mm. of mercury. After levallorphan was administered observations were continued for an average of 8.2 minutes, during which time CSFP fell 70 mm. of water and P_{CO_2} decreased almost to control value. Mean blood pressure rise averaged 5 mm. of mercury. Intrathoracic venous pressure fell an average of 17 mm. of water.

Morphine, Then Levallorphan, in Dogs with Increased Intracranial Pressure, Artificially Ventilated (*Table* 3). In four dogs, CSFP *decreased* an average of 75 mm. of water, from its control level of 371 mm. of water. Arterial P_{CO_2} remained unchanged (41 mm. of mercury) during this 34.3-minute observation period. Mean blood pressure fell 16 mm. of mercury, while intrathoracic venous pressure was decreasing 4 mm. of water. During the average six-minute period following levallorphan P_{CO_2} did not change significantly, and average CSFP *increased* 10 mm. of water. Mean blood pressure rose 8 mm. of mercury, while intrathoracic venous pressure continued to fall.

Levallorphan, Then Morphine, in Normal Dogs Breathing Spontaneously. These data are not presented because the frequent hypotensive effect of levallorphan itself, and its in-

ability to prevent the hypotensive effect of morphine when present, made it difficult either to complete the experiments or to interpret the results. This proved to be true whenever this drug sequence or the morphine-levallorphan mixture was used. For example, in the four dogs in which levallorphan was administered before morphine, an initial 6 mm. of mercury decline in mean blood pressure occurred, followed by a further 17 mm. of mercury fall after morphine. An even greater fall, 29 mm. of mercury, occurred following the use of the mixture. Therefore, no data are presented for these drug combinations.

Discussion

This study was designed to confirm the belief that the rise in intracranial pressure (or cerebrospinal fluid pressure) following narcotic administration in the dog with normal

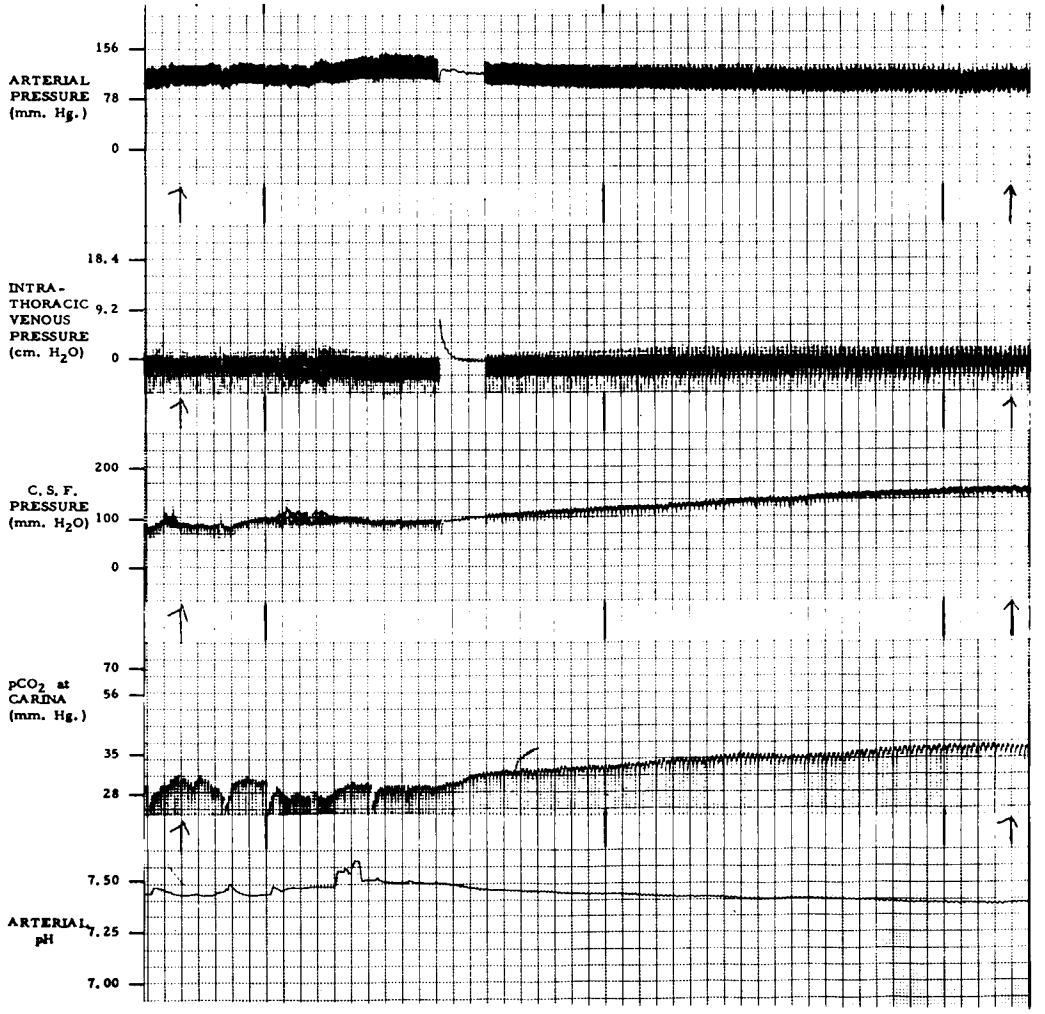

FIG. 2A and B. Response of a spontaneously-breathing dog (with normal intracranial pressure) to morphine, and then to levallorphan. The arrows indicate points at which representative values were taken. These continuous records overlap so that the arrow at end of the first record (fig. 2A) and the arrow at the beginning of the second (fig. 2B, p. 296) are the same. The distance between dark vertical lines represents 20 seconds. Narrowed tracings are the result of electrical averaging. Morphine was given just after the first arrow. The break in the intrathoracic venous pressure after the last arrow is the point of levallorphan administration.

and with elevated intracranial pressure is due to the hypercarbia caused by hypoventilation. The results in the "normal intracranial pressure" group support this assumption: When P_{CO_2} rises following morphine, CSFP rises; when P_{CO_2} changes are kept to a minimum by artificial ventilation, CSFP changes are also minimal. Moreover, when levallorphan is used to reverse morphine-induced respiratory depression during spontaneous ventilation,

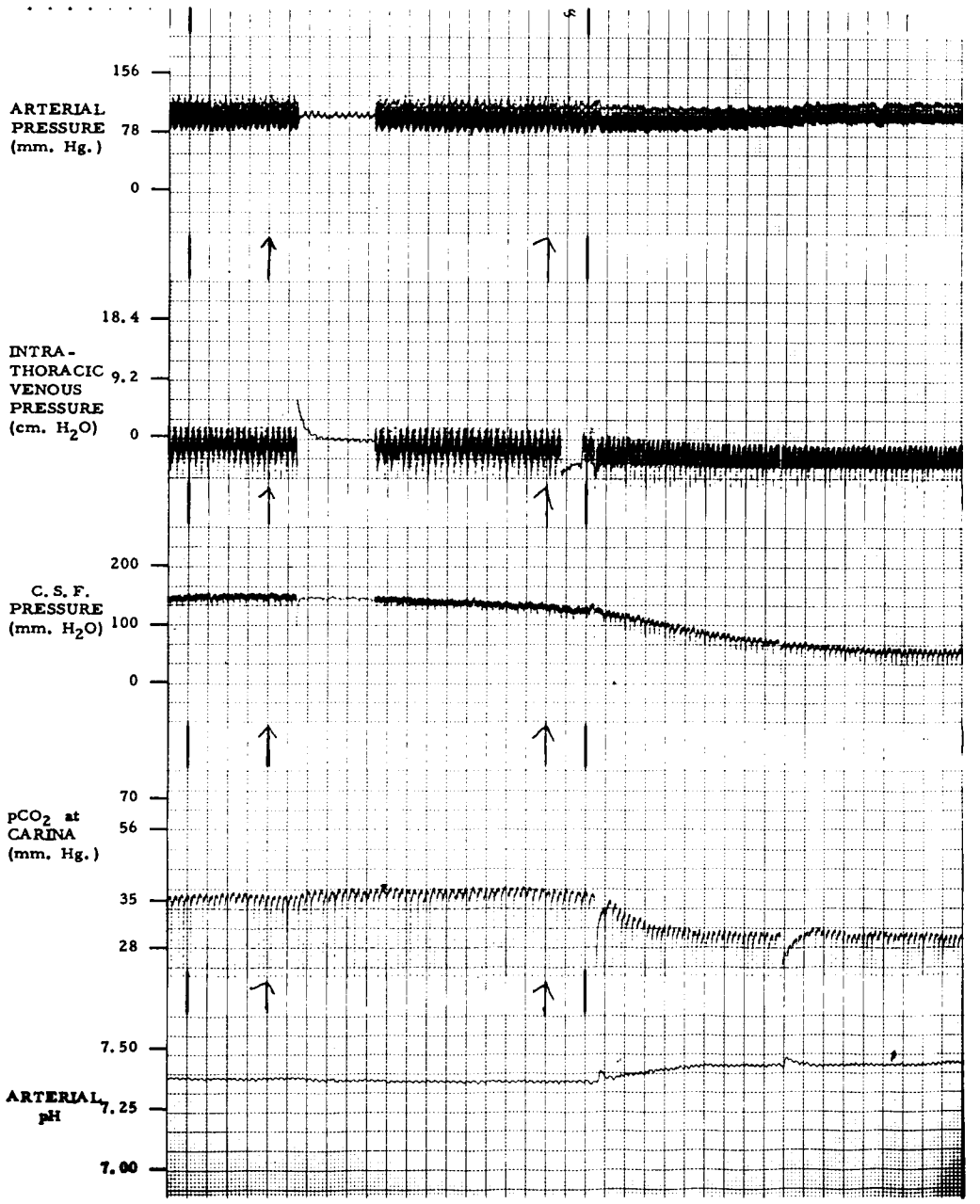

FIG. 2B. Continuation of figure 2A (see legend) showing response of a spontaneously-breathing dog to morphine and then to levallorphan.

P_{CO_2} is lowered and CSFP falls. When levallorphan is given during artificial ventilation the changes in P_{CO_2} and hence the changes in CSFP are negligible.

Surgical approaches previously reported [9, 10] to provide a standard preparation of increased intracranial pressure were considered, and were rejected because they involved either production of brain injury or were not reproducible in our hands.[11] The use of a hyperosmolar solution injected into the subarachnoid space to increase cerebrospinal fluid volume, and hence CSFP, was therefore evaluated. The utilization of Cytal resulted in a relatively controllable and stable elevation of CSFP. After the initial equilibration period and following the stable period, CSFP gradually declined. This observation is in agreement with the findings of Prockop and coworkers,[12] who have reported that saccharides

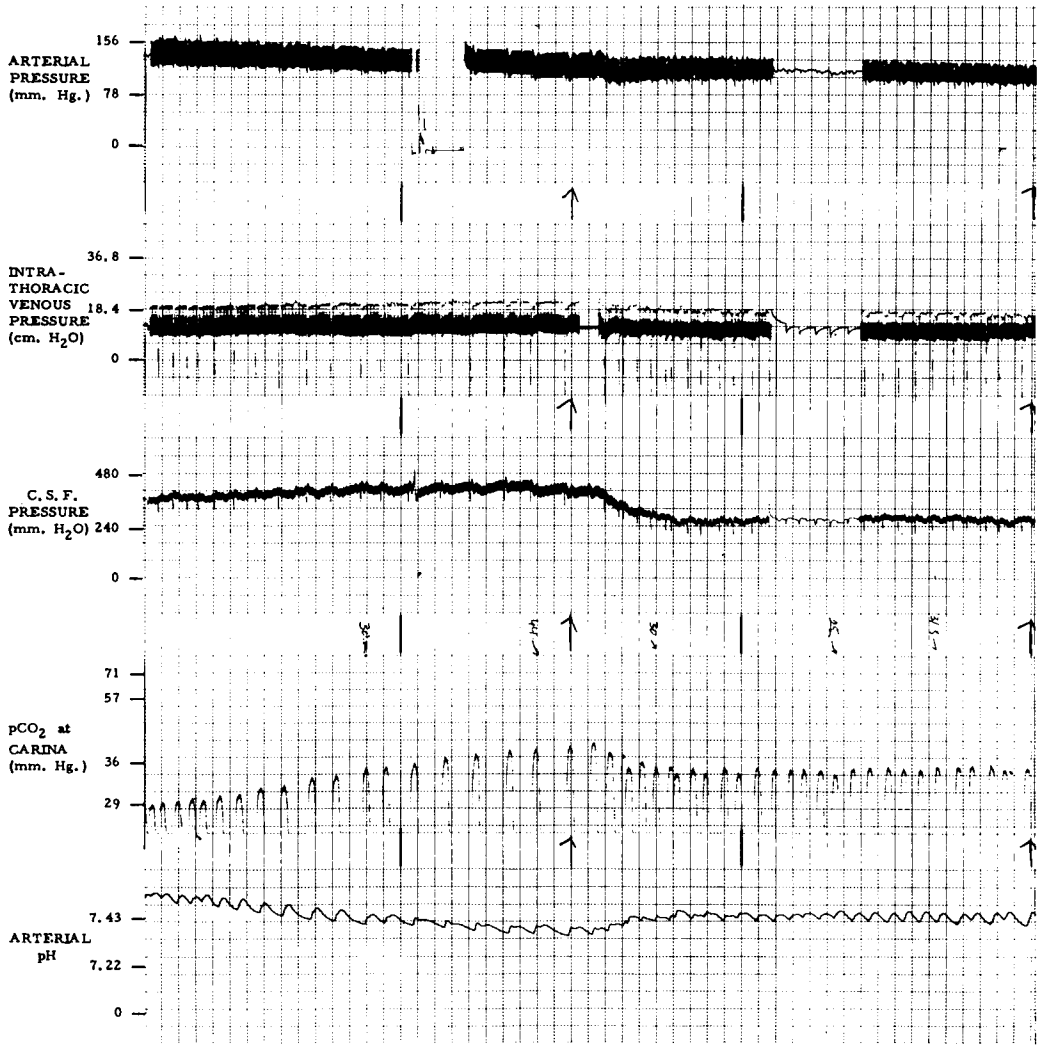

FIG. 3. Response of a spontaneously-breathing dog (with elevated intracranial pressure) to morphine, and then levallorphan. The arrows indicate points at which representative values were taken. The first arrow represents peak depression 25 minutes after morphine injection and just precedes levallorphan injection (break in venous pressure recording). Electrically averaged pressure curves are shown in latter half of records. The distance between dark vertical lines represents 20 seconds.

such as mannitol (molecular weight of 182) pass from cerebrospinal fluid to plasma at a slow rate. We presume that this holds true for sorbitol (molecular weight of 191). Mannitol and sorbitol are responsible for the osmotic effects of Cytal.

The first series of studies (apneic oxygenation, and ventilation with 5 per cent CO_2, and with 8 per cent O_2) using Cytal to elevate CSFP revealed a response (increase in CSFP) qualitatively identical to that previously mentioned for the normal anesthetized dog.[5] However, the relatively slow rate of CSFP fall was appreciably altered as a result of apneic oxygenation and ventilation with 5 per cent CO_2; therefore the "recovery" CSFP was always significantly lower than "control" CSFP.

This study indicates: (1) the dog with elevated intracranial pressure responds to hypercarbia and hypoxia as does the dog with normal intracranial pressure; (2) the increase in CSFP following morphine is due to its depressant effect on ventilation; (3) whenever hypercarbia due to morphine is prevented by artificial ventilation, or is reversed by a narcotic antagonist, CSFP elevation is prevented or reversed.

Because of these findings in the dog, and the parallel observations in normal man reported by Keats and Mithoefer,[2] and by Swerdlow and associates,[13] it is our opinion that morphine is not intrinsically harmful in the presence of increased intracranial pressure and may be of use to the anesthesiologist in the management of the neurosurgical patient.

Summary

A series of experiments are reported in which the effects of morphine and levallorphan are compared in normal dogs and in dogs with artificially-elevated intracranial pressure. Hypercarbia caused a rise of intracranial pressure in both groups. If the hypercarbia following morphine was reversed or prevented, so were the concomitant changes in intracranial pressure reversed or prevented. In view of these findings, it is suggested that morphine under proper circumstances may be used in the neurosurgical patient.

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