Anesthesiology
V 37, No 6, Dec 1972

The Effects of Morphine and N-Allylnormorphine on Canine Cerebral Metabolism and Circulation

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The effects of morphine and nalorphine on cerebral metabolism and circulation were examined in 18 dogs. Incremental doses of morphine caused progressive decreases in CMR_{O_2} and CBF to 85 per cent and 45 per cent of control, respectively, until a dose of 1.2 mg/kg had been given in a one-hour period. Subsequent doses had no further significant effect. The decrease in CBF resulted from both a direct action of morphine (approximately 30 per cent) and the effect of time on experimental canine CBF. A single large dose of morphine (2 mg/kg) had similar effects on CMR_{O_2} and CBF. These effects were reversed by nalorphine (0.3 mg/kg), which initially produced overshoots in both CMR_{O_2} and CBF. Subsequent doses of nalorphine had no further effect. EEG changes correlated with CMR_{O_2} changes caused by morphine and nalorphine. Nalorphine given alone (0.3 mg/kg) produced small decreases in both CMR_{O_2} and CBF, an effect not magnified by subsequent larger doses. (Key words: Morphine; Nalorphine; Cerebral metabolism; Cerebral blood flow.)

MORPHINE, one of the oldest drugs in common use, is currently recommended by some as the primary anesthetic agent for open-heart surgical procedures.[1] Yet little is known about the effects of this narcotic on cerebral metabolism and circulation. Moyer *et al.*,[2] in 1957, reported that a single dose of 60 mg in man produced a 40 per cent decrease in cerebral oxygen consumption (CMR_{O_2}), with little effect on cerebral blood flow (CBF); the observed metabolic depression was rapidly reversed by the administration of N-allylnormorphine (nalorphine). Other investigators[3,4] reported no significant change in the cerebral metabolism of man following doses of 10 to 30 mg. Sokoloff[5] concluded that narcotic drugs had only a minor influence on the cerebral circulation; this effect, when it did occur, was probably not direct, but secondary to systemic alterations. A review of the more recent literature has failed to reveal any further reports of the effects of morphine or nalorphine on cerebral metabolism or circulation *in vivo*. In an effort to resolve these discrepancies, we examined the independent and combined effects of morphine and nalorphine on canine CMR_{O_2} and CBF.

Material and Methods

Eighteen fasted unpremedicated dogs (weight, 14 to 20 kg) were anesthetized with halothane (1.0 to 2.0 per cent) and nitrous oxide (70 per cent) in oxygen. Succinylcholine was given to facilitate endotracheal intubation (40 mg) and thereafter to maintain muscular paralysis (150 mg/hr). Ventilation was controlled with a Harvard pump. Cannulas were placed in a femoral artery for blood sampling and pressure determinations, in a femoral vein for replacement of blood, and in a cephalic vein for drug administration. The dogs were then placed in a prone position.

The surgical preparation used in this laboratory for direct measurement of CBF has been described.[6] (In this technique, blood flow from the sagittal sinus is diverted by cannula to an external reservoir, measured by automatic, timed collection, and returned by pump to a peripheral vein.) In our initial studies, the cannula was placed approximately 1.5 cm anterior to the torcular; in a series of 15 dogs, after postmortem injection of vinyl acetate into the sinus and subsequent dissection, the weight of the brain drained by the cannula was found to average 43 per cent of the total brain weight.[6] In recent studies, because of improvement in surgical technique, it

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Received from the Department of Anesthesiology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. Accepted for publication June 14, 1972. Supported in part by Research Grants NS-7507 and HL-4881 from the National Institutes of Health, Public Health Service.

has been possible to place the cannula more posteriorly and thus to collect flow from a larger portion of the cerebral hemispheres. In a series of 20 dogs, this more posterior placement increased the average weight of brain drained to 54 per cent of the total brain weight. This percentage is used to convert units of flow (from ml/min to ml/100 g/min).

The oxygen content of arterial and sagittal sinus blood was calculated from measurements of oxyhemoglobin concentration (IL 182 CO-Oximeter) and P_{O_2} (IL 313 electrodes).[7] The glucose content of blood was determined by an enzymatic method.[8] Additional measurements included arterial pressure (strain gauge), pH and Pa_{CO_2} (electrodes, 37 C), and brain temperature (parietal epidural thermistor). The electroencephalogram (EEG) was recorded from the frontal lobes (bipolar silver–silver chloride disk electrodes). CMR_{O_2} and cerebral metabolic rate for glucose ($CMR_{glucose}$) were calculated as the product of CBF and arterial sagittal sinus blood content differences [$C_{(a-v)}$]. The oxygen–glucose index (OGI) was calculated as suggested by Cohen *et al.*[9]

After completion of the surgical preparation, the inspired halothane was discontinued for an hour. Thereafter, inspired halothane was maintained at 0.1 per cent so that any possible effects of residual halothane on CMR_{O_2} or CBF could be kept constant throughout the study. Ventilation and FI_{O_2} were adjusted to maintain Pa_{CO_2} at 38 ± 0.3 mm Hg (SE) and Pa_{O_2} at 143 ± 1.0 mm Hg. Sodium bicarbonate was given as needed to keep the buffer base normal. Epidural temperature was maintained at 37.0 ± 0.1 C. Hemoglobin levels were maintained above 12 g/100 ml. After establishment of these conditions, control measurements were obtained during a 50-minute period and mean values were calculated from ten consecutive determinations of CBF and $C_{(a-v)O_2}$ and three determinations of $C_{(a-v)glucose}$.

Following control determinations, the dogs were divided into three groups, with five dogs in each, according to the type and sequence of drug administration. Dogs in one group (the morphine group) were each given five incremental doses of morphine at 30-minute intervals, resulting in total accumulated doses of 0.2, 0.6, 1.2, 2.0, and 3.0 mg/kg, respectively. Dogs in the morphine–nalorphine group were first given morphine (2 mg/kg) and thereafter, at one-hour intervals, two doses of nalorphine (0.3 mg/kg and 2 mg/kg). Dogs in the nalorphine–morphine group were given nalorphine (0.3 mg/kg), followed at 30-minute intervals by additional nalorphine (2 mg/kg) and morphine (2 mg/kg). In each instance, morphine and nalorphine were given intravenously at rates of 0.2 mg/kg/min and 0.4 mg/kg/min, respectively. CBF and [$C_{(a-v)O_2}$] were measured every 5 minutes, and $C_{(a-v)glucose}$, mean arterial pressure (MAP), arterial blood gases, and sagittal sinus P_{O_2} (Pss_{O_2}) were measured every 15 minutes. EEG's were monitored continuously and recorded at frequent intervals.

Neither morphine nor nalorphine was given to an additional three dogs. In these, control conditions were maintained; changes in CMR_{O_2} and CBF with time were observed, beginning two hours after sagittal sinus cannulation and continuing for three hours in order to cover the entire period of observation in the experimental dogs.

The significances of the cerebral metabolic and circulatory effects of morphine and nalorphine were tested by Student's t test for paired data, assuming $P < 0.05$ to be statistically significant.

Results

The effects of morphine on cerebral metabolism, cerebral circulation, and the EEG are summarized in table 1 and figures 1 and 2.

Effects of Morphine

The initial dose of morphine (0.2 mg/kg) produced no significant change in mean CMR_{O_2} (table 1). Moreover, with this dose, CMR_{O_2} increased slightly and the EEG became further desynchronized in three of the five dogs; in the other two, CMR_{O_2} decreased, and the EEG became more synchronized (fig. 1). With a total dose of 0.6 mg/kg, reductions in CMR_{O_2} in all dogs were accompanied by the appearance of high-amplitude slow waves in the EEG. With the next increment of morphine (total, 1.2 mg/kg), CMR_{O_2} decreased further, to 85 per cent of control; but with

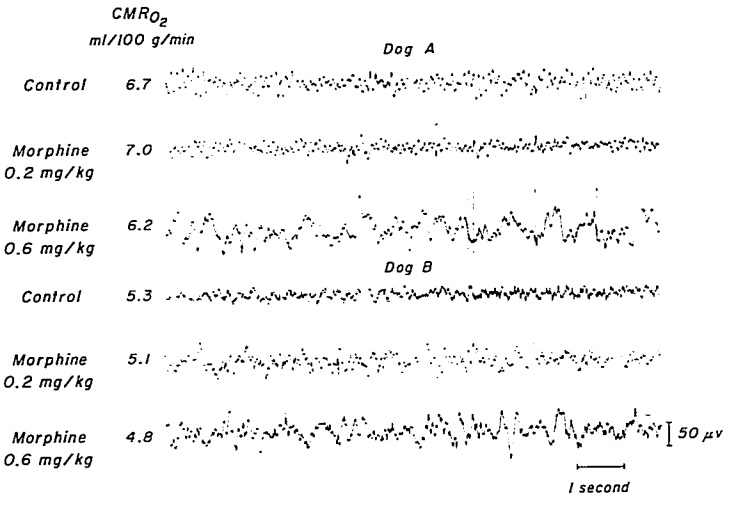

FIG. 1. EEG tracings to illustrate the two types of responses to an initial dose of 0.2 mg/kg of morphine. *Upper panel* (Dog A), response characterized by increase in CMR_{O_2} and desynchronization of the EEG. *Lower panel* (Dog B), response characterized by decrease in CMR_{O_2} and synchronization of the EEG. In both dogs, the second dose of morphine (total then, 0.6 mg/kg) decreased CMR_{O_2}, accompanied by synchronization of the EEG.

subsequent doses (to a total of 3.0 mg/kg), no further decrease occurred. The decrease in CMR_{O_2} was not related to the effect of time, since in the absence of morphine, CMR_{O_2} remained unchanged in three dogs over a similar period of observation (fig. 2).

The effects of morphine on CBF were apparent with the initial 0.2 mg/kg dose, which produced a 30 per cent decrease. With the second dose of morphine, there was a further decrease in CBF to 55 per cent of control, and thereafter subsequent doses of morphine were associated with gradual further decreases in CBF, accompanied by significant decreases in MAP. The progressive decrease in CBF is in part accounted for by the effect of time alone (fig. 2). However, the initial decrease observed following the first two doses of morphine was largely accounted for by the effect of morphine. Thereafter, the rate of decrease of CBF was not different from that observed with time alone. The progressive significant decrease in Pss_{O_2} was compatible with the observed changes in CMR_{O_2} and CBF (table 1).

EFFECTS OF MORPHINE–NALORPHINE

The effects of morphine followed by nalorphine are summarized in table 2 and figures 3 and 4. Following a single 2-mg/kg dose of morphine, mean CMR_{O_2} decreased to 84 per cent of control in one hour, a response identical to that produced by a cumulative dose of 1.2 mg/kg (table 1). At the same time, CBF decreased to 50 per cent of control, accompanied by a significant decrease in MAP (table 2). With subsequent administration of nalorphine (0.3 mg/kg), both CMR_{O_2} and CBF returned rapidly toward control (fig. 3), mean CMR_{O_2} peaking at a level significantly above (111 per cent) control at 0.5 hour (table 2). Thereafter, mean CMR_{O_2} returned

TABLE 1. Effects of Morphine on Canine Cerebral Metabolism and Circulation (Mean ± SE)

	$CMRO_2$ (ml/100 g/min)	CBF (ml/100 g/min)	MAP (mm Hg)	P_{SSO_2} (mm Hg)
Control	5.75 ± 0.35	87 ± 5	129 ± 6	52 ± 2
Morphine, accumulated dosage (mg/kg)				
0.2	5.89 ± 0.61	61* ± 5	124 ± 4	42* ± 2
0.6	5.22* ± 0.39	47* ± 5	119 ± 6	37* ± 2
1.2	4.97* ± 0.34	40* ± 5	113* ± 4	34* ± 3
2.0	4.82* ± 0.31	36* ± 4	111* ± 4	33* ± 2
3.0	4.78* ± 0.31	35* ± 4	109* ± 4	32* ± 2

* Significantly different from control ($P < 0.05$).

TABLE 2. Effects of Morphine and Subsequent Nalorphine on Canine Cerebral Metabolism and Circulation (Mean ± SE) (All Values and Actual Accumulated Times Are Given in Figure 3)

Drug Administered and Time of Measurement	$CMRO_2$ (ml/100 g/min)	CBF (ml/100 g/min)	MAP (mm Hg)	P_{SSO_2} (mm Hg)	OGI
Control	6.13 ± 0.28	80 ± 2	146 ± 8	49 ± 2	0.83 ± 0.06
Morphine (2 mg/kg)					
After 1 hr	5.08* ± 0.12	40* ± 1	114* ± 5	38* ± 1	0.93 ± 0.06
Nalorphine (0.3 mg/kg)					
After 0.5 hr	6.80* ± 0.18	58* ± 2	149 ± 7	40* ± 2	0.89 ± 0.07
After 1 hr	5.70 ± 0.22	43* ± 3	143 ± 6	33* ± 1	1.02 ± 0.10
Nalorphine (2 mg/kg)					
After 0.5 hr	6.19 ± 0.16	49* ± 5	139 ± 6	34* ± 1	— —

* Significantly different from control ($P < 0.05$).

TABLE 3. Effects of Nalorphine and Subsequent Morphine on Canine Cerebral Metabolism and Circulation (Mean ± SE)

Drug Administered and Time of Measurement	$CMRO_2$ (ml/100 g/min)	CBF (ml/100 g/min)	MAP (mm Hg)	P_{SSO_2} (mm Hg)	OGI
Control	6.06 ± 0.43	70 ± 4	139 ± 3	44 ± 3	0.94 ± 0.07
Nalorphine					
0.3 mg/kg (0.5 hr)	5.71* ± 0.38	51* ± 2	126 ± 6	38* ± 3	1.02 ± 0.05
2 mg/kg (0.5 hr)	5.76* ± 0.36	47* ± 2	135 ± 8	37* ± 3	1.00 ± 0.06
Morphine					
2 mg/kg (0.5 hr)	5.24*† ± 0.22	40* ± 2	137 ± 9	33* ± 3	0.93 ± 0.03

* Significantly different from control ($P < 0.05$).
† Significantly different from nalorphine value ($P < 0.05$).

to a level not significantly different from control. CBF peaked briefly (after 10 minutes) at 94 per cent of control, and then during a 60-minute period returned to pre-nalorphine levels (fig. 3). The initial return of CBF was to a level greater than that expected (when the effect of time is considered) and was accompanied by return of MAP to control levels. After 60 minutes, a second larger dose of nalorphine (2 mg/kg) caused modest insignificant increases in mean CMR_{O_2} and CBF. Changes in the EEG correlated well with the changes in CMR_{O_2} produced by both morphine and nalorphine (fig. 4).

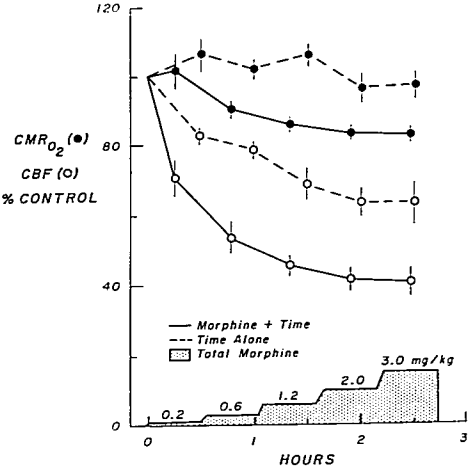

FIG. 2. Effects of accumulated doses of morphine plus time (——) and time alone (- - -) on CMR_{O_2} (●) and CBF (○). Note that CMR_{O_2} effects of accumulated doses of morphine can be clearly attributed to morphine alone, but that CBF effects were influenced not only by morphine but also by the passage of time. (Values, mean ±SE.)

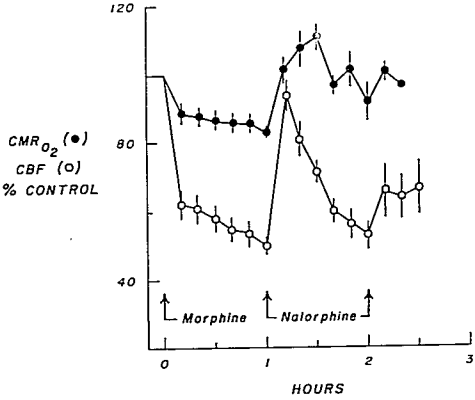

FIG. 3. Effects of morphine and nalorphine on CMR_{O_2} (●) and CBF (○).

EFFECTS OF NALORPHINE–MORPHINE

The effects of nalorphine followed by morphine are summarized in table 3. Following the initial dose of nalorphine (0.3 mg) there was a small, but significant, decrease in CMR_{O_2} to 94 per cent of control, CBF decreasing to 73 per cent of control. However, the latter could not be ascribed to the effect of nalorphine, considering the effect of time alone on CBF (fig. 2). With an additional

large dose of nalorphine (2 mg/kg), no further change in CMR_{O_2} or CBF was observed. Thirty minutes after the second dose of nalorphine, 2 mg/kg of morphine produced a further significant decrease in CMR_{O_2} to 91 per cent of the pre-morphine value, as well as a small reduction in CBF. As in the other dogs, the OGI remained normal throughout the period of observation. The EEG tended to slow with each dose of nalorphine, but the changes were slight and variable. Subsequent morphine produced a change in the EEG comparable to that seen in response to morphine in the other groups.

Discussion

In sufficient dosage, morphine consistently caused a significant decrease in CMR_{O_2}. With incremental doses of morphine, a direct relationship between dose and response was apparent until a cumulative dose of 1.2 mg/kg had been given. Thereafter, subsequent doses had no further measurable effects. Moreover, the finding that a single dose of morphine of 2 mg/kg had virtually the same quantitative effects on CMR_{O_2} as a cumulative dose of 1.2 mg/kg given over a 60-minute period suggests that there was little, if any, diminution of effect from the initial incremental doses. This observation is consistent with that of Mulé and Woods,[10] who found that after a single dose of 2 mg/kg of labeled morphine canine cerebral tissue levels remained essentially unchanged over a four-hour period. That the CMR_{O_2} effect reached a plateau at a cumulative dose of 1.2 mg/kg is consistent with the view that the sites responsible for this effect were saturated at this dose level. Assuming that the degree of CMR_{O_2} depression is a manifestation of the degree of cerebral functional depression, then there would seem to be little merit in using clinical doses greater than 1.0 to 2.0 mg/kg. This is consistent with the observation that patients may not lose consciousness even after doses as large as 3 mg/kg.[11] The variations in CMR_{O_2} following 0.2 mg/kg of morphine correlated well with changes in the EEG; these are indicative of the complex and unpredictable effects of morphine on the central nervous system. In certain species (for example, the cat), morphine—even in large doses—appears to stimulate cerebral function (CMR_{O_2} effects are unknown to us), although the distribution of morphine within the central nervous system and its metabolism do not differ strikingly from distribution and metabolism in other species, which show cerebral depression even with small doses of morphine.[12] This variation in functional response also occurs among individuals within species,[13] and was encountered in the present study (fig. 1).

Changes in CBF with incremental doses of morphine paralleled the changes in CMR_{O_2}, and they were accompanied by both a decrease in MAP and an increase in cerebrovascular resistance (CVR). Analysis of the effects of morphine on CBF was complicated by the effect of time alone on experimental canine CBF; this is not peculiar to the use of a direct-flow preparation. Raichle and colleagues,[14] using a relatively noninvasive indirect technique for measuring CBF, also detected a progressive decrease in CBF with passage of time and related the change to the situation of an immobile, mechanically ventilated dog. They demonstrated this effect in both anesthetized and nonanesthetized paralyzed dogs, and during a four-hour period observed a decrease in CBF of 6 per cent per hour. In our control dogs, the decrease in CBF was exponential, such that after three hours a 35 per cent decrease had occurred. This change in CBF with time is primarily the result of a progressive increase in CVR. This phenomenon might be explained in part by cerebral vasodilatation in response to surgical manipulation, which then gradually subsides. When evaluating the effects of short-acting drugs on canine CBF, this effect of time can be minimized by altering the sequence of drugs or concentrations administered. With a long-acting drug, such as morphine, this is not possible, and correction for time is necessary. Despite this complicating factor, it is clear from both figure 2 and figure 3 that morphine does have a direct effect on CBF, which differs significantly from the effect of time alone. With incremental doses of morphine, this effect was apparent following the initial two doses (total, 0.6 mg); thereafter,

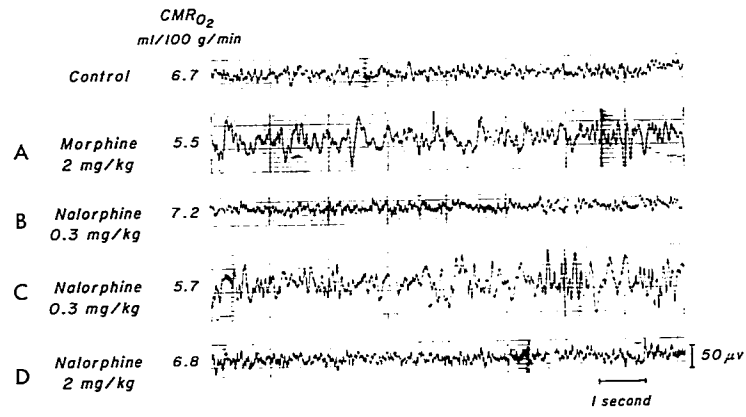

FIG. 4. EEG changes in a single dog after administration of morphine and nalorphine. *A*, decrease in CMR_{O_2} produced by 2 mg/kg of morphine was accompanied by synchronization of the EEG; *B*, nalorphine (0.3 mg/kg) initially returned the EEG to the control pattern, and CMR_{O_2} increased to above control; *C*, at the same dosage of nalorphine, but after 60 min, both CMR_{O_2} and the EEG had returned to postmorphine levels; *D*, a second dose of nalorphine again desynchronized the EEG and increased CMR_{O_2}.

the change in CBF with subsequent morphine paralleled the change in CBF with time alone.

The cerebral metabolic and circulatory effects of a relatively large dose of morphine (2 mg/kg) were reversed by a relatively small dose of nalorphine (0.3 mg/kg). Initially, following nalorphine, CMR_{O_2} increased to above control and CBF increased more than expected (when the effect of time on CBF is considered). Such an overshoot in response to nalorphine has been found in studies of the activity of spinal reflexes in chronic spinal dogs addicted to morphine.[15] In these studies, the hyperactivity produced by nalorphine was viewed as an unmasking of physical dependence; the authors concluded that physical dependence begins very early during morphine addiction, "possibly after a single dose."

When administered in the absence of morphine, nalorphine (0.3 mg/kg) had a modest, but significant, depressive effect on CMR_{O_2}, consistent with the clinical and experimental observation that nalorphine alone manifests the properties of a weak opiate. The further depression in CMR_{O_2} produced by morphine (2 mg/kg) given 30 minutes after nalorphine (2 mg/kg) suggests either that the antagonistic effects of nalorphine are brief or that when given in a reverse sequence, much larger doses of nalorphine are needed to block the cerebral metabolic depressive effect of morphine.

The changes in CMR_{O_2} and CBF produced by morphine and nalorphine, either alone or in combination, were not accompanied by any significant change in the OGI, thus indicating that normal cerebral metabolic pathways are not altered by these drugs. Similarly, the progressive reduction in CBF with time did not threaten cerebral oxygen delivery, as judged by the lack of an effect of time on either CMR_{O_2} or the OGI.

In the context of these effects on canine cerebral metabolism and circulation, morphine may be grouped with the other narcotics which have been examined in this laboratory —namely, meperidine[16] and fentanyl.[17] In clinically used doses, all three produce com-

parable reduction in CMR_{O_2} (10 to 20 per cent) and accompanying reductions in CBF. None alters the normal cerebral metabolic pathways. Morphine has a prolonged effect, which is completely reversed, at least temporarily, by nalorphine (in 1:7 dose ratio). The ease with which the CMR_{O_2} effects of morphine could be produced and then reversed with nalorphine offered an unusual opportunity to correlate changes in CMR_{O_2} with EEG changes. Invariably, a drug-induced decrease in CMR_{O_2} was accompanied by synchronization of the EEG, and a drug-induced increase in CMR_{O_2} was accompanied by desynchronization of the EEG. This observation, however, cannot be extrapolated and applied to all anesthetic states. For example, cyclopropane may induce sudden increases in CMR_{O_2} (possibly catecholamine-induced) without change in the EEG.[18] Conversely, increasing halothane concentrations from 0.8 to 1.2 per cent (expired) does not significantly reduce CMR_{O_2},[19] despite progressive changes in the EEG.

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