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Effects of Morphine–Nitrous Oxide Anesthesia on Cerebral Autoregulation

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The effects of morphine–nitrous oxide anesthesia on cerebral autoregulation were studied in healthy male volunteers. Anesthesia was morphine, 2 mg/kg, and 70 per cent nitrous oxide in oxygen. Ventilation was controlled and carbon dioxide added to keep Pa_{CO_2} constant at 40 torr. Cerebral blood flow was measured first at the subject's normal mean arterial blood pressure, then at 60 torr and at 120 torr in a randomly assigned balanced order. Last, in five subjects cerebral blood flow was measured again at normal mean pressure. Blood pressure alteration was accomplished using phenylephrine or trimethaphan. Cerebral blood flow and cerebral metabolic rate for oxygen were unaffected by changes in cerebral perfusion pressure. Cerebral blood flow was 38.9 ± 6.4 (SEM) ml/100 g/min at normal mean pressure, 49.5 ± 9.8 ml/100 g/min at 120 torr, and 44.0 ± 10.7 ml/100 g/min at 60 torr. These values are not different at $P < 0.05$. The data were analyzed for the possible effect of time on cerebral blood flow, and no change could be demonstrated. It is concluded that with Pa_{CO_2} constant at 40 torr morphine–nitrous oxide anesthesia does not significantly affect cerebral autoregulation in normal man. (Key words: Analgesics, narcotic: morphine; Brain: blood flow.)

WE KNOW the effects of many anesthetics on human cerebral blood flow (CBF) and are aware of some effects on cerebral autoregulation.[1] The effects of morphine sulfate–nitrous oxide anesthesia on autoregulation are not known. This knowledge is important, since large doses of morphine plus nitrous oxide anesthesia are widely used for cardiopulmonary bypass and other procedures during which large variations of arterial pressure may occur. This study measures the effects of morphine–nitrous oxide on human cerebral autoregulation.

Methods

Eight fully informed, healthy, male volunteers were accepted for the study after history, physical and laboratory examinations were performed. On the day of the study, peripheral venous, central venous, and radial artery catheters were inserted and electrocardiogram leads attached while the subject was awake.

Preanesthetic medication was atropine sulfate, 0.4 mg, administered intravenously 5 minutes before induction. Nitrous oxide–oxygen (70–30 per cent) was administered, along with *d*-tubocurarine, 0.7 mg/kg. The trachea was intubated and ventilation controlled with a Bird ventilator set to deliver 125 ml/kg/min through a nonrebreathing circuit. Expired ventilation was measured by a dry gas meter. Carbon dioxide was added to keep Pa_{CO_2} at 40 torr, and PET_{CO_2} was measured by a Godart Capnograph and continuously recorded on a Grass polygraph. Additional *d*-tubocurarine, average total dose 1.2 mg/kg, was given to prevent movement. The internal jugular bulb was punctured percutaneously for sampling and pressure measurement. Temperature was monitored via an esophageal thermistor probe and maintenance at 37 C was attempted by using infrared lamps. Morphine was given intravenously at approximately 10 mg/min to a total dose of 2 mg/kg.

Each subject was studied after morphine at his awake level of mean arterial blood pressure (MABP). The MABP was then raised

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TABLE 1. Experimental Conditions during Blood-pressure Alteration, Morphine–N_2O Anesthesia (Eight Subjects)

	Control Blood Pressure	High Blood Pressure	Low Blood Pressure
Mean arterial blood pressure (torr)			
Mean	88.0	120.0*	58.7*
SE	3.0	0.8	1.2
Cerebral perfusion pressure (MABP–JBVP) (torr)			
Mean	75.0	105.1*	46.4*
SE	2.9	1.3	1.5
Mean airway pressure (torr)			
Mean	5.87	5.81	4.93
SE	0.53	0.80	0.41
Esophageal temperature (C)			
Mean	36.3	36.8*	36.7*
SE	0.1	0.1	0.1
Pa_{O_2} (torr)			
Mean	170.8	156.1*	155.5*
SE	8.8	8.8	8.3
Pa_{CO_2} (torr)			
Mean	39.9	39.0	39.9
SE	0.4	0.5	0.2
PH_a			
Mean	7.388	7.371	7.379
SE	.006	.006	.007
Plasma morphine (μg/ml)			
Mean	1.601	1.223*	1.121*
SE	0.162	0.166	0.144

* Difference from control significant, $P < 0.05$.

to 120 torr and lowered to 60 torr in a randomly assigned balanced order and CBF measured at each level. Last, in five subjects, CBF was measured again at the awake level of MABP.

MABP pressure alterations were accomplished by continuous infusion of either phenylephrine or trimethaphan using a Harvard pump. An average of 40 ml of 0.01 per cent phenylephrine and 90 ml of 1.0 per cent trimethaphan was used. These drugs were chosen because they do not directly affect cerebral circulation.[2,3] Between drug infusions time was allowed for return of MABP to pre-infusion levels, and 15 minutes at the designated MABP was permitted for stabilization prior to measurements.

All pressures were continuously recorded on a Grass polygraph via Statham transducers. Plasma morphine levels were determined by radioimmunoassay.[4] In our laboratory the sensitivity of this test is 0.01 μg/ml and the precision is 7 per cent. Goat antiserum is used, and the method measures morphine glucuronide as well as morphine. Oxygen content was determined manometrically.[5] CBF was measured with a ^{85}Kr uptake technique utilizing a liquid scintillation counting method.[6,7] All data were analyzed by two-dimensional analysis of variance and by critical difference testing at $P < 0.05$.

Results

CBF during Blood-pressure Alteration

The experimental conditions for the study of cerebral autoregulation are shown in table 1. Blood pressure measurements show an increase of MABP of 32 torr above control and a decrease of 29.3 torr from control. The following parameters showed no significant difference from control: mean airway pressure,

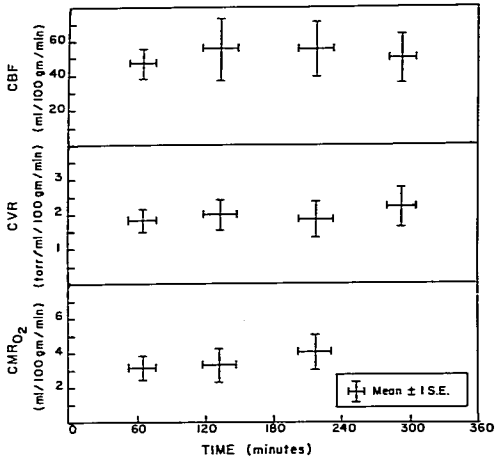

FIG. 1. Mean CBF, CVR, and CMR_{O_2} plotted *vs.* time elapsed from conclusion of morphine administration in five subjects. Mean values for the second and third measurements include both high and low pressures due to the balanced order.

Pa_{CO_2}, and pH_a. Esophageal temperature and Pa_{O_2} did differ significantly from control, but these changes were not sufficient to be of physiologic importance.[8,9] Plasma morphine levels were decreased from control during the hypotensive and hypertensive phases. There was a further decrease in plasma morphine during the fourth measurement at normotension (see below).

The CBF data are shown in table 2. Although seven of eight subjects showed increases from control in CBF during the hypertensive phase, this difference did not achieve significance at $P < 0.05$.

The increase in CBF from 38.9 to 44.0 ml/100 g/min with hypotension was not statistically significant. Cerebral vascular resistance (CVR) significantly decreased as MABP decreased. During hypertension five of eight subjects had increases in CVR which were not significant. CMR_{O_2} did not change significantly when blood pressure changed.

TABLE 2. Cerebral Circulatory Values during Blood-pressure Alteration, Morphine–N_2O Anesthesia (Eight Subjects)

	Control Blood pressure	High Blood Pressure	Low Blood Pressure
CBF (ml/100 g/min)			
Mean	38.9	49.5	44.0
SE	6.4	9.8	10.7
CVR (torr/ml/100 mg/min)			
Mean	2.37	2.53	1.46*
SE	.44	.35	.26
CMR_{O_2} (ml/100 mg/min)			
Mean	2.82	3.20	3.25
SE	.45	.55	.78

* Difference from control significant, $P < 0.05$.

CBF as a Function of Time

There was no demonstrable effect of time on the cerebrovascular modalities measured. The circulatory measurements are shown plotted against time (minutes elapsed from the end of morphine administration) in figure 1. Plasma morphine levels (fig. 2) showed a logarithmic decline during the study, changing from 1.601 μg/ml during the first measurement (control MABP) to 0.92 μg/ml during the fourth measurement. Although there was a 12.7 per cent increase in mean CBF comparing control with the fourth measurement, only two of five subjects showed increases and the average slope by linear regression analysis was not significant. CVR and CMR_{O_2} for these five subjects and for all eight subjects were not significantly different when similarly analyzed. Thus, decreasing plasma morphine levels did not affect the modalities measured.

Discussion

Our data show no statistically significant change in CBF over the range of MABP studied. At the lower range of 60 torr, CBF was within the normal range and the calculated CVR had decreased significantly. Thus, the cerebral autoregulatory mechanism was intact in response to lowered MABP.

Increasing MABP to 120 torr produced CBF and CVR values which were not significantly different from control. We would expect to see an increase in CVR to account for the unchanging CBF values.[10] In looking at the individual data, there were directional changes in seven of the eight subjects which indicated a slight increase in CBF and a slight increase in CVR. These individual changes, which did not reach significance in our study, suggest, however, that this dose of morphine may partially inhibit the ability of cerebral vessels to autoregulate in response to hypertension. This might be evaluated by another study employing a larger number of subjects, a higher blood pressure, or a more precise measurement technique. In the absence of such a study we can only say that we were unable to disprove the null hypothesis and that no change in cerebral autoregulation at a MABP of 120 torr could be demonstrated.

It is known that nitrous oxide alone or in combination with morphine does not affect CBF or cerebral autoregulation.[1,§] Halothane, on the other hand, increases CBF and probably disrupts cerebral autoregulation.[11] Recent studies in this laboratory have shown that isoflurane and enflurane cause increases in CBF when MABP is maintained at normal levels, also probably altering cerebral autoregulation. Thus, morphine and/or nitrous oxide may be unique, in that they can afford the patient a stable CBF with an intact autoregulatory mechanism to deal with wide swings in blood pressure. One must keep in mind, however, that patients with pre-existing neurologic disease such as intracerebral hemorrhage or infarction may have altered cerebral autoregulation mechanisms and respond differently.[12,13]

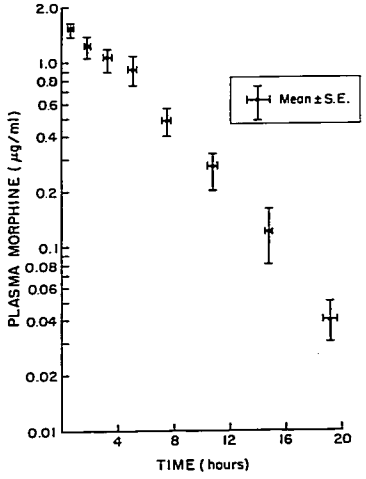

FIG. 2. The plasma morphine mean values plotted *vs.* time from conclusion of morphine administration on a semilog scale. Each point is the mean of values for eight subjects.

§ Bush G, Kennell E, Mull T, et al: Effects of morphine on cerebral blood flow, metabolism, and systemic hemodynamics in man (abstract), presented at the annual meeting of the American Society of Anesthesiologists, October 1972.

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