Title: The Interaction of N_2O and Isoflurane on Regional Cerebral Ischemia in the Rat

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Nitrous oxide (N_2O) is often used clinically as an adjunct to isoflurane (I) in order to provide more anesthesia with less respiratory or cardiovascular depression. The pharmacological action of N_2O is unclear but it may stimulate brain metabolism and increase cerebral blood flow (CBF) alone and in combination with other anesthetics (1). Reports indicate that N_2O may worsen the outcome following cerebral ischemia, possibly due to this cerebral stimulatory effect (2). In these studies we have evaluated neurological outcome using a model of regional cerebral ischemia in the rat comparing the effects of N_2O inhalation alone and given in combination with isoflurane, which has been reported to provide cerebral protection during ischemia (3).

Methods: Male Sprague-Dawley rats weighing 350-450 g were anesthetized, intubated and ventilated with isoflurane in 30% oxygen. Catheters were inserted in the right femoral artery and vein for pressure recording and drug infusion and the right subclavian vein for blood withdrawal. The right common carotid artery was isolated and a loose ligature placed around it for later clamping. At the completion of surgery the wounds were infiltrated with 0.5% bupivacaine. Regional ischemia was produced by clamping the carotid artery and decreasing MABP to either 30 mmHg or 25 mmHg. Two levels of cerebral ischemia were used. Inspired oxygen concentrations were 30% at 30 mmHg (moderate ischemia) and 20% at 25 mmHg (severe ischemia). The anesthetic concentrations were adjusted as follows: moderate ischemia = 70% N_2O alone, 1 MAC Isoflurane (1.38%), 70% N_2O with 1 MAC Isoflurane (total=1.5MAC), 70% N_2O with 0.5 MAC Isoflurane; severe ischemia = 80% N_2O alone, 1 MAC Isoflurane, 80% N_2O with 1 MAC Isoflurane, 80% N_2O with 0.45 MAC Isoflurane. Rectal temperature was maintained at 37°C and vecuronium was administered as needed to maintain paralysis. At the end of a 30 minute equilibration period the right common carotid was clamped and arterial blood pressure decreased by phlebotomy to either 30 or 25 mmHg and maintained at that level for 30 min with the appropriate anesthetic regimen. $PaCO_2$ was maintained between 30-40 mmHg by adjusting ventilation. Arterial pH was maintained at 7.40 by infusion of bicarbonate. Following the hypotensive period and a reinfusion/recovery period the catheters were removed, the incisions closed and the rat extubated. Neurological deficits were initially evaluated 3 hours after recovery and repeated for 3 days. Scores were rated from 0 to 5 as follows: 0 = no deficit, 1 = paw adduction or unusual posture, 2 = circling behavior and unilateral weakness, 3 = seizures initiated by stimulation, 4 = unstimulated seizures, 5 = death associated with progressive stroke.

Results: Arterial blood gas tensions were similar among treatment groups. PaO_2 was lower in rats breathing 20% vs 30% O_2, as expected. Arterial pH was also similar between treatment groups but rats receiving 70% or 80% N_2O alone or in combination with 0.5 MAC Isoflurane required a higher infusion rate of bicarbonate to maintain a normal pH. Mortality rates and deficit scores are shown in Table 1. Severe ischemia (25 mmHg, 20% O_2) produced a poorer recovery from the ischemic episode over all treatments. N_2O given alone produced the highest mortality rate at both moderate and severe ischemia. Isoflurane alone improved neurological outcome compared to N_2O alone but addition of N_2O to the inhalation anesthetic did not worsen outcome.

Table 1. Mortality rates and stroke deficit scores following regional cerebral ischemia (n = 10 in each group).

Drug	Ischemia	Mortality	Deficit Score
70% N_2O	moderate	80%	4.8
1 MAC I	moderate	20%	1.7
70% N_2O + 1 MAC I	moderate	20%	1.5
70% N_2O + 0.5 MAC I	moderate	30%	2.4
80% N_2O	severe	100%	5.0
1 MAC I	severe	70%	3.9
80% N_2O + 1 MAC I	severe	60%	3.2
80% N_2O + 0.45 MAC I	severe	60%	3.5

Discussion: These results support a conclusion that isoflurane provides better cerebral protection alone than N_2O but does not indicate that N_2O combined with isoflurane worsens outcome. Our data suggest that N_2O may stimulate cerebral metabolism and thereby increase cerebral acidosis during hypotensive episodes and this may worsen outcome. However, N_2O combined with isoflurane does not worsen outcome if arterial pH is controlled.

References:

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