

## Effects of Midazolam on Cerebral Blood Flow in Human Volunteers

A. Forster, M.D.,\* O. Juge, M.D.,† D. Morel, M.D.‡

The effects of intravenously administered midazolam on cerebral blood flow were evaluated in eight healthy volunteers using the  $^{133}\text{Xe}$  inhalation technique. Six minutes after an intravenous dose of 0.15 mg/kg midazolam, the cerebral blood flow decreased significantly ( $P < 0.001$ ) from a value of  $40.6 \pm 3.3$  to a value of  $27.0 \pm 5.0 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ . Cerebrovascular resistance (CVR) increased from  $2.8 \pm 0.2$  to  $3.9 \pm 0.6 \text{ mmHg}/(\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1})$  ( $P < 0.001$ ). Mean arterial blood pressure decreased significantly ( $P < 0.05$ ) from  $117 \pm 8$  to  $109 \pm 9 \text{ mmHg}$  and arterial carbon dioxide tension increased from  $33.9 \pm 2.3$  to  $38.6 \pm 3.2 \text{ mmHg}$  ( $P < 0.05$ ). Arterial oxygen tension remained stable throughout the study,  $484 \pm 95 \text{ mmHg}$  before the administration of midazolam and  $453 \pm 76 \text{ mmHg}$  after. All the subjects slept after the injection of the drug and had anterograde amnesia of  $24.5 \pm 5 \text{ min}$ . The decrease in mean arterial blood pressure was probably not important since it remained in the physiologic range for cerebral blood flow autoregulation. The increase in arterial carbon dioxide tension observed after the midazolam injection may have partially counteracted the effect of this new benzodiazepine on cerebral blood flow. Our data suggest that midazolam might be a safe agent to use for the induction of anesthesia in neurosurgical patients with intracranial hypertension. (Key words: Brain: blood flow. Hypnotics: benzodiazepines, midazolam.)

MIDAZOLAM is a new water-soluble short-acting benzodiazepine which has been recommended for the induction of anesthesia.<sup>1-4</sup> The effects of benzodiazepines on cerebral circulation and metabolism have been investigated in humans and animals.<sup>5-11</sup> Most studies report

a decrease in cerebral blood flow (CBF) and metabolism ( $\text{CMR}_{\text{O}_2}$ ). The action of midazolam on cerebral hemodynamics was evaluated in two studies in the dog<sup>9-10</sup> where conflicting results were found, and in anesthetized humans<sup>11</sup> in whom no significant changes in CBF were noted. In order to determine the cerebral hemodynamic effects of midazolam in humans without the possible confounding effects of other anesthetics, we studied its effects on CBF in healthy awake volunteers.

### Materials and Methods

Eight healthy volunteers, four women and four men were studied. Their mean age was  $31 \pm 4$  years (mean  $\pm$  SD) and mean weight  $62 \pm 9 \text{ kg}$ . The subjects had no previous medical problems and did not take regular medication or alcohol. Informed consent was obtained and the Committee for the ethics in human research of our institution approved the study. The volunteers fasted for at least 12 h before the study which took place always in the beginning of the afternoon. A Teflon<sup>®</sup> intravenous cannula was inserted in the dorsum of the hand and a 5 per cent glucose solution was administered at the rate of 100 ml/h. An arterial catheter was inserted in the left radial artery under local anesthesia, in order to measure continuously mean arterial blood pressure ( $\overline{\text{BP}}$ ), heart rate (HR), and to withdraw arterial blood for measurement of blood gases. Cerebral blood flow (CBF) was measured with the  $^{133}\text{Xe}$  inhalation technique described by Obrist *et al.*<sup>12</sup> Sixteen  $^{133}\text{Xe}$  detection probes were used, fixed on a plastic helmet directed toward both the middle cerebral artery and the posterior cerebral artery distribution bilaterally.

\* Research Fellow, Institute of Anesthesiology.

† Chief Resident, Department of Neurology.

‡ Research Assistant, Institute of Anesthesiology.

Received from the Institute of Anesthesiology, and the Department of Neurology, University of Geneva, Hôpital cantonal universitaire, 1211 Genève 4, Switzerland. Accepted for publication November 24, 1981.

Address reprint requests to Dr. Forster.

TABLE 1. Individual and Mean Values of Arterial Blood Pressure (BP)  $\text{Pa}_{\text{CO}_2}$  and  $\text{Pa}_{\text{O}_2}$  6 min after the Injection of a Normal Saline Solution and Midazolam (0.15 mg/kg)

Subject	Saline			Midazolam		
	$\text{Pa}_{\text{O}_2}$ (mmHg)	$\text{Pa}_{\text{CO}_2}$ (mmHg)	$\overline{\text{BP}}$ (mmHg)	$\text{Pa}_{\text{O}_2}$ (mmHg)	$\text{Pa}_{\text{CO}_2}$ (mmHg)	$\overline{\text{BP}}$ (mmHg)
1	526	31.1	122	533	39.5	100
2	448	32.8	120	448	32.3	107
3	510	36.2	117	458	40.9	107
4	458	33.2	110	404	37.1	107
5	525	35.5	115	503	39.8	100
6	278	32.8	120	473	38.6	100
7	527	37.6	107	511	37.4	103
8	600	32.0	108	293	43.0	100
MEAN $\pm$ SD	$484 \pm 95$	$33.9 \pm 2.3$	$117 \pm 8$	$453 \pm 76$	$38.6 \pm 3.2^*$	$103 \pm 3^*$

\*  $P < 0.05$  between saline and midazolam data;  $n = 8$ .

TABLE 2. Individual and Mean Values of CBF and CVR at the PaCO<sub>2</sub> Measured 6 min after the Injection of a Normal Saline Solution and Midazolam (0.15 mg/kg) and Corrected Values of These Data for a PaCO<sub>2</sub> of 40 mmHg

Subjects	Saline				Midazolam			
	CBF at Measured PaCO <sub>2</sub> (ml · 100 g <sup>-1</sup> · min <sup>-1</sup> )	CBF Corrected for a PaCO <sub>2</sub> of 40 mmHg (ml · 100 g <sup>-1</sup> · min <sup>-1</sup> )	CVR at Measured PaCO <sub>2</sub> [mmHg/(ml · 100 g <sup>-1</sup> · min <sup>-1</sup> )]	CVR Corrected for a PaCO <sub>2</sub> of 40 mmHg [mmHg/(ml · 100 g <sup>-1</sup> · min <sup>-1</sup> )]	CBF at Measured PaCO <sub>2</sub> (ml · 100 g <sup>-1</sup> · min <sup>-1</sup> )	CBF Corrected for a PaCO <sub>2</sub> of 40 mmHg (ml · 100 g <sup>-1</sup> · min <sup>-1</sup> )	CVR at Measured PaCO <sub>2</sub> [mmHg/(ml · 100 g <sup>-1</sup> · min <sup>-1</sup> )]	CVR Corrected for a PaCO <sub>2</sub> of 40 mmHg [mmHg/(ml · 100 g <sup>-1</sup> · min <sup>-1</sup> )]
1	42.0	50.1	2.9	2.4	27.5	28.0	3.6	3.6
2	42.7	49.9	2.8	2.4	31.5	39.2	3.4	2.7
3	39.9	43.7	2.9	2.7	27.6	26.7	3.9	4.0
4	46.2	53.0	2.4	2.1	36.1	39.0	3.0	2.7
5	37.2	41.7	3.1	2.8	23.5	23.7	4.3	4.2
6	41.6	48.8	2.9	2.5	23.6	25.0	4.2	4.0
7	36.4	38.8	2.9	2.8	25.6	28.6	4.0	3.6
8	38.4	46.4	2.8	2.3	20.2	17.2	5.0	5.8
MEAN ± SD	40.6 ± 3.3	46.6 ± 4.8	2.8 ± 0.2	2.5 ± 0.3	27.0 ± 5.0*	28.4 ± 7.5*	3.9 ± 0.6*	3.8 ± 1.0*

\*  $P < 0.001$  between saline and midazolam data.

A mixture of oxygen and 4–5 mCi of <sup>133</sup>Xe was inhaled through a face mask using a closed breathing circuit during the one minute saturation period. An open circuit was utilized during the desaturation period which lasted 10 min. End-tidal CO<sub>2</sub> and <sup>133</sup>Xe were monitored by continuous aspiration of gas samples through a small catheter within the mask at the rate of 1.5 l/min. CBF measurements were averaged from the 16 desaturation curves and calculated between the second and third minute of desaturation using Risbergs' Initial Slope Index which represents mainly cortical flow.<sup>13</sup> For CBF calculation with midazolam, we could not use the biexponential analysis because most volunteers had an irregular respiratory pattern, thus, we could not determine precisely the beginning of the exhalation phase.

Two CBF measurements were made during the same session; the first time 6 min after injection of 2 ml of a normalsaline solution, and the second time, 6 min after intravenous injection of 0.15 mg/kg midazolam over a 15-s period.

PaCO<sub>2</sub> and BP values measured at that time were respectively correlated with CBF and used to calculate cerebrovascular resistance (CVR). The laboratory was kept in quiet darkness during the whole procedure. An interval of 30 min was allowed between the two measurements so that background activity of <sup>133</sup>Xe from the first measurement was negligible, *i.e.*, less than 10 per cent. Five minutes before the second run, the subjects were stimulated verbally to try to reproduce the same mental state observed during the first run. Student's *t* test for paired data was used for the statistical comparison.

## Results

The neurobehavioral status after the injection of 0.15 mg/kg midazolam was as reported previously.<sup>4</sup> All volunteers lost consciousness for at least 10 min and had an anterograde amnesia of 24 ± 5 min. CBF data are summarized in tables 1 and 2. Six minutes after the injection of midazolam, CBF was decreased from a control value of 40.6 ± 3.3 to 27.0 ± 5 ml · 100 g<sup>-1</sup> · min<sup>-1</sup>. ( $P < 0.001$ ). We were not able to detect regional changes in CBF; the decrease in flow was a generalized phenomenon. The CVR increased from 2.8 ± 0.2 to 3.9 ± 0.6 mmHg/(ml · 100 g<sup>-1</sup> · min<sup>-1</sup>) ( $P < 0.001$ ).

The  $\overline{BP}$  decreased from 117 ± 8 to 106 ± 9 mmHg ( $P < 0.05$ ) and arterial carbon dioxide tension increased from 33.9 ± 2.3 to 36.6 ± 3.2 mmHg ( $P < 0.05$ ). There were no significant changes in arterial oxygen tension between the control and the drug measurement, 484 ± 95 and 453 ± 76 mmHg, respectively. When CBF and CVR were corrected for a PaCO<sub>2</sub> value of 40 mmHg according to Kety and Schmidt,<sup>14</sup> the changes were even

greater after midazolam, since CBF decreased from  $46.6 \pm 4.8$  to  $28.4 \pm 7.5$   $\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ . CVR increased from  $2.5 \pm 0.3$  to  $3.8 \pm 1.0$   $\text{mmHg}/(\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1})$ .

### Discussion

In each subject, midazolam decreased CBF and increased CVR. Our results are in agreement with one animal study<sup>9</sup> but are conflicting with another animal and one human investigation.<sup>10,11</sup> In the latter studies little or no change in CBF was observed after midazolam injection. This discrepancy may be explained by the fact that CBF was measured in these latter two investigations during fentanyl-nitrous oxide anesthesia in the human investigation and during fentanyl halothane anesthesia in the animals.

In our study, the fall in  $\overline{\text{BP}}$  was statistically significant, but clinically not important. It always remained in the physiologic range for CBF autoregulation in awake humans<sup>15</sup> and thus should not have influenced CBF. When we corrected values for a  $\text{PaCO}_2$  of 40 mmHg, our data show that our intravenous administration of midazolam of 0.15 mg/kg produced a 39 per cent decrease in CBF and 52 per cent increase in CVR. The mechanism of CBF reduction by midazolam probably is related to a decrease in cerebral metabolism produced by the drug as suggested in a recent study.<sup>9</sup> Since midazolam has similar cerebrovascular properties as thiopental, it could be used for induction of anesthesia in patients with increased intracranial pressure as an alternative.

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