Anesthesiology
67:314-319, 1987

Cerebral Vascular and Metabolic Effects of Fentanyl and Midazolam in Young and Aged Rats

Verna L. Baughman, M.D., William E. Hoffman, Ph.D.,† Ronald F. Albrecht, M.D.,‡ David J. Miletich, Ph.D.§*

With the technical assistance of: *Susan Anderson and Chris Prekezas*

Cerebral blood flow (CBF) and cerebral oxygen consumption ($CMRO_2$) were measured, and electroencephalogram (EEG) was recorded in young (6-month-old) and aged (28-month-old) rats during ventilation with 70% N_2O/30% O_2 and following fentanyl or midazolam administration. Cerebral blood flow (CBF) was measured with radioactive microspheres, and cerebral oxygen consumption ($CMRO_2$) was calculated from the arterial-sagittal sinus oxygen content difference and CBF measurements. Fentanyl at the highest dose used (200 $\mu g/kg$ and 400 $\mu g \cdot kg^{-1} \cdot h^{-1}$) depressed the EEG and decreased CBF 49% and $CMRO_2$ 39% in young rats, whereas in old rats, this fentanyl dose decreased CBF 37% and $CMRO_2$ 34%, both significantly less than in young rats ($P < 0.05$). Midazolam at the highest dose used (5.75 mg/kg) also depressed EEG in both age groups, and decreased CBF 51% and $CMRO_2$ 38% in young rats. This depression was significantly less than the 62% decrease in CBF and 59% decrease in $CMRO_2$ produced by midazolam in old rats ($P < 0.05$). These results indicate that aging attenuates the cerebrovascular and cerebral metabolic depression produced by fentanyl, but potentiates the same effects produced by midazolam. The enhanced cerebral metabolic depression produced by midazolam in the aged is similar to that seen with phenobarbital, and suggests a similar action of these drugs at the central GABA-benzodiazepine-barbiturate receptor complex. (Key words: Age factors: geriatrics. Anesthetics, intravenous: fentanyl; midazolam. Brain: blood flow; electroencephalogram; metabolism. Hypnotics: benzodiazepines; midazolam.)

IT IS KNOWN THAT geriatric patients are at greater risk for cardiovascular and neurologic complications during general surgical procedures, due in part to altered responses to anesthetic drugs.[1] The aged have been described as more sensitive to, or requiring smaller doses of, inhalation anesthetics and barbiturates to produce anesthesia.[2-4] It has been suggested that benzodiazepines and narcotics may be the drugs of choice for the geriatric patient because of their ability to produce sedative/hypnotic effects with minimal cardiovascular depression.[5,6] Little is known, however, about how central narcotic and benzodiazepine receptor responses are altered as a function of aging. We have evaluated the cardiovascular, electrophysiological, cerebrovascular, and cerebral metabolic depression produced by fentanyl and midazolam in young (6-month-old) and aged (28-month-old) rats. These rat ages may be equated to a young adult and an approximately 70-year-old human, respectively, when the two species are compared physiologically and in terms of longevity.[7,8]

Methods

Surgical Preparation

Six- and 28-month-old male Sprague-Dawley rats were anesthetized with halothane in a bell jar. Following tracheostomy, they were ventilated with 1% halothane in O_2 using a small animal respirator. Bilateral femoral cutdowns were performed, and both femoral arteries and veins were cannulated with polethylene catheters filled with heparinized normal saline solution. These catheters were used for monitoring heart rate and blood pressure, as well as for blood withdrawal and drug administration. The left ventricle was catheterized *via* the right common carotid artery for microsphere injections. Pressure tracings were monitored to ensure proper left ventricular catheter placement. The animal was then turned to the prone position and the skull exposed. A small hole was drilled into the posterior sagittal sinus and a catheter inserted for withdrawal of sagittal sinus blood samples. Stainless steel screw electrodes were applied bilaterally over the parietal cortices for continuous bipolar EEG monitoring. A third screw electrode over the frontal cortex served as a ground electrode. All leads were shielded to prevent 60-cycle interference. EEG was recorded using a Grass® Instruments P15 differential AC amplifier and a Hewlett-Packard® strip chart recorder using filter settings of 1 and 30 Hz.

* Associate Attending Physician, Department of Anesthesiology, Michael Reese Hospital and Medical Center; and Clinical Assistant Professor of Anesthesiology, Pritzker School of Medicine.

† Director, Anesthesiology Research Laboratory, Michael Reese Hospital and Medical Center; and Research Associate/Associate Professor of Anesthesiology, Pritzker School of Medicine.

‡ Chairman, Department of Anesthesiology, Michael Reese Hospital and Medical Center; and Clinical Professor of Anesthesiology, Pritzker School of Medicine.

§ Director of Anesthesiology Research, Michael Reese Hospital and Medical Center; and Research Associate/Associate Professor of Anesthesiology, Pritzker School of Medicine.

Received from the Michael Reese Hospital and Medical Center, Chicago, Illinois; and the Pritzker School of Medicine, University of Chicago, Chicago, Illinois. Accepted for publication March 27, 1987. Presented in abstract form at the 1984 Society of Neurosurgical Anesthesia and Neurologic Supportive Care Meeting, New Orleans, Louisiana.

Address reprint requests to Dr. Hoffman: Department of Anesthesiology, Michael Reese Hospital and Medical Center, Lake Shore Drive at 31st Street, Chicago, Illinois 60616.

Following completion of surgery, halothane was discontinued, and 70% N_2O/30% O_2 was administered for a 45-min equilibration period. Muscle relaxation was produced with 1 mg/kg d-tubocurarine immediately after discontinuation of halothane. Arterial P_{CO_2} was adjusted to 35–40 mmHg, and arterial P_{O_2} was maintained greater than 100 mmHg. Rectal temperature was measured with a thermistor probe and maintained at 37° C using an overhead heat lamp. Mean arterial blood pressure was recorded continuously from a femoral artery catheter. Heart rate was measured from arterial pressure pulses periodically throughout the experiment. These experiments were carried out with IRB approval for animal experiments. Care was taken to maintain appropriate anesthetic management under all experimental conditions.

Testing Procedures

At the end of the 45-min equilibration period, four groups of young and four groups of old rats received iv fentanyl (25, 100, or 200 μg/kg or placebo) over a 5-min period. The injection was followed by a continuous infusion at a rate equal to two times the loading dose per hour (*i.e.*, 50, 200, or 400 $\mu g \cdot kg^{-1} \cdot h^{-1}$). With the administration of fentanyl, nitrous oxide was discontinued, and the animals were ventilated with 70% nitrogen in oxygen, except for the placebo-treated control animals. Twenty minutes after the start of the fentanyl injection, CBF was measured using radioactive microspheres. EEG was recorded throughout the experiment.

Midazolam experiments were performed separately from the fentanyl studies, including separate sham-treated control groups for both young and old rats. These rats received iv midazolam injections of 0.02, 0.2, or 2 mg/kg given over a 5-min period. This was followed by a 15-min infusion of 0.0025, 0.025, or 0.25 $mg \cdot kg^{-1} \cdot min^{-1}$ for a total dose of 0.057, 0.575, or 5.75 mg/kg, respectively. The volume infusion rate was $0.1\ ml \cdot kg^{-1} \cdot min^{-1}$ in each rat, irrespective of midazolam dose. The control groups of rats received only sham saline treatment, and were ventilated with 70% N_2O/30% O_2. CBF was measured at the end of the infusion, and EEG was recorded continuously. Isopotency curves were not constructed for fentanyl and midazolam data, due to the difficulty in equating the analgesic actions of fentanyl with the sedative effects of midazolam.

Microspheres

Microsphere injections were performed using 15-μm microspheres labeled with cobalt-57 (New England Nuclear®). Stock solutions containing 500,000 microspheres/ml were suspended in isotonic saline with 0.1% tween-80. Ventricular pressure tracings were monitored before each microsphere injection to assure proper catheter placement. Microspheres were vortexed for 1 min, 0.2 ml withdrawn (100,000 microspheres), injected into the left ventricle *via* the ventricular catheter (dead space = 0.06 ml) and flushed in with 0.2 ml saline. Starting immediately before the microsphere test and continuing 45 s after the end of each injection, blood was withdrawn from a femoral artery at a rate of 0.4 ml/min using an infusion-withdrawal pump. Arterial and sagittal sinus blood samples were also taken after each microsphere test for measurement of arterial blood gases and O_2 content and cerebral venous O_2 content for determination of cerebral oxygen extraction ($A\text{-}VO_2$). Blood gas tensions and *p*H were measured with an IL 1303® blood gas analyzer. Oxygen content was measured using an IL 282® CO-oximeter and adding the oxygen dissolved in the plasma of each sample. Mean arterial blood pressure was monitored continuously throughout the microsphere tests from the second femoral artery to ensure that blood pressure did not change appreciably. Heart rate was measured before each microsphere injection. After the microsphere test, the rat was killed, and the brain was removed and dissected into left and right cortical samples and weighed. The microsphere activity in brain and blood samples was analyzed using a Nuclear Chicago 1035® Gamma Counter and a Nuclear Data 600® multichannel analyzer. Cerebral blood flow was determined using the method of Heymann *et al.*[9] Cerebral cortical oxygen consumption ($CMRO_2$) was calculated as the product of cortical CBF, corrected for brain weight, and arterial minus cortical venous blood O_2 content ($Ca\text{-}vO_2$).

Drug and Reagents

Midazolam maleate (RO 21-3981/1 Hoffman-La-Roche®, Inc., Nutley, N. J.) was dissolved in normal saline. Fentanyl (Sublimaze®) was available in injectable form in a concentration of 0.05 mg/ml. Subsequent dilutions of these drugs were made with normal saline.

Statistical Methods

Data are reported as mean ± SE. The effects of fentanyl and midazolam on young and aged rats were compared using a two-way analysis of variance evaluating age and anesthetic effects. Supplemental F-tests were used to analyze fentanyl and midazolam treatment effects separately in young and aged test groups. Multiple tests comparing the means of young and aged rats for each drug were performed using Scheffe's tests.

TABLE 1. Mean Arterial Blood Pressure, Heart Rate, Blood Gas Tensions, CBF, and $CMRO_2$ in Young and Old Rats during Fentanyl and Midazolam Infusion

Fentanyl Dose (μg/kg)	Blood Pressure n	Blood Pressure mmHg	Heart Rate (min^{-1})	$Paco_2$ (mmHg)	Pao_2 (mmHg)	*p*H	Cortical CBF ($ml \cdot 100g^{-1} \cdot min^{-1}$)	Cortical $CMRO_2$ ($ml \cdot 100g^{-1} \cdot min^{-1}$)
Young								
0	9	132 ± 2	356 ± 11	36.9 ± .5	143 ± 7	7.40 ± .01	170 ± 4	10.1 ± .2
25	11	133 ± 2	327 ± 14	38.8 ± .6	137 ± 6	7.36 ± .02	105 ± 2*	7.1 ± .2*
100	11	136 ± 2	391 ± 15	36.2 ± .3	142 ± 3	7.39 ± .01	89 ± 2*	6.2 ± .1*
200	9	157 ± 3*	430 ± 5*	36.7 ± .8	151 ± 8	7.38 ± .01	86 ± 2*	6.1 ± .2*
Old								
0	9	126 ± 5	410 ± 7†	36.7 ± .6	139 ± 8	7.41 ± .02	166 ± 4	10.4 ± .2
25	7	131 ± 2	392 ± 15†	38.1 ± .6	133 ± 5	7.38 ± .01	116 ± 5*	7.3 ± .2*
100	12	126 ± 2	418 ± 4	37.2 ± .4	141 ± 4	7.39 ± .01	113 ± 2*†	6.9 ± .1*†
200	9	131 ± 2†	441 ± 7	38.3 ± .9	160 ± 6	7.38 ± .01	104 ± 2*†	6.8 ± .1*†
Midazolam Dose (mg/kg)								
Young								
0	14	140 ± 2	416 ± 8	36.5 ± .4	135 ± 5	7.40 ± .01	210 ± 6	10.4 ± .2
0.057	10	109 ± 3*	382 ± 13	35.3 ± .6	160 ± 18	7.39 ± .01	131 ± 5*	8.4 ± .2*
0.575	12	111 ± 3*	413 ± 5	37.2 ± .3	131 ± 3	7.38 ± .01	106 ± 2*	7.0 ± .2*
5.750	10	121 ± 4*	378 ± 10	36.7 ± .7	125 ± 4	7.40 ± .02	104 ± 4*	6.4 ± .3*
Old								
0	8	129 ± 3	333 ± 18†	37.4 ± .2	146 ± 10	7.37 ± .02	182 ± 5†	11.1 ± .3
0.057	8	108 ± 3*	356 ± 6	38.8 ± .9	117 ± 11†	7.39 ± .02	140 ± 5†	9.0 ± .3*
0.575	8	96 ± 3†	353 ± 10†	37.3 ± 1.0	113 ± 5	7.41 ± .01	71 ± 2*†	4.9 ± .1*†
5.750	8	89 ± 4*†	356 ± 6	37.1 ± .9	115 ± 7	7.38 ± .01	69 ± 3*†	4.6 ± .2*†

Data presented as mean ± SE.
* = $P < 0.05$ drug treatment compared to N_2O control within each age group.
† = $P < 0.05$ old compared to young at each drug dose.

Results

The effects of fentanyl on mean blood pressure, heart rate, and arterial blood gas tensions are shown in table 1. Fentanyl produced a modest increase in blood pressure and heart rate in young rats that was significant at 200 μg/kg. No significant changes in blood pressure or heart rate were seen in fentanyl-treated aged rats. Arterial blood gas tensions and *p*H were maintained at control levels in both age groups with no significant differences between young and old rats. EEG changes produced by fentanyl are shown in figure 1. Fentanyl produced an increase in amplitude and a decrease in frequency in both age groups, but these changes were less pronounced in old compared to young rats at the lower fentanyl doses. Changes in CBF and $CMRO_2$, shown in table 1, demonstrate a dose-related decrease with fentanyl in both young and aged rats that plateaus with the 100- and 200-μg/kg doses. The depression in CBF and $CMRO_2$ produced by fentanyl was significantly less in old compared to young rats when compared by analysis of variance ($P < 0.05$). One young rat treated with a fentanyl dose of 200 μg/kg showed seizure-like EEG activity. This rat had a higher than normal $CMRO_2$ value of 13.6 ml 100 $g^{-1} \cdot min^{-1}$, and was excluded from further analysis. No old rats showed epileptiform EEG activity or had elevated $CMRO_2$ values at any fentanyl dose.

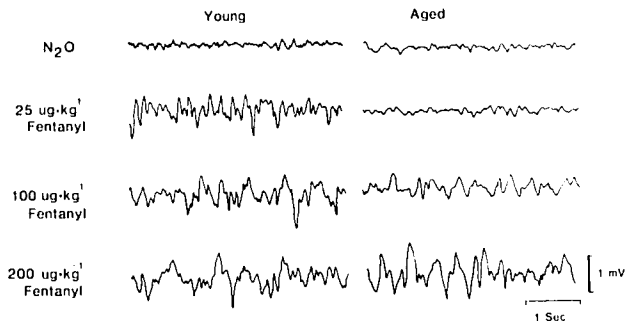

FIG. 1. EEG changes during fentanyl anesthesia. Individual records of separate young and old rats given 70% N_2O, 30% O_2 as a control (N_2O), or increasing doses of fentanyl. Fentanyl produced high-amplitude, slow-wave activity, with changes more readily apparent in young than in old rats at lower fentanyl doses.

Cardiovascular, arterial blood gas, CBF, and $CMRO_2$ effects of midazolam are also shown in table 1. Although blood pressure decreased more in old than in young with the higher midazolam doses, pressure remained within the autoregulatory range for both

groups. Midazolam produced a dose-related slowing of EEG frequency and an increase in amplitude with little difference in response between young and old rats (fig. 2). CBF and $CMRO_2$ also decreased with increasing doses of midazolam, and plateaued in both young and old rats with the 0.57 and 5.75 mg/kg doses (table 1). Both variables decreased more in old than in young rats, as indicated by analysis of variance ($P < 0.05$).

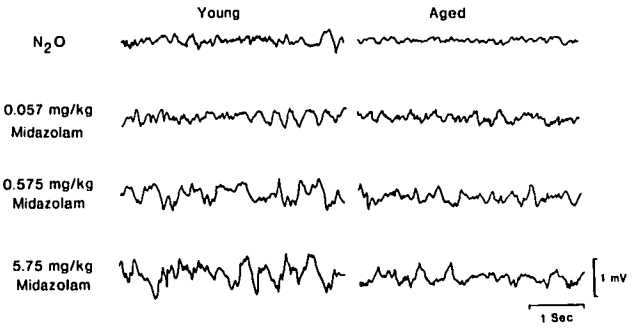

FIG. 2. EEG changes during midazolam treatment in young and aged rats. Midazolam produced an increase in amplitude and a decrease in frequency which was similar in both young and old rats.

Discussion

These results show that fentanyl depresses CBF and $CMRO_2$ significantly more in young than in old rats. This suggests that opiate receptors in aged rats may be decreased in number or be less responsive to the cerebral metabolic depressant effects of fentanyl administration. In contrast, midazolam decreased CBF and $CMRO_2$ more in older rats, suggesting that aged neurons may be more sensitive to the depressant effects of benzodiazepines.

Several methodological factors should be considered in this study. First is the appropriateness of N_2O as a control condition. Studies in dogs[10] and goats[11] have shown that N_2O increases regional CBF compared to unanesthetized animals. In contrast, in rats, investigators have shown that cortical CBF and brain metabolism are not different between anesthetized and unanesthetized rats or from values reported here.[12-14] We have reported N_2O control cortical CBF and $CMRO_2$ values of 120 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ and 7 $ml \cdot 100\ g^{-1} \cdot min^{-1}$, respectively, in a recent report,[4] which are lower than observed here. This may be related to the use of Wistar rats in the previous study and Sprague-Dawley rats here. Other possible factors which may be involved include the source of animals, time of year of the study, and undefined technical aspects of each study. For this reason, we felt it necessary to use separate young and aged control groups for both the fentanyl and the midazolam studies. Another methodological concern is the possible interaction of N_2O with midazolam. Carlsson *et al.*[15] showed that diazepam decreased $CMRO_2$ in rats during N_2O, but not nitrogen ventilation, suggesting that N_2O may potentiate the cerebral metabolic depressant effects of benzodiazepines. However, the work of Nugent *et al.*[16] and results from our laboratory[17] indicate that N_2O does not potentiate, but may slightly attenuate, the depressant effects of midazolam. We conclude that the above reports suggest that N_2O ventilation produces a control state in the rat, and that N_2O allows the cerebrovascular and cerebral metabolic depressant effects of midazolam to take place.

It is possible that changes in fentanyl and midazolam distribution and/or clearance between young and old rats produced differences in plasma and brain tissue drug concentrations at the time of testing. Reports indicate that the volume of distribution and plasma half-life of benzodiazepines are increased in aged subjects.[18,19] However, brain concentrations of diazepam are not different between young and old rats following intravenous injection, in spite of these changes.[20] Plasma clearance of fentanyl may be decreased[21] or not significantly different between young and old subjects,[22,23] but little is known about how these changes may relate to brain fentanyl concentrations. Brain concentrations of fentanyl and midazolam are of primary importance in comparing dose-response effects of young *versus* old rats in order to determine a possible change in receptor sensitivity. However, significant differences in CBF and $CMRO_2$ were only seen between young and old rats with the highest doses of fentanyl and midazolam. At these doses, the depressant effects of both drugs had reached a plateau. These plateaus represent the maximum depressant effects of fentanyl and midazolam, and indicate pharmacological saturation of central opiate and benzodiazepine receptors, respectively.[24,25]¶ These results do not suggest a change in sensitivity to submaximal doses of fentanyl or midazolam with aging, but indicate a change in the maximum cerebral metabolic depression produced by both drugs. These differences in response between young and old rats should be apparent over a range of brain tissue fentanyl and midazolam concentrations that produce maximal cerebral metabolic depression (*i.e.*, receptor saturation).

The depressant effects of fentanyl on EEG, CBF, and $CMRO_2$ are similar to those seen by others.[26-28] They also agree quantitatively with the results of Carlsson *et al.*,[25] who showed, in rats, that fentanyl decreased cortical CBF from 168 to 85 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ and

¶ Michenfelder JD: Midazolam: Uses in neurosurgery. Anesthesiology Review 13:45-46, 1986

$CMRO_2$ from 10.3 to 7.0 ml 100 $g^{-1} \cdot min^{-1}$. In that study, both CBF and $CMRO_2$ were maximally depressed with 100 μg/kg fentanyl, and no further decreases were seen with doses up to 400 μg/kg. This is consistent with our findings that neither CBF nor $CMRO_2$ decreased significantly more with a doubling of fentanyl dose from 100 to 200 μg/kg. The fact that aged rats show less CBF and $CMRO_2$ depression with higher doses of fentanyl suggests that the maximum cerebral metabolic depressant effects of the narcotic may be attenuated in the aged. EEG records also showed less slow-wave, high-amplitude activity in old rats at lower fentanyl doses. This is different from the results of Scott and Stanski,[29] who found that smaller doses of fentanyl were required to produce delta-wave activity in old compared to young subjects. The major difference between the studies appears to be that Scott and Stanski infused fentanyl into their patients until a specific EEG change was observed, while, in this study, a constant infusion of fentanyl was given for 15 min, after which EEG was measured. In addition, rats may show a different EEG response to fentanyl than humans. It has also been reported that fentanyl can induce seizures in rats. Carlsson *et al.*[25] suggested that the incidence of seizures may be significant in young rats given fentanyl in doses of 200–400 μg/kg. In this study, we observed epileptiform-like EEG activity and an elevated $CMRO_2$ in one young rat given 200 μg/kg fentanyl, suggesting seizure activity. No abnormal EEG or elevated $CMRO_2$ values were seen in old rats at any fentanyl dose, suggesting that their lack of sensitivity to the epileptiform effects of fentanyl.

It has been previously shown that midazolam and other benzodiazepines decrease CBF and $CMRO_2$ coincident with their sedative/hypnotic effects.[16,17,30,31] The cerebral metabolic depressant effects of benzodiazepines are apparently linked with the ability of central benzodiazepine receptors to modulate the activity of the gamma aminobutyric acid (GABA) receptor-chloride ionophore complex.[32,33] Midazolam has been shown to facilitate the pharmacological action of GABA at the post-junctional receptor in addition to inhibiting GABA reuptake.[33] In this study, midazolam decreased $CMRO_2$ more in aged than in young rats, even though EEG suppression was similar between both age groups. In general, there is an association between EEG suppression and $CMRO_2$ reduction; however, linkage between these two may not be very close if a drug also depresses cellular metabolism not related to neuronal electrophysiological function. Depression of non-electrical metabolic function by midazolam in the aged rat would explain why $CMRO_2$ decreased 59% in these animals, but EEG was not isoelectric. These results are similar to those in a previous report, where $CMRO_2$ decreased more in old rats (55%) than in young rats (43%) with doses of phenobarbital that produced a quiescent EEG in both groups.[4] The correlation between barbiturate and benzodiazepine effects in young *versus* aged rats may reflect a similar action of both drugs at the GABA receptor complex.[32] Drugs which produce cerebral depression at this complex may induce greater decreases in non-electrical brain metabolism in old rats because of an age-dependent change in the number or activity of the benzodiazepine-GABA receptor-chloride ionphore complex.[32,33]

In summary, these results show that aging alters the maximal cerebral metabolic and cerebrovascular response to fentanyl and midazolam treatment. Old rats show less cerebral metabolic depression to fentanyl and more depression to midazolam compared to young animals. Although increases in drug elimination time in the aged have been reported for fentanyl and benzodiazepines,[19,21] this probably played little role here, since both fentanyl and midazolam were given by continuous iv infusion, and differences were observed at doses of each drug representing the maximum pharmacological effect. It is more likely that the age-related changes in drug-induced depression reflect alterations in central narcotic and benzodiazepine receptor responsiveness, due to changes in receptor number or binding characteristics.[34,35]

The authors wish to thank Sherry Alonzo for typing this manuscript.

References

1. McLeskey CH: Anesthesia for the geriatric patient, Advances in Anesthesia. Edited by Stoelting RK, Barash PG, Gallagher TH. Chicago, Year Book Medical Publishers, 1985, pp 31–68
2. Christensen F, Andreasen F, Jansen JA: Influence of age and sex on the pharmacokinetics of thiopentone. Br J Anaesth 53:1189–1196, 1981
3. Gregory GA, Eger EL, Munson ES: The relationship between age and halothane requirement in man. ANESTHESIOLOGY 30:488–491, 1969
4. Baughman VL, Hoffman WE, Miletich DJ, Albrecht RF: Effects of phenobarbital on cerebral blood flow and metabolism in young and aged rats. ANESTHESIOLOGY 65:500–505, 1986
5. Kaiko RF, Wallenstein SL, Rogers AG, Grabinski PY, Houde RW: Narcotics in the elderly. Med Clin North Am 66:1079–1089, 1982
6. Kanto J, Aaltonen L, Himberg JJ, Hovi-Viander M: Midazolam as an intravenous induction agent in the elderly: A clinical and pharmacokinetic study. Anesth Analg 65:15–20, 1986
7. Brizzee KR: Structural correlates of the aging process in the brain. Psychopharmacol Bull 17:43–52, 1981
8. Terry RD: Some biological aspects of the aging brain, Mechanisms of Ageing and Development Vol. 14. Lausanne, Elsevier Sequoia SA, 1980, pp 191–201
9. Heymann M, Payne B, Hoffman JIE, Rudolph AM: Blood flow measurements with radionuclide-labelled particles. Prog Cardiovasc Dis 20:55–69, 1977

10. Theye RA, Michenfelder JD: The effect of nitrous oxide on canine cerebral metabolism. ANESTHESIOLOGY 29:1119–1124, 1976
11. Pelligrino DA, Miletich DJ, Hoffman WE, Albrecht RA: Nitrous oxide markedly increases cerebral cortical metabolic rate and blood flow in the goat. ANESTHESIOLOGY 60:405–412, 1984
12. Dahlgren N, Ingvar M, Yokoyama H, Siesjo BK: Influence of nitrous oxide on local cerebral blood flow in awake, minimally restrained rats. J Cereb Blood Flow Metabol 1:211–218, 1981
13. Carlsson C, Hagerdal M, Siesjo BK: The effect of nitrous oxide on oxygen consumption and blood flow in the cerebral cortex of the rat. Acta Anaesthesiol Scand 20:91–95, 1976
14. Carlsson C, Hagerdal M, Siesjo BK: Increase in cerebral oxygen uptake and blood flow in immobilization stress. Acta Physiol Scand 95:206–208, 1975
15. Carlsson C, Hagerdal M, Kaasik AE, Siesjo BK: The effects of diazepam on cerebral blood flow and oxygen consumption in rats and its synergistic interaction with nitrous oxide. ANESTHESIOLOGY 45:319–325, 1976
16. Nugent M, Artru AA, Michenfelder JD: Cerebral metabolic, vascular and protective effects of midazolam maleate. ANESTHESIOLOGY 56:172–176, 1982
17. Hoffman WE, Miletich DJ, Albrecht RF: The effects of midazolam on cerebral blood flow and oxygen consumption and its interaction with nitrous oxide. Anesth Analg 65:729–733, 1986
18. Choneim MM, Korttila K: Pharmacokinetics of intravenous anaesthetics: Implications for clinical use. Clin Pharmacokinet 2:344, 1977
19. Greenblatt DJ, Abernethy DR, Locniskar A, Harmatz JS, Limjuco RA, Shader RI: Effect of age, gender, and obesity on midazolam kinetics. ANESTHESIOLOGY 61:27–35, 1984
20. Klotz U: Effect of age on levels of diazepam in plasma and brain of rats. Naunyn-Schmiedebergs Arch Pharmacol 307:167–169, 1979
21. Bentley JB, Borel JD, Nenad RE, Gillespie TJ: Age and fentanyl kinetics. Anesth Analg 61:968–971, 1982
22. Cartwright P, Prys-Roberts C, Gill K, Dye A, Stafford M, Gray A: Ventilatory depression related to plasma fentanyl concentrations during and after anesthesia in humans. Anesth Analg 62:966–974, 1983
23. Hudson RJ, Thomson IR, Cannon JE, Friesen RM, Meatherall RC: Pharmacokinetics of fentanyl in patients undergoing abdominal aortic surgery. ANESTHESIOLOGY 64:334–338, 1986
24. Hoffman WE, Miletich DJ, Albrecht RF: The effects of midazolam on cerebral blood flow and oxygen consumption and its interaction with nitrous oxide. Anesthesiology Review 65:729–733, 1986
25. Carlsson C, Smith DS, Keykhah MM, Englebach I, Harp JR: The effects of high dose fentanyl on cerebral circulation and metabolism in rats. ANESTHESIOLOGY 57:375–380, 1982
26. Michenfelder JD, Theye RA: The effects of fentanyl, droperidol, and innovar on canine cerebral metabolism and blood flow. Br J Anaesth 43:630–635, 1971
27. Freeman J, Ingvar DH: Effects of fentanyl on cerebral cortical blood flow and EEG in the cat. Acta Anaesthesiol Scand 11:381–391, 1967
28. Scott JC, Ponganis KV, Stanski DR: EEG quantitation of narcotic effect: The comparative pharmacodynamics of fentanyl and alfentanil. ANESTHESIOLOGY 62:234–241, 1985
29. Scott JC, Stanski DR: Decreased fentanyl/alfentanil dose requirements with increasing age: A pharmacodynamic basis (abstract). ANESTHESIOLOGY 63:A374, 1985
30. Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ: Midazolam: Pharmacology and uses. ANESTHESIOLOGY 62:310–324, 1985
31. Forster A, Juge O, Morel D: Effects of midazolam on cerebral blood flow in human volunteers. ANESTHESIOLOGY 56:453–455, 1982
32. Olsen RW: GABA-benzodiazepine-barbiturate receptor interactions. J Neurochem 37:1–13, 1981
33. Cheng SC, Brunner EA: Inhibition of GABA metabolism in brain synaptosome by midazolam (RO 21-3981). ANESTHESIOLOGY 55:411–445, 1981
34. Tsang CC, Speeg KV Jr, Wilkinson GR: Aging and benzodiazepine binding in the rat cortex. Life Sci 30:343–346, 1982
35. Pedigo NW, McDougal JN, Burks TF, Yamamura HI: Benzodiazepine receptor binding in the frontal cortex and cerebellum from aged rats. Fed Proc 40:311–18, 1981