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Regional Blood Flow and Cerebral Metabolic Changes during Alcohol Withdrawal and Following Midazolam Therapy

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Regional blood flows and cerebral oxygen consumption (CMR_{O_2}) were measured following alcohol withdrawal in alcohol-dependent rats. In addition, the authors tested the ability of midazolam (0.057, 0.575, or 5.75 $mg \cdot kg^{-1}$) to modify alcohol-induced changes. Rats received a 3-week treatment of daily *ad libitum* access to a liquid diet containing 6.54% ethanol or a sham treatment with the same caloric intake but with white dextrin substituted for alcohol. Regional blood flow was measured 12 h after alcohol withdrawal with radioactive microspheres. Nitrous oxide (70% in oxygen) was used as the control anesthetic. Rats withdrawn from alcohol treatment had significantly increased heart rate, cortical cerebral blood flow (CBF) (39 ± 8%, mean ± SE), and CMR_{O_2} (41 ± 9%) compared with sham-treated rats ($P < 0.05$). Subcortical CBF (49 ± 8%), myocardial (52 ± 18%), and hepatic arterial blood flow (298 ± 47%) also were increased in alcohol-withdrawn rats. Renal blood flow decreased 47 ± 5%, while skeletal muscle and small intestinal blood flow were not significantly different between the two groups. Midazolam infusion decreased CBF, CMR_{O_2}, and hepatic arterial blood flow in alcohol-withdrawn rats to similar levels as sham-treated rats and increased renal blood flow in both groups. Skeletal muscle and intestinal tissues showed no change in blood flow in response to midazolam. The authors conclude that midazolam may be effective in lowering blood pressure and brain metabolism and reversing regional blood flow changes produced by alcohol withdrawal in the rat. (Key words: Alcohol. Anesthetics, gases: nitrous oxide. Anesthetics, intravenous: midazolam. Brain: blood flow; metabolism.)

THE ANESTHETIC MANAGEMENT of alcoholics is associated with several problems, including cardiovascular instability[1,2] and increased resistance to neuroleptic and analgesic agents.[3–5] While the withdrawing person with alcoholism may show greater resistance to several anesthetic agents,[6–8] paradoxically the steady state anesthetic requirements of these patients may not be different from normal.[9] Studies suggest the increased tolerance to the depressant effects of sedative or anesthetic drugs may be due to enhancement of neuroexcitatory mechanisms.[9,10] Withdrawal of alcohol unmasks this neuronal excitability, producing cerebral metabolic stimulation and behavioral withdrawal symptoms.[11]

In earlier experiments, it was shown that withdrawal of alcohol after 3 weeks of daily intake produced a physiologic picture in rats qualitatively similar to that seen in the human alcoholic, with significant changes produced in the behavioral response to anesthetic and sedative agents.[12] It was the purpose of these experiments to determine, using this model, the effect of alcohol withdrawal on regional blood flows and cerebral oxygen consumption (CMR_{O_2}). The ability of midazolam maleate, a short-acting benzodiazepine, to modify alcohol withdrawal effects also was tested. It was hypothesized that midazolam may depress neuronal excitability and alter regional blood flow changes associated with alcohol withdrawal.

Methods

Animal Preparation

Male Sprague-Dawley rats, housed two per cage, were allowed *ad libitum* access to a sustacal liquid diet containing 6.54% ethanol as their only source of food and water for 3 weeks, according to previous reports.[13,14] The diet provides 35% of the caloric needs as alcohol.[13] Pair-fed controls were given the same diet except that white dextrin was isocalorically substituted for the alcohol. The diets of alcohol- and sham-treated rats were adjusted so that each group received the same caloric intake. Twelve hours before testing, animals of both groups were deprived of food and given free access to water. A qualitative evaluation of behavior was performed before surgical preparation.

Surgical Preparation

Rats were anesthetized with halothane in a bell jar, tracheostomized and ventilated with 1.5% halothane in O_2 with the use of a Harvard® small-animal respirator. Body temperature was maintained at 37° C, and arterial blood P_{CO_2} was maintained between 35–40 mmHg by adjusting ventilation. Bilateral femoral cutdowns were performed, and both femoral arteries and femoral veins were cannulated with Clay-Adams Intramedic® polyethylene catheters filled with heparinized normal saline solution. These catheters were used for continuous heart rate and pressure monitoring, blood withdrawal, and drug administration. The left ventricle was catheterized via the right

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common carotid artery for microsphere injections. Pressure tracings were monitored to ensure proper catheter placement. A Hewlett-Packard® pressure transducer and chart recorder was used in all cases. The skull was exposed, a small hole drilled into the sagittal sinus and a catheter inserted for withdrawal of sagittal sinus blood samples. Following completion of surgery, halothane was discontinued and the animal was ventilated with 70% N_2O and 30% O_2 for a 45-min equilibration period. Muscle relaxation was achieved with 1 $mg \cdot kg^{-1}$ *d*-tubocurarine iv.

Protocol

Alcohol- and sham-treated rats were assigned to one of several treatment conditions (n = 8–13 per treatment). These treatment conditions included control nitrous oxide anesthesia or intravenous infusions of midazolam. Rats given midazolam also received nitrous oxide. Midazolam treatments included an initial iv injection of 0.02, 0.20, or 2.00 $mg \cdot kg^{-1}$ midazolam, followed by a 15-min infusion of 0.0025, 0.025, or 0.25 $mg \cdot kg^{-1} \cdot min^{-1}$ to reach a total dose of 0.057, 0.575, or 5.750 mg/kg, respectively over the 15-min infusion period. With respect to rats, the doses of midazolam used here produced behavioral effects ranging from sedation at 5.75 $mg \cdot kg^{-1}$ to no observable effect at 0.057 $mg \cdot kg^{1}$. Clinical doses of midazolam are in the range of 0.07–0.25 mg/kg,[15,16] while experimental doses have been tested up to 10 mg/kg.[17,18] Control-treated rats received saline vehicle infusions. The volume infusion rate for all treatments was 0.1 $ml \cdot kg^{-1} \cdot min^{-1}$.

Microspheres

Fifteen micrometer microspheres, labeled with cobalt-57, (New England Nuclear) were injected at the end of the 15-min infusion period indicated above. Fifteen-micrometer microspheres were chosen because shunting or migration occurs to a minimal extent in target organs with this sphere size.[19] A stock solution containing 500,000 microsphere/ml was suspended in isotonic saline with 0.01% Tween-80. Ventricular pressure pulses were monitored before the microsphere injection. Microspheres were suspended with the use of a vortex mixer 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 with 0.2 ml saline according to previous methods.[20] Starting immediately before the microsphere test and continuing 45 s after the end of the injection, blood was withdrawn from a femoral artery at a rate of 0.4 $ml \cdot min^{-1}$ with the use of a Harvard infusion-withdrawal pump. Arterial blood-gas measurements were made at the end of the microsphere injection procedure. Arterial and sigittal sinus blood samples also were taken after the microsphere test for measurement of cerebral arterial–venous O_2 content difference ($C(a\text{-}v)_{O_2}$). A 0.1-ml blood sample also was taken for measurement of blood ethanol concentrations by gas chromatograph. A total of 1.5–2 ml was withdrawn for all testing procedures. Blood gases and *p*H were measured with an Il 1303® blood gas analyzer and oxygen content was measured with the use of an Il 282 CO-oximeter®. Mean arterial blood pressure was measured continuously throughout the microsphere test from the second femoral artery to ensure blood pressure did not change appreciably during the procedure. Heart rate was measured before the microsphere injection. At the end of the microsphere test the rat was killed with iv ethanol, and the brain, whole heart, both kidneys and a portion of liver, foreleg skeletal muscle, and small intestine were dissected out and weighed. The brain was sectioned into left and right cortical and subcortical samples and weighed. Microsphere activity in tissue and blood samples was analyzed with the use of a Nuclear Chicago 1035 Gamma Counter® and a Nuclear Data 600® multichannel analyzer. Tissue blood flow was analyzed according to the methods of Heymann *et al.*[21] CMR_{O_2} was calculated as the product of cortical CBF corrected for brain weight and $C(a\text{-}v)_{O_2}$. The blood flow in the left and right kidneys was compared to evaluate the adequacy of microsphere mixing, but the average of right and left kidney blood flow was used for statistical analysis.

Drug and Reagents

Midazolam maleate (RO 21-3981/1. Hoffman-La-Roche, Inc. Nutley, New Jersey) was dissolved in normal saline to a stock concentration of 0.2 $mg \cdot ml^{-1}$. Blood ethanol levels were measured by placing 0.1-ml blood samples into 0.9-ml deionized water to lyse the red blood cells. One-microliter samples of this solution were injected directly onto a Teflon® Column 18″ × ¼″ OD packed with Chromosorb® P-AW-DMCS 60-80 mesh in a Packard® gas chromatograph equipped with flame ionization detector. Alcohol calibration standards were diluted in water in concentrations from 1 to 50 $mg \cdot dl^{-1}$.

Statistical Methods

All data are reported as mean ± SE. A group-by-treatments analysis of variance was used to compare the effects of midazolam infusion in alcohol-withdrawn *versus* sham-treated rats. Where significant group-treatment interactions existed, supplemental analyses of variance were used to determine midazolam treatment effects separately in alcohol- and sham-treated groups as described by Bruning and Kintz.[22] Independent *t* tests were used to compare withdrawal *versus* sham treatment during nitrous oxide anesthesia (no midazolam). These tests were planned before the start of the experiment to ensure that the tenet of probability theory was not violated.[22]

TABLE 1. Blood Pressure, Heart Rate, and Arterial Blood Gas Tensions during Nitrous Oxide Anesthesia and Midazolam Infusions

Midazolam Dose (mg/kg)	n	Blood Pressure (mmHg)	Heart Rate (min^{-1})	Pa_{CO_2} (mmHg)	Pa_{O_2} (mmHg)	pH
Sham treated						
0	8	141 ± 5	380 ± 12	37 ± 1	133 ± 11	7.39 ± 0.01
0.057	9	111 ± 4	386 ± 16	35 ± 1	150 ± 23	7.39 ± 0.01
0.575	10	111 ± 6	400 ± 9	37 ± 1	136 ± 6	7.40 ± 0.01
5.750	9	110 ± 6	389 ± 14	37 ± 1	126 ± 7	7.41 ± 0.01
Alcohol treated						
0	13	138 ± 2	451 ± 5*	35 ± 1	156 ± 13	7.39 ± 0.01
0.057	11	117 ± 4	438 ± 12	38 ± 1	172 ± 14	7.39 ± 0.01
0.575	13	120 ± 4	383 ± 6	38 ± 1	174 ± 8	7.41 ± 0.01
5.750	10	101 ± 3	344 ± 9	38 ± 1	141 ± 10	7.36 ± 0.01
Analyses of variance						
F for groups		0.791	1.522	2.817	7.716†	0.0
F for treatment		14.505†	4.993†	0.565	1.883	0.783
F for group × treat		1.756	10.522†	2.428	0.263	2.284

* $P < 0.05$ as analyzed by t test, sham- *versus* alcohol-treated rats. † $P < 0.01$ for analyses of variance.

Results

Preliminary behavioral analysis was performed on alcohol-withdrawn and sham-treated rats before anesthesia. Although no spontaneous seizures or tremors were seen, alcohol-treated rats consistently showed increased motor activity and hyperresponsiveness to touch and sound stimuli.

Arterial blood pressure, heart rate, and blood gas tensions are shown in table 1. Heart rate was increased in alcohol-withdrawn rats, but blood pressure was not statistically different between the two groups. Blood gases were controlled by artificial ventilation. Blood ethanol concentrations were measured and found to be undetectable (<1 $mg \cdot dl^{-1}$) in both test groups at the time of the study.

Comparison of right and left kidney blood flow in each rat suggested a good mixing of microspheres. The average difference in flow between the two kidneys was 5 ± 1% for all rats. Regional blood flow changes produced by alcohol withdrawal are shown in figure 1. Rats withdrawn from alcohol had elevated blood flow in brain, heart, and liver and decreased kidney blood flow during N_2O anesthesia compared with sham-treated rats. CMR_{O_2} was also increased significantly in alcohol-withdrawn rats (fig. 2).

Midazolam produced a significant decrease in heart rate in alcohol-withdrawn ($F = 22.32, P < 0.01$) but not sham-treated rats ($F = 0.74, P > 0.10$) and a significant difference in response between the two groups ($F = 10.52, P < 0.01$) (see table 1). Midazolam also decreased blood pressure 10–30% with no difference in response between the two treatment groups (table 1). The decrease in blood pressure produced by midazolam was seen even with the lowest subsedative dose, suggesting that both sham- and alcohol-withdrawn rats were sensitive to the cardiovascular effects of midazolam. Midazolam also produced significant decreases in cortical and subcortical CBF and myocardial blood flow in both alcohol-withdrawn and sham-treated rats (table 2). Cortical and subcortical CBF decreased significantly more in alcohol-withdrawn rats during midazolam treatment ($F = 5.11$, $F = 4.35$ respectively, $P < 0.01$). Midazolam produced a significant decrease in liver blood flow in alcohol-withdrawn ($F = 24.71$, $P < 0.01$) but not sham-treated rats ($F = 2.74$, $P < 0.05$). Renal blood flow increased with midazolam treatment in both alcohol ($F = 3.65$, $P < 0.05$) and sham-treated rats ($F = 3.63$, $P < 0.05$) but remained elevated in the sham-treated animals. As with blood pressure, the changes in blood flow produced by midazolam in cerebral, liver, and renal tissues were apparent even at the lowest dose (0.057 $mg \cdot kg^{-1}$) in alcohol-withdrawn rats. Skeletal muscle and intestinal blood flow did not change significantly in either test group during midazolam infusion. As indicated by

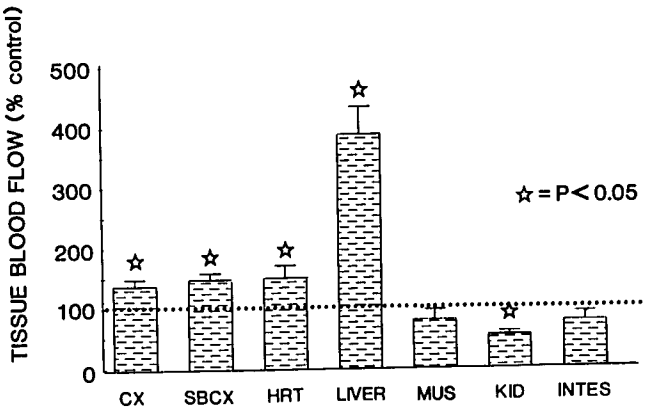

FIG. 1. Tissue blood flow in alcohol-treated rats under N_2O-anesthetized conditions, plotted as a per cent of sham-treated controls tested under the same treatment conditions. Significance indicates difference from sham-treated rats for each tissue.

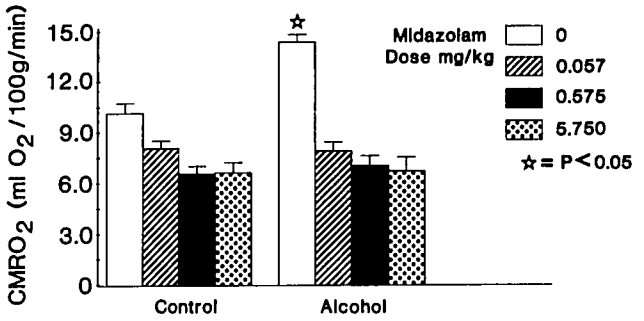

FIG. 2. Cerebral O_2 consumption changes in alcohol- and sham-treated (control) rats during midazolam infusion. Number of rats in each treatment group are shown in table 1. Significance value indicate differences between sham- and alcohol-treated rats at each midazolam dose. Midazolam produced a decrease in CMR_{O_2} in both alcohol- and sham-treated rat ($F = 26.95$, $P < 0.01$) and a significantly greater decrease in CMR_{O_2} in alcohol-treated rats ($F = 6.97$, $P < 0.01$).

analysis of variance, blood flow to muscle tissue was significantly depressed in alcohol-withdrawn rats when considered over the N_2O anesthetized and all midazolam treatment conditions. Midazolam also decreased CMR_{O_2} in both treatment groups ($F = 26.95$, $P < 0.01$) with a greater decrease in alcohol-withdrawn *versus* sham-treated rats ($F = 6.97$, $P < 0.01$) (fig. 2).

Discussion

There are several animal models that have been proposed to study the physiologic and behavioral effects of chronic ethanol administration and withdrawal. These include a miniature swine, which voluntarily drinks alcohol,[23] as well as mouse, rat, and dog models, which do not.[10,11,13,14,24-27] In each of these models it has been shown that chronic administration of alcohol will produce alcohol tolerance and dependence. Withdrawal of alcohol after dependence has produced results of classic withdrawal symptoms.[11,24,26] These symptoms depend on the degree of alcohol dependence and include hyperresponsiveness to external stimuli, stereotyped movements, tremor, rigidity, and production of stimulus-induced or spontaneous seizures.[11] Ethanol dependence and ethanol withdrawal symptoms can be induced in as little as 3–4 days in the rat by continual maintenance of severe intoxication (blood alcohol concentrations = 6.6 mg/ml).[10,11] However, the clinical relevance of such an extreme model may be questioned. A more moderate and longer term of alcohol intoxication can be performed in rats by combining ethanol with a nutritionally complete liquid diet.[13,14] Daily administration of this diet produces blood alcohol levels of 1–2 mg/ml throughout the day (unpublished results) and results in significant increases in tolerance to anesthetic drugs after 3 weeks of treatment.[12] As shown here, rats withdrawn from alcohol after 3 weeks of the diet showed signs of increased motor activity and hyperresponsiveness to external stimuli. Judging from previous reports, these symptoms may be indicative of moderate alcohol dependence as defined in humans and animals.[9,11,28,29]

Several changes were observed in alcohol-withdrawn rats when compared with their sham-treated controls. Alcohol-withdrawn rats had elevated CBF, myocardial and liver arterial blood flow, and a 47% decrease in renal blood flow. The increase in CBF paralleled the increase in CMR_{O_2}, suggesting normal coupling of flow and metabolism. Increases in myocardial blood flow in withdrawn rats were consistent with an increase in heart reate. Other studies also have shown that alcohol withdrawal produces cardiovascular stimulation.[9,29] Liver blood flow changes agree with the enhancement of liver enzymatic activity associated with alcohol dependence.[30]

TABLE 2. Regional Blood Flow during Nitrous Oxide Anesthesia and Intravenous Midazolam Infusion

Midazolam dose (mg/kg)	Cerebral Cortex	Subcortex	Heart	Liver	Muscle	Kidney	Intestine
Sham							
0	175 ± 11	140 ± 9	387 ± 37	20.7 ± 2.7	8.3 ± 1.3	237 ± 41	92 ± 13
0.057	130 ± 9	120 ± 8	510 ± 60	35.9 ± 6.2	12.0 ± 2.0	358 ± 50	105 ± 21
0.575	101 ± 7	104 ± 10	275 ± 26	21.0 ± 4.3	10.2 ± 1.4	336 ± 38	78 ± 10
5.750	100 ± 12	92 ± 9	290 ± 46	26.1 ± 6.8	10.9 ± 0.9	310 ± 26	92 ± 11
Alcohol withdrawn							
0	243 ± 18*	209 ± 15*	588 ± 75*	82.3 ± 9.0*	6.6 ± 1.3	125 ± 15*	70 ± 15
0.057	138 ± 8	129 ± 10	536 ± 52	29.0 ± 1.7	8.7 ± 2.7	210 ± 7	76 ± 6
0.575	135 ± 12	132 ± 11	450 ± 56	26.6 ± 7.1	6.0 ± 0.8	278 ± 20	94 ± 9
5.750	108 ± 12	112 ± 13	301 ± 46	22.6 ± 4.9	6.6 ± 1.3	336 ± 32	92 ± 18
Analyses of Variance							
F for groups	4.616†	6.116‡	7.499‡	7.301‡	7.947†	11.666‡	0.500
F for treatment	26.729‡	11.435‡	7.520‡	3.837†	1.410	3.722†	0.163
F for G × T	5.110‡	4.345†	1.929	14.505‡	0.536	1.342	1.131

Tissue blood flow reported as $ml \cdot 100\ g^{-1} \cdot min^{-1}$.
Number of animals in group given in table 1.
* $P < 0.05$ as analyzed by *t* test, alcohol- *versus* sham-treated (zero dose only).
† $P < 0.05$ for analyses of variance.
‡ $P < 0.01$ for analyses of variance.

Midazolam reversed many of the measured effects of alcohol withdrawal and returned regional blood flow toward sham-treated levels. Heart rate and CMR_{O_2} decreased more in alcohol-dependent rats together with CBF and liver blood flow. Midazolam also produced significant increases in renal blood flow, but these changes were not different between the two treatment groups. It may be noted that midazolam produced significant cardiovascular, regional blood flow and CMR_{O_2} with changes in alcohol-withdrawn rats even at subsedative doses (0.057 $mg \cdot kg^{-1}$). This is consistent with the sensitive neuromodulatory role of benzodiazepines at specific receptor sites.[31] It also suggests that many of the cardiovascular and metabolic stimulatory effects of alcohol withdrawal may be effectively treated in doses that do not produce behavioral sedation.

The ability of acute alcohol administration to produce central nervous system (CNS) depression and anesthesia in high doses and to potentiate these actions in combination with other anesthetic agents is well established. Chronic alcohol intake apparently produces tolerance to these effects. True alcohol withdrawal symptoms occur only after prolonged intake following adaptation to the pharmacologic actions of ethanol.[25] Minor symptoms may become evident with the daily consumption of 20 ounces of 100-proof alcohol for several days, but chronic daily consumption of 25–30 ounces of alcohol for 1–3 months are necessary to produce major withdrawal symptoms.[24] In humans, minor withdrawal symptoms include anorexia, insomnia, hallucinations, tremors, disorientation, and occasionally convulsions.[29] These symptoms begin within a few hours of withdrawal and peak at 10–30 h. Major withdrawal symptoms are seen in only a small percentage of patients and begin 60–80 h after cessation of drinking. These symptoms include autonomic hyperactivity with tremors, tachycardia, fever and anxiety, perceptual disorders, and hallucinations. The autonomic hyperactivity may involve beta-adrenergic receptors as the number and sensitivity of these receptors are increased following withdrawal.[32] Central beta-adrenergic mechanisms also may modulate increases in CMR_{O_2}. Propranolol treatment has been shown to lower the elevated brain metabolism seen following withdrawal and is used clinically to treat tremors and anxiety.[33] Data here suggest the benzodiazepine receptor also may alter the response to alcohol withdrawal, possibly by interacting with central B-adrenergic mechanisms.

A widespread distribution of benzodiazepine receptor subtypes in the brain and peripheral tissues suggests that the drug may act centrally as well as peripherally to alter tissue metabolism and regional vascular resistance.[31] The presence of high affinity, saturable stereospecific binding sites for benzodiazepines was first established in 1977.[34] The correlation between the potencies of benzodiazepine compounds in displacing (H^3)-diazepam binding *in vitro* and their potencies as anxiolytics, anticonvulsants, and muscle relaxants strongly suggest that these binding sites are pharmacologic receptors.[31] Biochemical evidence suggests that benzodiazepine receptors are physically as well as functionally associated with the gamma aminobutyric acid (GABA) receptor and the chloride ionophore. GABA acts at the benzodiazepine–GABA-receptor chloride ionophore complex by directly increasing chloride conductance and depressing neuronal activity.[35] The interaction of benzodiazepines and alcohol have been established in several reports. Alcohol may facilitate the action of benzodiazepines by enhancing benzodiazepine receptor affinity.[36] As an example, benzodiazepines have been shown to decrease CBF and CMR_{O_2} alone.[17] When given with alcohol, this effect is potentiated, producing a greater depression in brain metabolism than either alcohol or benzodiazepines given alone.[37] This potentiation suggests that alcohol may interact directly with the benzodiazepine–GABA receptor complex to enhance depression. This is supported by the fact that benzodiazepine antagonists will reverse the cerebral metabolic depression produced by midazolam–alcohol treatment.[37] Tolerance may be produced following chronic alcohol administration by alteration of the sensitivity and activity of the benzodiazepine receptor complex. This may explain why alcohol-withdrawn rats have an elevated CMR_{O_2} and why midazolam produces a greater decrease in brain metabolism in these animals.

The anesthesiologist is confronted with several complications in the management of the withdrawing alcoholic patient. He must be aware of and treat minor and major withdrawal symptoms as well as dealing with a generalized increase in tolerance to anesthetic agents.[29] Autonomic, cardiovascular, metabolic, and regional blood flow changes also may be apparent following alcohol withdrawal, increasing the risk of stroke, myocardial infarction, and renal failure. These results suggest that midazolam infusion may be of use in anesthetic management of the alcoholic because of its ability to decrease brain metabolism and heart work while increasing renal perfusion. The ability of midazolam to produce these changes in subanesthetic and often at subsedative doses suggests that many of the deleterious effects of alcohol withdrawal can be altered by very small drug doses. This may be of value in the treatment of alcoholics apart from surgical procedures. It also may be relevant to the anesthesiologist, particularly if he can "normalize" the alcoholic patient by midazolam pretreatment.

References

1. Dyer AR, Stamler J, Paul O, Berkson DM, Lepper MH, McKean H, Shekelle RB, Lindberg HA, Garside D: Alcohol consumption, cardiovascular risk factors, and mortality in two Chicago epidemiologic studies. Circulation 56:1067–1074, 1977
2. Orkin LR, Chen CH: Addiction, alcoholism, and anaesthesia. South Med J 70:1172–1174, 1977

3. Dundee JW, Howard AJ, Issac M: Alcohol and the benzodiazepines. The interaction between intravenous ethanol and chlordiazepoxide and diazepam. Quarterly Journal of Studies on Alcohol 32:960–968, 1971
4. Lee KYP, Cho MH, Dobkin AB: Effects of alcoholism, morphinism and barbiturate resistance on induction and maintenance of general anaesthesia. Can Anaesth Soc J 11:354–381, 1964
5. Johnstone RE, Kulp RA, Smith TC: Effects of acute and chronic ethanol administration on isoflurane requirement in mice. Anesth Analg 54:277–281, 1975
6. Wolfson B, Freed B: Influence of alcohol of anesthetic requirements and acute toxicity. Anesth Analg 59:826–830, 1980
7. Abreu EB, Emerson GA: Susceptibility to ether anesthesia of mice habituated to alcohol, morphine or cocaine. Anesth Analg 18: 294–300, 1939
8. Frankel D, Khanna JM, LeBlanc AE, Kalant H: Effect of p-chorophenayalanine on development of cross-tolerance between pentobarbital and ethanol. Can J Physiol Pharmacol 55:954–957, 1977
9. Haxholdt OS, Krintel JJ, Johansson G: Pre-operative alcohol infusion. Anaesthesia 39:240–245, 1984
10. Hemmingsen R, Barry DI: Adaptive changes in cerebral blood flow and oxygen consumption during ethanol intoxication in the rat. Acta Physiol Scand 106:249–255, 1979
11. Hemmingsen R, Barry DI, Hertz MM, Klinken L: Cerebral blood flow and oxygen consumption during ethanol withdrawal in the rat. Brain Res 173:259–269, 1979
12. Newman LM, Curran MA, Becker GL: Chronic alcoholism attenuates the anesthetic effects of diazepam (abstract). ANESTHESIOLOGY 61:A349, 1984
13. Goldman ME, Miller SS, Shorey RL, Erickson CK: Ethanol dependence produced in rats by nutritionally complete diets. Pharmacol Biochem Behav 12:503–507, 1980
14. Miller SS, Goldman ME, Erickson CK, Shorey RL: Induction of physical dependence on and tolerance to ethanol in rats fed a nutritionally complete and balanced liquid diet. Psychopharmacology 68:55–59, 1980
15. Rutz R, Asbury AJ, Thornton JA: Midazolam—does it cause resedation? ANESTHESIOLOGY 38:898–902, 1983
16. Massaut J, d'Hollander AA, Barvais L, Dubois-Primo J: Haemodynamic effects of midazolam in the anaesthetized patient with coronary artery disease. Acta Anaesthesiol Scand 27:299–302, 1983
17. Nugent M, Artru AA, Michenfelder JD: Cerebral metabolic, vascular and protective effects of midazolam maleate. ANESTHESIOLOGY 56:172–176, 1982
18. Gelman S, Reves JG, Harris D: Circulatory responses to midazolam anesthesia: emphasis on canine splanchnic circulation. Anesth Analg 62:135–139, 1983
19. Hales JRS, King RB, Fawcett AA: Observations on the validity of using "NEN-TRAC: Microspheres for measuring organ blood flow. Pflugers Arch 379:295–296, 1979
20. Hoffman WE, Miletich DJ, Albrecht RF: Repeated microsphere injections in rats. Life Sci 28:2167–2172, 1981
21. Heymann M, Payne B, Hoffman JIE, Rudolph AM: Blood flow measurements with radionuclide-labeled particles. Prog Cardiovasc Dis 36:1–17, 1980
22. Bruning JL, Kintz BL: Computational Handbook of Statistics. Glenview, Scott Forsman & Co, 1968, pp 38–123
23. Dexter JD, Tumbleson ME, Hutcheson DP, Middleton CC: Sinclair (S-1) miniature swine as a model for the study of human alcoholism. Ann NY Acad Sci 273:188–193, 1976
24. Essig CF, Lam RC: Convulsions and hallucinatory behavior following alcohol withdrawal in the dog. Arch Neurol 18:626–632, 1968
25. Falk JL, Samson HH, Winger G: Behavioral maintenance of high concentration of blood ethanol and physical dependence in the rat. Science 177:811–813, 1969
26. Goldstein DB, Pal N: Alcohol dependence produced in mice by inhalation of ethanol: grading the withdrawal reaction. Science 172:288–290, 1971
27. Goldstein DB: Alcohol withdrawal reactions in mice: effects of drugs that modify neurotransmission. J Pharmacol Exp Ther 186:1–9, 1973
28. Morton RC, Adriani J: Drug dependence: important considerations from the anesthesiologist's viewpoint. Anesth Analg 47:472, 1968
29. Wolfson B, Freed B: Influence of alcohol on anesthetic requirements and acute toxicity. Anesth Analg 59:826–830, 1980
30. Van Dyke RA: Enflurane, isoflurane, and methoxyflurane metabolism in rat hepatic microsomes from ethanol-treated animals. ANESTHESIOLOGY 58:221–224, 1983
31. Skolnick P, Paul SM: Benzodiazepine receptors in the central nervous system. Int Rev Neurobiol 23:103–140, 1982
32. Banerjee SP, Sharma VK, Khanna JM: Alterations in B-adrenergic receptor binding during ethanol withdrawal. Nature 276:407–409, 1968
33. Edwards R, Mosher VB: Alcohol abuse, anaesthesia and intensive care. Anaesthesia 35:474–489, 1980
34. Squires R, Braestrup C: Benzodiazepine receptors in rat brain. Nature 266:732–734, 1977
35. Bolme P, Fuxe K: Possible involvement of GABA mechanisms in central cardiovascular and respiratory control. Studies on the interaction between diazepam, picrotoxin and clonidine. Med Biol 55:301–309, 1977
36. Hunt WA: The effect of ethanol of GABAergic transmission. Neurosci Biochem Rev 7:87–95, 1983
37. Van Gorder PN, Hoffman WE, Baughman V, Albrecht RF, Miletich DJ, Guzman S, Cook JM: Midazolam-ethanol interactions and reversal with a benzodiazepine antagonist. Anesth Analg 64:129–135, 1985