THE CARDIOVASCULAR EFFECTS OF DIAZEPAM AND OF DIAZEPAM AND PANCURONIUM DURING FENTANYL AND OXYGEN ANAESTHESIA

WEN-SHIN LIU,* ARUN V. BIDWAI,† THEODORE H. STANLEY,‡
EDWARD A. LOESER,† AND VANAMALA BIDWAI§

FENTANYL, 1-(2-phenethyl)-4-(n-propionylpiperidino)-piperidine, in doses of 0.02 mg/kg, has little effect on left ventricular dynamics in the neurally intact, blood-perfused dog heart.^{1,2} Large doses of the drug (0.05–2.0 mg/kg) administered together with oxygen have been shown to maintain normal arterial blood pressure and cardiac output in the dog and to produce adequate anaesthesia for thoracotomy.³ Preliminary data indicate that 0.01–0.5 mg/kg of fentanyl with oxygen produces no significant change in cardiovascular dynamics in patients with mitral stenosis undergoing mitral valve replacement.⁴ However, the amnesic qualities of these doses of fentanyl appear to be inferior to equi-anaesthetic doses of morphine.⁴ This suggests that an amnesic supplement will be required with fentanyl for complete anaesthesia. While the addition of droperidol or nitrous oxide is known to significantly decrease myocardial contractility and cardiovascular dynamics after large doses of fentanyl,^{1,5} the effects of diazepam, another popular amnesic, on myocardial mechanics and cardiovascular dynamics after fentanyl are unknown. This study was undertaken to investigate the cardiovascular effects of diazepam and of diazepam and pancuronium after 0.5 mg/kg of fentanyl in dogs.

METHODS

Thirteen fasted, mongrel dogs of 16 kg average weight (range 12–20 kg) served as the experimental animals. Each was premedicated with atropine (0.3–0.5 mg) intramuscularly one hour before induction of anaesthesia and had an intravenous infusion of lactated Ringer's solution (10 ml/kg/hour) started in a foreleg immediately before anaesthesia. Following this anaesthesia was induced with 2 to 3 mg/kg of sodium thiopentone and each animal was then given succinylcholine 2 mg/kg intravenously. The trachea was intubated and the lungs were ventilated with 100 per cent oxygen at a tidal volume of 5 to 12 ml/kg with a volume limited respirator. The minute volume was adjusted as necessary to maintain P_{aCO_2} between 30 torr and 35 torr as measured in aortic blood every 15 to 30 minutes. Basal anaesthesia was maintained with thiopentone 1 to 3 mg/kg administered every 15 to 20 minutes throughout the experiment.

*Fellow in Anaesthesiology.

†Instructor in Anaesthesiology.

‡Associate Professor of Anaesthesiology.

§Adjunct Fellow in Anaesthesiology.

From the Department of Anesthesiology, University of Utah College of Medicine, 50 North Medical Drive, Salt Lake City, Utah, 84132.

TABLE I
CARDIOVASCULAR EFFECTS OF FENTANYL AND FENTANYL PLUS DIAZEPAM

	Stroke volume (ml)	Cardiac output (l/min)	Heart rate (beats/min)	Peripheral vascular resistance (PRU)	Blood pressure		
					Systolic (mm Hg)	Mean (mm Hg)	Diastolic (mm Hg)
Control (pre-fentanyl)	25 ±8	3.2 ±1.5	142 ±14	216 ±47	161 ±34	137 ±22	120 ±24
Fentanyl (0.1 mg/kg)	±26 ±6	2.2* 1.2	88† ±27	258 ±72	145† ±23	115† ±19	93† ±22
Fentanyl (0.2 mg/kg)	26 ±8	2.1* ±1.4	79† ±22	279 ±58	146† ±21	117† ±18	94† ±19
Fentanyl (0.3 mg/kg)	27 ±4	2.1* ±1.5	80† ±19	242 ±78	142† ±25	111† ±20	87† ±20
Fentanyl (0.4 mg/kg)	28 ±9	2.2* ±1.4	80† ±14	245 ±67	143† ±24	110† ±19	86† ±20
Fentanyl (0.5 mg/kg)	29 ±10	2.2* ±1.2	84† ±15	230 ±49	142† ±19	110† ±17	84† ±19
Fentanyl (0.5 mg/kg)† Diazepam (0.5 mg/kg)	29 ±8	2.8*§ ±1.0	96†¶ ±18	193 ±65	136† ±13	104† ±14	81† ±14
Fentanyl (0.5 mg/kg)† Diazepam (1.0 mg/kg)	26§ ±5	2.5* ±1.2	95†¶ ±18	165¶* ±49	121†¶ ±13	90†¶ ±12	67†¶ ±13

*P < 0.05, students paired t-test when compared to control (pre-fentanyl) values.

†P < 0.01, students paired t-test when compared to control (pre-fentanyl) values.

‡P < 0.005, students paired t-test when compared to control (pre-fentanyl) values.

§P < 0.05, students paired t-test when compared to fentanyl (0.5 mg/kg) values.

¶P < 0.01, students paired t-test when compared to fentanyl (0.5 mg/kg) values.

||P < 0.05, students paired t-test when compared to fentanyl (0.5 mg/kg) + diazepam (0.5 mg/kg).

Immediately after intubation a teflon catheter was implanted in a femoral artery through a small groin incision and threaded 20 to 35 cm into the central aorta. The aortic pressure catheter was connected through a Statham P₂₃ Db arterial pressure transducer to a central digital computer substation (Tektronix memory oscilloscope) in the laboratory. After appropriate dye dilution calibration, Warner, Gardner and Toronto's⁶ method of analyzing the central aortic pulse pressure curve was used to determine arterial blood pressure, cardiac output, heart rate, stroke volume and peripheral arterial resistance.

Following completion of the preparatory procedures, a period of five to ten minutes was allowed to elapse before control cardiovascular measurements were obtained. Fentanyl citrate in lactated Ringer's solution was then administered intravenously as a continuous infusion at a rate of 0.3 mg/minute. Cardiovascular measurements were repeated after each 0.1 mg/kg increment of fentanyl. Following 0.5 mg/kg of fentanyl and with the fentanyl infusion continuing, 1.0 mg/kg of diazepam was given in increments of 0.5 mg/minute. Additional data were collected after 0.5 mg/kg and 1.0 mg/kg of diazepam. Finally a single dose of pancuronium bromide (1.0 mg/kg) was administered intravenously and cardiovascular measurements repeated one, three, five, seven and ten minutes later. All data were examined for significance using Student's paired t-test.

TABLE II
CARDIOVASCULAR EFFECTS OF FENTANYL, FENTANYL PLUS DIAZEPAM AND
FENTANYL PLUS DIAZEPAM AND PANCURONIUM

	Stroke volume (ml)	Cardiac output (l/min)	Heart rate (beats/min)	Peripheral vascular resistance (PRU)	Blood pressure		
					Systolic (mm Hg)	Mean (mm Hg)	Diastolic (mm Hg)
Control (pre-fentanyl)	25 ±8	3.2 ±1.5	142 ±14	216 ±47	161 ±34	137 ±22	120 ±24
F (0.5 mg/kg)†	26	2.5*	95†	165*	121†	90†	67†
D (1.0 mg/kg)	±5	±1.2	±18	±49	±13	±12	±13
F (0.5 mg/kg)†							
D (1.0 mg/kg)†	25	2.6*	100†	174*	126†	92†	74†
Pan (0.1 mg/kg)	±7	±0.9	±21	±36	±21	±27	±23
<i>After 1 Minute</i>							
F (0.5 mg/kg)†							
D (1.0 mg/kg)†	24	3.0§	128¶	189§	139§	108§	86*§
Pan (0.1 mg/kg)	±8	±1.1	±24	±34	±31	±31	±30
<i>After 3 Minutes</i>							
F (0.5 mg/kg)†							
D (1.0 mg/kg)†	23	3.1§	131¶	194§	147¶	111§	90§
Pan (0.1 mg/kg)	±9	±1.2	±26	±32	±32	±29	±31
<i>After 5 Minutes</i>							
F (0.5 mg/kg)†							
D (1.0 mg/kg)†	24	2.8§	127¶	191§	140¶	108§	88§
Pan (0.1 mg/kg)	±7	±1.1	±27	±37	±38	±32	±29
<i>After 7 Minutes</i>							
F (0.5 mg/kg)†							
D (1.0 mg/kg)†	24	2.8§	125§	187§	138§	107§	86*§
Pan (0.1 mg/kg)	±6	±1.1	±24	±38	±31	±27	±30
<i>After 10 Minutes</i>							

*P < 0.05, students paired t-test when compared to control (pre-fentanyl) values.

†P < 0.01, students paired t-test when compared to control (pre-fentanyl) values.

‡P < 0.005, students paired t-test when compared to control (pre-fentanyl) values.

§P < 0.05, students paired t-test when compared to fentanyl (0.5 mg/kg) + diazepam (1.0 mg/kg) values.

¶P < 0.01, students paired t-test when compared to fentanyl (0.5 mg/kg) + diazepam (1.0 mg/kg) values.

F = Fentanyl, D = Diazepam, Pan = Pancuronium.

RESULTS

Changes in cardiovascular dynamics after fentanyl and fentanyl plus diazepam are summarized in Table I. Changes after fentanyl, diazepam and pancuronium are given in Table II. Fentanyl (0.1 mg/kg) caused a significant decrease in heart rate ($P < 0.005$), cardiac output ($P < 0.05$), and systolic ($P < 0.01$), mean ($P < 0.005$) and diastolic ($P < 0.005$) arterial blood pressures but did not significantly change stroke volume or peripheral vascular resistance. Additional fentanyl caused no significant further change in any of these parameters. No dog had a systolic arterial blood pressure of less than 100 mm Hg, a heart rate below 69 beats/minute or a cardiac output of less than 1.6 litres/minute (127 ml/min/kg) whatever the dose of fentanyl.

Administration of diazepam (0.5 mg/kg) after fentanyl did not significantly alter stroke volume, arterial blood pressure or peripheral vascular resistance but did increase heart rate ($P < 0.01$) and cardiac output ($P < 0.05$). Additional

diazepam did not further change the heart rate but did reduce stroke volume ($P < 0.05$), cardiac output ($P < 0.05$), arterial blood pressure ($P < 0.01$) and peripheral vascular resistance ($P < 0.01$).

Administration of pancuronium after fentanyl and diazepam was followed after three minutes by significant elevations in heart rate ($P < 0.01$), cardiac output ($P < 0.05$) and arterial blood pressure ($P < 0.05$) which were maintained throughout the rest of the study. There was no significant difference in mean heart rate, systolic and mean arterial blood pressure, peripheral vascular resistance and cardiac output when values obtained prior to fentanyl and those obtained three minutes after pancuronium were compared. Pancuronium was not followed by significant changes in stroke volume.

DISCUSSION

In a recent report³ we demonstrated that in the unpremedicated dog 2 mg/kg of fentanyl produced reductions in heart rate and cardiac output which were maximal (52 and 34 per cent respectively) after 0.5 mg/kg. Fentanyl 1.75 mg/kg also reduced arterial blood pressure and peripheral vascular resistance and increased stroke volume. We pointed out that while all changes were significant the lowest cardiac output measured was similar to that of normal, unanaesthetized, unstimulated dogs of the same age and weight and that after fentanyl 2 mg/kg systolic arterial blood pressure was usually above 120 mm Hg. We also indicated that fentanyl-induced bradycardia could be almost completely reversed with atropine 0.5 mg/kg intravenously.

On the basis of these findings, we suggested that large doses of fentanyl and oxygen might be an attractive alternative to morphine and oxygen anaesthesia in critically ill patients. However, we advised that before fentanyl and oxygen is used as the sole anaesthetic in man, investigation in two areas be undertaken: prevention of the profound bradycardia caused by large doses of the drug; and determination of the cardiovascular effects of adding certain amnesic drugs after large doses of fentanyl because in equi-analgesic doses fentanyl is a poorer amnesic than either meperidine or morphine.⁷

The results of this study demonstrate that premedication with atropine 0.025 mg/kg (the recommended premedication dose of atropine in dogs⁸) while increasing heart rate an average of 11 per cent (128 ± 16 in our previous study versus 142 ± 14 in this study) did not significantly change pre-induction cardiovascular parameters from that in our previous study and only slightly altered the response of these parameters to fentanyl 0.5 mg/kg. Heart rate was decreased 40 per cent, cardiac output 32 per cent and systolic arterial blood pressure 12 per cent while peripheral vascular resistance and stroke volume remained unchanged. These data as well as those of our previous study indicate that the reductions in output and blood pressure after large doses of fentanyl are primarily due to bradycardia. They also suggest that higher vagolytic doses of atropine must be used to counteract the well known vagal stimulating properties of fentanyl. However, while vagolytic doses of atropine (1 mg/kg) have been shown to more than double heart rate in dogs and might be effective in preventing fentanyl-induced bradycardia, it is likely that doses of atropine which produce even less increase in pre-

induction heart rate would be unsafe in critically ill patients with marginal cardiac reserve.

Because of its benign effects on cardiovascular dynamics both in normal patients⁹ and in those with marginal cardiovascular reserve,^{10,11} diazepam has been advocated as an induction agent¹² and as a supplement to nitrous oxide-morphine anaesthesia¹³ in poor risk patients. In this study diazepam 0.5 mg/kg following a like dose of fentanyl resulted in a 20 per cent increase in heart rate and a 22 per cent increase in cardiac output but little change in other cardiovascular parameters. An additional 0.5 mg/kg of diazepam produced significant decreases in stroke volume and cardiac output and a marked reduction in arterial blood pressure and peripheral arterial resistance.

While our data do not demonstrate a mechanism they do suggest that small doses of diazepam (0.5 mg/kg) stimulate and large doses (1.0 mg/kg) depress the cardiovascular system of dogs after large doses of fentanyl. Myocardial stimulation after diazepam (0.1 mg/kg) has also been reported by Abel, Starosch and Reis¹⁴ during cardiopulmonary bypass in dogs anaesthetized with pentobarbitone. In experiments in which heart rate and arterial blood pressure were held constant they showed that diazepam produced coronary artery dilatation and increased myocardial contractility. They suggested that since diazepam does not influence the contractile state of isolated ventricular papillary muscle,¹⁵ the positive inotropic effect of the drug probably was due to improved oxygen delivery to the heart or increased sympathetic nervous activity. In a subsequent study in patients given diazepam 0.1 mg/kg for sedation following cardiac operations Abel and Reis¹¹ found evidence of beta-adrenergic stimulation, that is increases in stroke volume and cardiac index and a decrease in peripheral vascular resistance. Unfortunately, plasma catecholamine concentrations were not measured. Plasma and urine catecholamine concentrations also were not measured in the present study, but preliminary data¹⁶ obtained from another series of dogs subjected to somewhat larger doses of fentanyl and doses of diazepam similar to those used in this study, indicate that plasma epinephrine and norepinephrine concentrations and urine catecholamine excretion are decreased rather than increased by diazepam.

Significant cardiovascular depression after diazepam, while uncommon, has also been reported both in experimental animals¹⁷ and in man.¹⁸ Chai and Wang¹⁷ found that diazepam 0.1 mg/kg produced reductions in resting blood pressure, heart rate and cardiac contractile force in the cat which were more marked in anaesthetized than in non-anaesthetized animals. In supine unanesthetized man diazepam 5 to 10 mg has been found not to alter cardiovascular dynamics significantly, or to produce only a slight depression.^{10,11} On the other hand, diazepam 12 to 20 mg has been reported to produce marked reductions in stroke volume, cardiac output and arterial blood pressure¹⁸ and, on occasion, to result in complete cardiovascular collapse.¹⁹ In man anaesthetized with morphine Stanley²⁰ has shown that as little as 5 mg of diazepam reduced cardiac output and stroke volume 19 and 12 per cent respectively, decreased heart rate and systolic arterial blood pressure 7 per cent and increased peripheral arterial resistance 22 per cent in 10 minutes. An additional 5 mg of diazepam produced further alterations in most parameters.

All this shows that while small doses of diazepam are benign, larger doses may produce significant cardiovascular depression, especially if they follow other anaesthetics. The cardiovascular effects of diazepam as well as the doses required for amnesia after large doses of fentanyl have not been established in man. If diazepam produces similar changes in man as it does in the dog after large doses of fentanyl, it would appear that the anaesthetic technique of fentanyl and diazepam will only be of benefit if relatively small amounts of the latter are required for amnesia.

Absence of adverse circulatory effects, especially reductions in blood pressure and pulse rate, are considered advantages of pancuronium over d-tubocurarine and have resulted in recent increased popularity of this newer muscle relaxant.^{21,22} Smith and co-workers²³ have shown that pancuronium 0.088 to 0.176 mg/kg causes a slight rise in heart rate, arterial blood pressure and cardiac output in dogs. Stoelting²¹ found significant increases in heart rate, cardiac output and arterial blood pressure and no changes in stroke volume or peripheral vascular resistance after pancuronium 0.08 mg/kg in man anaesthetized with halothane. It has been suggested,²² on the basis of significantly smaller increases in heart rate after pre-medication with atropine than before, that the cardiac stimulating properties of pancuronium are primarily related to cardiac vagal inhibition. This has been confirmed by Bonta²⁴ and again by Saxena and Bonta²⁵ who showed that pancuronium 0.05 mg/kg completely and selectively blocked cardiac muscarinic cholinergic receptors to vagal stimulation as well as that by acetylcholine, carbamylcholine and methacholine. It would seem reasonable, considering the above, that pancuronium might be a particularly good muscle relaxant to use to counteract bradycardia after large doses of fentanyl. Our findings in this study confirm this impression. Pancuronium produced 35 and 20 per cent increases respectively in heart rate and cardiac output within three minutes thereby returning both parameters to pre-fentanyl levels. Pancuronium also produced 15 per cent elevations in systolic arterial blood pressure and peripheral vascular resistance. These findings suggest that cardiac muscarinic blocking effects of pancuronium are capable of completely reversing the profound vagal stimulating action of fentanyl. Unfortunately, we did not determine whether prior or simultaneous administration of pancuronium will prevent bradycardia induced by fentanyl. If subsequent studies confirm that either of these can indeed block bradycardia after large doses of fentanyl in dogs, it would appear warranted to investigate in man the cardiovascular and amnesic properties of large doses of fentanyl and pancuronium, or of fentanyl, pancuronium and small doses of diazepam.

SUMMARY

The cardiovascular effects of diazepam 0.5 and 1.0 mg/kg and diazepam with pancuronium 0.1 mg/kg after fentanyl 0.5 mg/kg were determined in thirteen dogs premedicated with atropine. Fentanyl produced significant reductions in heart rate, cardiac output and arterial blood pressure. Administration of 0.5 mg/kg of diazepam after fentanyl did not significantly alter stroke volume, arterial blood pressure or peripheral vascular resistance but did increase heart rate and cardiac output. Additional diazepam did not further change the heart rate, but did reduce stroke volume, cardiac output, arterial blood pressure and peripheral vascular

resistance. Administration of pancuronium after fentanyl and diazepam produced marked elevations in heart rate, cardiac output and arterial blood pressure. There was no difference in mean heart rate and cardiac output when values prior to fentanyl and those obtained three minutes following pancuronium were compared. These data demonstrate that large doses of fentanyl decrease heart rate, cardiac output and arterial blood pressure in dogs premedicated with atropine but that these changes can be partially reversed with diazepam 0.5 mg/kg and completely antagonized with pancuronium 0.1 mg/kg.

RÉSUMÉ

Des travaux antérieurs ont montré que le Fentanyl n'a pas d'effet déprimeur sur la contractilité du myocarde du chien à petites comme à fortes doses. (0, 0,2 mg/kg-2 mg/kg).

Employé seul pour l'anesthésie clinique, il assure la stabilité cardiovasculaire mais sa puissance amnésique est nettement inférieure à celle de la Morphine. Comme l'addition au Fentanyl à hautes doses de protoxyde d'azote et de Droperidol déprime de façon sensible la contractilité du myocarde (1, 5), on a voulu savoir si le Diazepam et le Pancuronium pouvaient s'employer comme adjuvants sans entraîner cette dépression myocardique.

On a donc administré du Fentanyl à des chiens selon trois différents régimes: 1. Fentanyl seul, 2. Fentanyl avec Valium, 3. Fentanyl avec Valium-Pancuronium. Les effets cardiovasculaires de ces combinaisons ont été étudiés en mesurant le volume d'éjection, le débit et la fréquence cardiaques, la résistance périphérique et les pressions artérielles, systolique, diastolique et moyenne.

Méthode: Le Fentanyl étant administré à raison de 0,3 mg/min par voie intraveineuse, les mesures furent effectuées à divers stades de l'opération:

1. Après chaque dose cumulative de 0,1 mg/kg et ce jusqu'à un total de 0,5 mg/kg.
2. Après Fentanyl 0,5 mg/kg et Diazepam 1 mg/kg.
3. Après Fentanyl 0,5 mg/kg et Diazepam 1 mg/kg.
4. Après addition de 0,1 mg/kg de Pancuronium, les mesures étant effectuées à 1, 3, 5, 7 et 10 minutes après l'injection.

Résultats: Voir les tableaux 1 et 2. Le Fentanyl seul à 0,1 mg/kg a occasionné une diminution significative de la fréquence et du débit cardiaque et des pressions artérielles, systolique, diastolique et moyenne, sans modification de la résistance périphérique ou du volume d'éjection. L'écart maximal observable de ces différents paramètres était déjà atteint à cette dose.

L'addition de Diazepam à la dose de 0,5 mg/kg a augmenté de façon significative la fréquence et le débit cardiaques sans modification du volume d'éjection, de la pression artérielle ou de la résistance périphérique; cependant, à la dose de 1 mg/kg, le Diazepam diminue le volume d'éjection, la résistance périphérique et toutes les pressions artérielles; de plus, le débit cardiaque revient au niveau observé avant l'injection de Diazepam.

Trois minutes après l'injection du Pancuronium, on voit apparaître une tachycardie significative, une augmentation du débit cardiaque, de la résistance périphérique et des pressions artérielles. Ces phénomènes, une fois installés, ont persisté tout au long de l'expérience.

Ces constatations, chez le chien, démontrent:

1. Que le Fentanyl à fortes doses, malgré une prémédication à l'Atropine, entraîne chez le chien une bradycardie, une réduction du débit cardiaque et une diminution de la pression artérielle,
2. Que ces effets cardiovasculaires peuvent être partiellement renversés par l'administration de Diazepam à dose de 0,5 mg/kg et
3. Que ces effets cardiovasculaires peuvent être complètement corrigés par du Pancuronium à dose de 0,1 mg/kg.

REFERENCES

1. OSTHEIMER, G.W., SHANAHAN, E.A., GUYTON, R.A., DACCETT, W.M., & LOWENSTEIN, E. Effects of fentanyl and droperidol on canine left ventricular performance. *Anesthesiology* 42: 288 (1975).
2. FREYE, E. Cardiovascular effects on high doses of fentanyl, meperidine and naloxone in dogs. *Anesth. Analg. (Cleve.)* 53: 40 (1974).
3. LIU, W.S., BIDWAI, A.V., STANLEY, T.H., & ISERN-AMARAL, J. Cardiovascular dynamics after large doses of fentanyl and fentanyl plus nitrous oxide in dogs. *Anesth. Analg.* 55: 168 (1976).
4. ISERN-AMARAL, J. (Unpublished data.)
5. STOETLING, R.K., GIBBS, P.S., CREASSER, C.W., & PETERSON, C. Hemodynamic and ventilatory responses to fentanyl, fentanyl-droperidol, and nitrous oxide in patients with acquired valvular heart disease. *Anesthesiology* 42: 319 (1975).
6. WARNER, H.R., GARDNER, R.M., & TORONTO, A.R. Computer-based monitoring of cardiovascular functions in postoperative patients. *Circulation* 38: 68 (1968).
7. MOSTERT, J.W., TRUDNOWSKI, R.J., SENIFF, A.M., MOORE, R.H., & CASE, R.W. Clinical comparison of fentanyl with meperidine. *J. Clin. Pharmacol.* 8: 382 (1968).
8. SOMA, L.R. Preanesthetic medication. *Textbook of Veterinary Anesthesia*. Edited by Soma, L.R. Baltimore, Williams & Wilkins, pp. 138 (1971).
9. WYANT, G.M. & STUDNEY, L.J. A study of diazepam for induction of anesthesia. *Canad. Anaesth. Soc. J.* 17: 166 (1970).
10. DALEN, J.E., EVANS, G.L., BANAS, J.S., BROOKS, H.L., PARASKOS, J.A., & DEXTER, L. The hemodynamic and respiratory effects of diazepam (Valium). *Anesthesiology* 30: 259 (1969).
11. ABEL, R.M. & REIS, R.L. Intravenous diazepam for sedation following cardiac operations: Clinical and hemodynamics assessments. *Anesth. Analg. (Cleve.)* 50: 244 (1971).
12. KNAPP, R.B. & DUBOW, H.S. Diazepam as an induction agent for patients with cardiopulmonary disease. *South. Med. J.* 63: 1451 (1970).
13. EISENBERG, L. & KWAN, A.M. Neuroleptanaesthesia with diazepam morphine in poor risk surgical patients. *Canad. Anaesth. Soc. J.* 18: 465 (1971).
14. ABEL, R.M., STAROSCIK, R.N., & REIS, R.L. The effects of diazepam (Valium) on left ventricular function and systemic vascular resistance. *J. Pharmacol. Exp. Ther.* 173: 364 (1970).
15. PRINDLE, K.H., GOLD, H.K., CARDON, P.V., & EPSTEIN, S.E. Effects of psychopharmacologic agents on myocardial contractility. *J. Pharmacol. Exp. Ther.* 173: 133 (1970).
16. LIU, W.S. & BIDWAI, A.V. (Unpublished data.)
17. CHAI, C.Y. & WANG, S.C. Cardiovascular actions of diazepam in the cat. *J. Pharmacol. Exp. Ther.* 154: 271 (1966).
18. JENKINSON, J.L., MACRAE, W.R., SCOTT, D.B., & GOULD, J.F. Haemodynamic effects of diazepam used as a sedative for oral surgery. *Brit. J. Anaesth.* 46: 294 (1974).
19. ROLLASON, W.N. Diazepam as an intravenous induction agent for general anaesthesia. *Diazepam in Anaesthesia*. Edited by Knight, P.F. & Burgess, C.G. Bristol, Wright, pp. 70 (1968).
20. STANLEY, T.H., BENNETT, G.M., LOESER, E.A., KAWAMURA, R., & SENTKER, C.R. Effects of diazepam and droperidol on cardiovascular dynamics during morphine anesthesia. *Anesthesiology* 44: 255 (1976).
21. STOETLING, R.K. The hemodynamic effects of pancuronium and d-tubocurarine in anesthetized patients. *Anesthesiology* 36: 612 (1972).

22. KELMAN, G.R. & KENNEDY, B.R. Cardiovascular effects of pancuronium in man. *Brit. J. Anaesth.* 43: 335 (1971).
23. SMITH, G., PROCTOR, D.W., & SPENCE, A.A. A comparison of some cardiovascular effects of tubocurarine and pancuronium in dogs. *Brit. J. Anaesth.* 42: 923 (1970).
24. BONTA, I.L. Pharmacological interaction between pancuronium bromide and anaesthetics. *Eur. J. Pharmacol.* 4: 83 (1968).
25. SAXENA, P.R. & BONTA, I.L. Specific blockade of cardiac muscarinic receptors by pancuronium bromide. *Arch. Int. Pharmacodyn.* 189: 410 (1971).