The Hemodynamic and Respiratory Effects of Diazepam (Valium®)

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Diazepam, 5–10 mg, was given intravenously to treat anxiety occurring during cardiac catheterization in 15 patients. Anxiety was effectively relieved in 11 patients. Hemodynamic and ventilatory parameters were assessed before, and ten and 30 minutes after diazepam. The cardiac index decreased significantly in only three patients, each of whom had a control cardiac index in the high-normal range. No significant changes occurred in patients whose control cardiac indexes were below normal. Systolic blood pressure decreased by more than 10 mm Hg in eight patients. Pulmonary arterial pressure, heart rate, stroke volume and pulmonary and systemic resistance did not change significantly. Hypoventilation occurred in all patients. Ten minutes after diazepam minute ventilation had decreased by 28 per cent and tidal volume by 23 per cent. $Paco_2$ increased by 5 mm Hg and Pao_2 decreased by 10 mm Hg. The observed changes in blood pressure and ventilation were without clinical correlates and did not require therapy.

DIAZEPAM (Valium®), a benzodiazepine derivative, has been widely used for the treatment of anxiety,[1] and for muscle spasm associated with acute and chronic neuromuscular and musculoskeletal disorders.[2] It has been reported to be a more potent tranquilizer and muscle relaxant than its analog, chlordiazepoxide (Librium®).[3] The principal side effects are drowsiness, vertigo and ataxia.

Recently, diazepam has been evaluated for the treatment of seizures,[4] as preanesthetic medication,[5] and in preparation for endoscopy,[6] bronchoscopy[7] and cardioversion.[8] The increasing parenteral use of this agent in patients who are often elderly or have heart disease underscores the need for an assessment of its acute hemodynamic and respiratory effects.

During a six-month period, diazepam was given intravenously to treat anxiety occurring during diagnostic cardiac catheterization in 15 patients. Use in this setting allowed evaluation of its acute hemodynamic and respiratory effects.

Methods

Diazepam was administered after baseline hemodynamic and respiratory parameters had been measured. These parameters were reassessed ten and 30 minutes after the drug had been administered.

The 15 patients ranged in age from 24 to 65 years. Twelve patients had rheumatic heart disease, two had congenital heart disease, and one was found at catheterization to have no significant heart disease. No preoperative medication was given. Ten of the 15 patients had hemodynamic evidence of left heart failure at the time of cardiac catheterization (left ventricular end-diastolic pressure > 12 mm Hg).

Diazepam was injected through a catheter positioned in the pulmonary artery, in a dose of 5 to 10 mg (table 1), over a three-minute period.

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TABLE 1. Ventilatory Changes

Patient	Body Wt. (kg)	Dose (mg)	Minute Ventilation (l/min)			Respiratory Rate			Tidal Volume (ml)			Pa_{O_2} (mm Hg)			Pa_{CO_2} (mm Hg)			pH		
			C*	10**	30***	C	10	30	C	10	30	C	10	30	C	10	30	C	10	30
1	82	5.0	9.1	5.4	5.6	20	25	30	234	210	180	100	92	90	36	40	40	7.43	7.42	7.41
2	61	10.0	6.0	6.2	6.7	16	16	13	430	387	515	101	93	93	31	33	32	7.53	7.48	7.48
3	74	10.0	—	—	—	—	—	—	—	—	—	85	76	82	36	47	41	7.54	7.46	7.49
4	57	10.0	6.7	3.0	4.0	13	14	15	510	215	200	94	66	74	—	—	—	—	—	—
5	55	7.5	8.6	5.6	7.8	30	18	22	287	310	355	89	77	84	37	43	45	7.46	7.43	7.42
6	42	7.5	—	—	—	—	—	—	—	—	—	86	82	88	47	40	42	7.42	7.40	7.45
7	73	10.0	—	—	—	—	—	—	—	—	—	100	93	107	36	37	33	7.49	7.48	7.51
8	53	7.5	—	—	—	20	18	13	—	—	—	—	—	—	—	—	—	—	—	—
9	42	5.0	—	—	—	14	15	16	—	—	—	91	89	86	33	39	33	7.45	7.47	7.48
10	83	10.0	7.7	7.4	9.4	20	19	15	385	380	620	89	111	98	47	52	41	7.38	7.45	7.46
11	54	7.5	—	—	—	17	15	14	—	—	—	90	82	87	34	44	33	7.47	7.41	7.47
12	55	7.5	9.2	5.9	5.9	17	13	12	540	454	492	85	71	80	31	36	33	7.51	7.49	7.52
13	50	7.5	10.6	5.6	9.0	17	14	10	625	400	564	108	85	106	37	40	34	7.60	7.45	7.55
14	74	7.5	8.2	6.2	7.6	25	24	28	327	258	250	64	46	51	45	53	46	7.45	7.41	7.44
15	76	7.5	8.6	6.6	6.9	19	24	19	450	275	360	75	60	73	49	54	45	7.51	7.46	7.47
Mean			8.1	5.8	7.0	20	18	18	422	323	401	90	80	86	38	43	38	7.48	7.45	7.47
S.E.			0.46	0.40	0.57	1.5	1.2	1.7	42	29	51	3.1	4.3	3.8	1.8	1.9	1.5	0.02	0.01	.01
P†				<0.01	<0.05		x	x		<0.05	x		<0.01	<0.05		<0.001	x		<0.05	x

* Control; ** 10 minutes after diazepam; *** 30 minutes after diazepam. x Not significant ($P > .05$). † Difference from control value, t test for correlated means.

Cardiac output was measured before and ten and 30 minutes after treatment with diazepam. The direct Fick method was used in 12 cases and the indicator dilution technique in three patients.

Lead II electrocardiogram and systemic and pulmonary arterial pressures were monitored continuously during the 30-minute period of observation. During determination of cardiac output, the following were measured:

1. Heart rate and rhythm by electrocardiogram.
2. Intra-arterial blood pressure (systolic, diastolic, mean), using a P23Db Statham strain-gauge manometer and Sanborn recorder.
3. Pulmonary arterial mean pressure by a cardiac catheter attached to a P23Db Statham strain-gauge manometer.
4. Blood gases (Pa_{O_2}, pH, Pa_{CO_2}) by an Instrumentation Laboratories blood gas analyzer, utilizing duplicate samples and correcting for temperature.
5. Oxygen consumption by collecting expired air for three minutes, utilizing a Douglas bag. Minute ventilation determined by use of a Tissot Spirometer.
6. Respiratory rate by visual count during collection of expired air for three minutes.

These measurements allowed calculation of the following according to standard formulas:

1. Cardiac index (l/min/m²).
2. Total systemic resistance (dynes/sec/cm⁻⁵).
3. Total pulmonary resistance (dynes/sec/cm⁻⁵).
4. Pulmonary tidal volume (ml).
5. Minute ventilation (l/min).

Results

Mental Status

In two patients there was no observable change in mental status after administration of diazepam. In eleven patients, light sleep began within one to two minutes after they re-

ceived the drug, and lasted for 10 to 30 minutes. These patients could easily be aroused. Two patients exhibited unusual responses. One, who had pre-existent psychiatric disease, slept for ten minutes, then was disoriented and agitated for 20 minutes. Another patient became drowsy, but then became moderately restless and anxious. The overt effects of the drug lasted 30 to 45 minutes.

Ventilatory Changes (Table 1)

Minute ventilation had decreased in each patient ten minutes after diazepam and had not returned to control values at 30 minutes. The average minute ventilation was 28 per cent less than the control value at ten minutes ($P < 0.01$) and 14 per cent less than control at 30 minutes ($P < 0.05$). Respiratory rate decreased significantly in only one patient (from a control of 30/min to 18/min ten minutes after diazepam). Thus, hypoventilation was due primarily to a decrease in tidal volume. Tidal volume decreased at ten minutes in seven of nine patients (average decrease 23 per cent, $P < 0.05$) and remained less than the control value in six patients at 30 minutes.

Arterial Blood Gases

Arterial blood gas analysis reflected the observed hypoventilation. There was a significant mean decrease in Pa_{O_2} of 10 mm Hg at ten minutes ($P < 0.01$), and 4 mm Hg at 30 minutes ($P < 0.05$). Pa_{CO_2} had increased in each patient at ten minutes. The increases ranged from 1 to 11 mm Hg (average increase 5 mm Hg, $P < 0.001$). There was a corresponding decrease in arterial *p*H ten minutes after diazepam (average decrease 0.03, $P < 0.05$). By 30 minutes Pa_{O_2}, Pa_{CO_2} and *p*H had nearly returned to control values (fig. 1).

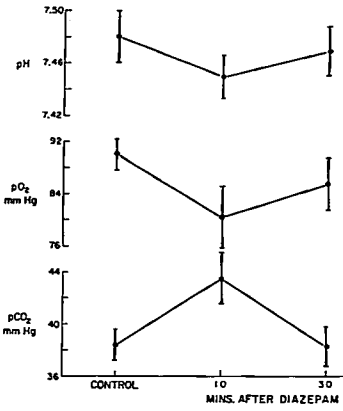

FIG. 1. Arterial blood gas values (mean +/− S.E.) before, and ten and 30 minutes after diazepam. Top panel, *p*H; middle panel, P_{O_2} (mm Hg); lower panel, P_{CO_2} (mm Hg).

Hemodynamic Effects (Table 2)

Heart Rate. There were no changes in heart rate or cardiac rhythm.

Cardiac Index. Cardiac index was measured ten minutes after diazepam in 12 patients. It was unchanged in eight (within 10 per cent of control value), increased in one (24 per cent), and decreased in three (19 per cent, 31 per cent, 32 per cent). In each of the three patients whose cardiac indexes had decreased ten minutes after diazepam, the control cardiac index had been elevated to more than 3.5 l/min/m² (normal resting value for this laboratory is 3.1 ± 0.1). In each of four patients whose control cardiac index was below normal (<2.5 l/min/m²), there was no change after diazepam. The observed changes in cardiac index were not related to the dose of diazepam.

Systemic Blood Pressure. At ten minutes, systolic blood pressures were unchanged in six patients (within 10 mm Hg of control pressure). In one patient pressure increased by 16 mm Hg. Decreases from 12 to 25 mm Hg occurred in eight patients. There were small decreases in the average diastolic and mean pressures at ten minutes, of 3 and 6 mm Hg, respectively. Calculated total systemic resistances did not change, indicating that significant peripheral vasoconstriction or vasodilatation did not occur. The observed changes in systemic blood pressure were without clinical correlates and did not require therapy.

Pulmonary Arterial Pressure. Pulmonary arterial mean pressures changed by 5 mm Hg or more in only six of 15 patients. In each of these six patients calculated total pulmonary

TABLE 2. Hemodynamic Changes

Patient	Cardiac Index (l/min/m²)			Systolic B. P. (mm Hg)			Diastolic B.P. (mm Hg)			Mean B.P. (mm Hg)			Systemic Resistance (Dynes/sec/cm⁻⁵)			Pulmonary Arterial Mean Pressure (mm Hg)		
	C*	10**	30***	C	10	30	C	10	30	C	10	30	C	10	30	C	10	30
1	3.2	4.0	2.4	109	105	115	65	59	68	83	80	82	1,054	821	1,428	15	14	16
2	2.5	2.5	2.6	102	100	102	64	64	61	82	73	77	1,562	1,358	1,400	20	16	16
3	6.8	—	5.3	130	116	120	56	64	56	80	90	78	941	—	1,179	14	18	15
4	1.3	1.3	1.3	121	102	106	71	59	64	91	72	80	3,467	2,800	3,048	20	18	18
5	3.5	2.4	2.8	128	115	115	64	62	61	90	79	80	1,400	1,663	1,420	33	22	19
6	3.8	3.1	2.9	116	104	102	68	60	62	84	70	76	1,244	1,273	1,483	26	20	20
7	3.8	3.7	3.7	140	124	128	74	72	72	96	90	95	800	800	800	34	33	34
8	5.3	5.6	5.6	146	146	143	65	70	79	96	97	100	650	607	752	24	28	28
9	8.6	—	5.5	127	102	124	67	62	68	82	78	88	760	—	1,280	38	23	20
10	9.0	8.5	9.7	116	110	116	72	72	74	90	84	86	1,130	—	—	15	12	13
11	13.4	—	10.6	172	154	164	40	38	40	84	76	84	1,320	—	—	20	33	20
12	3.2	2.9	2.8	118	103	107	58	52	54	84	73	75	1,315	1,240	1,330	45	37	39
13	4.0	2.7	3.8	140	130	136	68	62	60	88	86	96	1,200	1,750	1,400	22	16	14
14	2.4	2.4	2.6	150	160	146	86	86	82	112	104	106	2,240	2,030	1,930	60	66	60
15	1.5	1.6	1.6	146	162	150	90	80	80	104	100	110	3,100	3,000	3,000	49	50	51
Mean	4.8	3.4	4.2	131	122	125	67	64	65	90	84	88	1,479	1,582	1,573	30	27	27
S.E.	0.86	0.57	0.71	4.7	5.9	4.9	3.0	2.9	2.9	2.3	2.8	2.9	214	234	197	3.5	3.8	3.7
P†		x	x		<0.01	<0.01		<0.02	x		<0.01	x		x	x		x	x

† Difference from control value, *t* test for correlated means.
* Control; ** 10 minutes after diazepam; *** 30 minutes after diazepam.
x Not significant ($P > 0.05$)

resistance remained stable, indicating that the small changes in pulmonary arterial pressure were secondary to similar small changes in cardiac output. These small changes in pulmonary arterial mean pressure and total pulmonary resistance were not significant.

Discussion

The degree of sedation noted in these patients was comparable to that reported by others who have utilized similar intravenous doses.[9, 10] Anxiety was effectively relieved in 11 of the 15 patients.

We noted significant decreases in cardiac indexes in only three patients, and each of these three patients had elevated control cardiac indexes (>3.5 l/min/m^2). There were no decreases in cardiac index in the four patients with low control cardiac indexes secondary to advanced heart disease.

The observed decreases in systemic blood pressure were not accompanied by changes in systemic resistance, indicating that significant peripheral effects did not occur. It is possible that the observed decreases in blood pressure were due, in part, to sedation. Comparable decreases in blood pressure have been observed during normal sleep.[11]

In contrast to the minimal changes in cardiac function, significant changes in ventilation were noted in *all* patients. The consistent decreases in minute ventilation after diazepam were due primarily to decreases in tidal volume. These decreases were accompanied by consistent decreases in Pa_{O_2} and *p*H and increases in Pa_{CO_2}. These respiratory changes did not correlate with the overt sedative effect of the drug. The respiratory changes in the three patients who did not sleep and were not relieved of anxiety were comparable to those of the remainder of the group.

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Anesthesia

RESPIRATORY DISTRESS Immediate treatment in the delivery room of respiratory distress in the newborn consisted of establishing warmth, pulmonary inflation, and intravenous sodium bicarbonate therapy via the umbilical vein. One or two injections of bicarbonate in doses of 1 mg/lb were given in the delivery room. Follow-up acid-base determinations were done in the nursery, and further bicarbonate was given as needed. Preliminary results with 129 newborns show decreased fetal morbidity and mortality, especially in the respiratory distress syndrome. (*Roberts, P., and others: Immediate Treatment of Respiratory Distress in the Newborn, Amer. J. Obstet. Gynec. 101: 293 (June) 1968.*)