Large Dose of Flunitrazepam Attenuates Baroreflex Control of Heart Rate in Man

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The effects of intravenous tranquilizers such as flunitrazepan, diazepam and droperidol on baroreflex control of heart rate were investigated using both pressor and depressor tests. The dose-dependency was also studied by the administration of the drugs at the usual or twofold dosage. The usual dosage caused no significant change in neuronal controlling mechanism of circulation. However, flunitrazepam at double the usual dosage produced a decrease in baroreflex sensitivity at depressor tests. The results suggest that flunitrazepam when given repeatedly might accelerate hemodynamic derangements induced by an acute decrease in blood pressure. (Key words: baroreflex, flunitrazepam, diazepam, droperidol)

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Baroreflex plays a key role in the short-term adjustment of blood pressure when relatively abrupt changes in blood pressure, cardiac output or peripheral resistance occur. It is well known that many modern inhalational anesthetics depress the baroreflex. Some intravenous anesthetics may also decrease the sensitivity of the baroreflex when they are administered for maintenance of anesthesia. However, few reports have been written on the intravenous tranquilizers. Marty et al.[1] and Balagny et al.[2] reported a decrease in baroreflex sensitivity by diazepam and droperidol in man.

In the present study, the effect of flunitrazepam, a potent intravenous tranquilizer newly introduced clinically, on baroreflex control of heart rate was investigated using both pressor and depressor test. In addition, the effects of flunitrazepam were compared to those of diazepam and droperidol.

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Materials and Methods

One hundred and twenty patients who received elective operations were selected as subjects and classified as either class I or II of ASA physical status. Their ages ranged from 18 to 50 yr, with mean of 34.6 yr. No patient with histories of neural, circulatory and/or pulmonary diseases was included. Institutional approval and informed consent from all of the objective patients were obtained. No patient received any premedication before the study. In the operating theater, Teflon catheters (18 and 20G) were placed into a forearm vein and a radial artery under local anesthesia (1% lidocaine). Blood pressure and ECG were displayed on a polygraph (Nippon Colin Co., Ltd. model CBM-3000), using a Gould P-50 transducer and electrical amplifiers.

After the hemodynamic condition of the patients stabilized, the pressor baroreceptor response was analyzed by the method originally described by Smyth et al.[3]: In this method 2–3 $\mu g \cdot kg^{-1}$ of phenylephrine (Neosynesin® manufactured by Kowa Co., Ltd.) were injected intravenously to elevate

Table 1. Physical and clinical characteristics of patients in twelve groups

Group	Age (year)	Systolic blood pressure (mmHg)	R-R interval (msec)	Pa_{O_2} (mmHg)	Pa_{CO_2} (mmHg)	pHa
$F_{0.02}$(p) (n=10)	38.7±5.5	127.4±13.0	916.0±150.5	99.1±7.9	37.7±2.7	7.425±0.012
$F_{0.04}$(p) (n=10)	38.9±8.0	120.7±12.7	856.1±110.9	90.8±7.7	39.6±2.5	7.421±0.012
$Di_{0.2}$(p) (n=10)	35.1±9.0	131.4±17.4	912.8±123.4	96.2±9.4	38.4±4.2	7.415±0.016
$Di_{0.4}$(p) (n=10)	36.3±8.5	133.0±16.8	810.9±91.9	96.5±7.3	38.4±4.8	7.427±0.021
$Dr_{0.2}$(p) (n=10)	30.9±11.8	130.7±19.6	922.3±124.2	97.3±7.7	39.1±3.6	7.425±0.014
$Dr_{0.4}$(p) (n=10)	35.1±6.8	123.4±15.4	985.2±139.7	97.6±11.4	39.1±4.6	7.424±0.046
$F_{0.02}$(d) (n=10)	28.8±9.4	137.5±14.1	940.0±114.6	100.7±10.0	38.7±5.4	7.434±0.039
$F_{0.04}$(d) (n=10)	30.9±8.9	127.9±13.1	883.2±119.1	96.2±8.4	38.6±3.9	7.424±0.022
$Di_{0.2}$(d) (n=10)	34.0±6.9	122.8±8.0	912.2±163.4	93.8±12.9	38.0±4.1	7.426±0.022
$Di_{0.4}$(d) (n=10)	41.0±4.2	129.9±14.2	879.3±122.7	91.3±4.6	39.3±3.2	7.416±0.011
$Dr_{0.2}$(d) (n=10)	36.9±7.8	128.6±11.1	923.2±116.0	92.1±10.8	38.9±2.5	7.422±0.013
$Dr_{0.4}$(d) (n=10)	28.1±8.7	135.7±17.8	921.9±140.7	98.5±15.0	39.6±3.5	7.413±0.017

Values are expressed as mean±SD

arterial blood pressure by 20–30 mmHg. After the arterial blood pressure returned to the preinjection level, one of the tranquilizers was administered intravenously. The pressor baroreceptor response was reevaluated five minutes after the administration of tranquilizer by the same technique.

The depressor baroreceptor response was quantified by the injection of 8–10 $\mu g \cdot kg^{-1}$ of nitroglycerine (Millisrol® manufactured by Nipponkayaku Co., Ltd.) reducing arterial blood pressure by 20–30 mmHg.

The usual dosage of tranquilizers was adopted in the first series of the study: 0.02 $mg \cdot kg^{-1}$ of flunitrazepam, 0.2 $mg \cdot kg^{-1}$ of diazepam and 0.2 $mg \cdot kg^{-1}$ of droperidol. To observe the dose-depending effects of the drugs, a twofold dosage was tried in the second series: 0.04 $mg \cdot kg^{-1}$ of flunitrazepam, 0.4 $mg \cdot kg^{-1}$ of diazepam and 0.4 $mg \cdot kg^{-1}$ of droperidol. The two dosages of three drugs and two tests for each dosage and drug resulted in twelve study groups. Each group consisted of 10 patients and was abbreviated as follows; $F_{0.02}$(p), $F_{0.04}$(p), $Di_{0.2}$(p), $Di_{0.4}$(p), $Dr_{0.2}$(p), $Dr_{0.4}$(p), $F_{0.02}$(d), $F_{0.04}$(d), $Di_{0.2}$(d), $Di_{0.4}$(d), $Dr_{0.2}$(d) and $Dr_{0.4}$(d).

The relationship between changing values of systolic arterial blood pressure and R-R interval was automatically plotted on a computer display (NEC Co., Ltd. personal computer PC-9801 VX21) using an analysis package software, "autonomic nerve system package".[4] A regression line of systolic blood pressure and R-R interval was obtained by least-square linear regression analysis. Only patients in whom regression slopes had a correlation coefficient greater than 0.8 were included in the data. The slope of this regression line expressed in $msec \cdot mmHg^{-1}$ was adopted as an index of baroreceptor response.

The data were represented by mathematical means and central tendencies were expressed by standard deviations. Analysis of variance and paired Student's t-tests were used to analyze the values obtained. A p-value less than 0.05 was used to accept or reject statistical hypotheses.

Results

There were no significant differences in age, systolic blood pressure, R-R interval, Pa_{O_2}, Pa_{CO_2} and pHa among the twelve groups before the study (table 1).

Table 2 shows Pa_{O_2}, Pa_{CO_2} and pHa before and after the injection of a tranquilizer in all groups. In group $F_{0.02}$(p), $F_{0.04}$(p), $F_{0.02}$(d) and $F_{0.04}$(d), Pa_{O_2} and pHa decreased significantly after the injection, but Pa_{CO_2} elevated significantly.

Table 2. Blood gas analysis of pre-injection and post-injection of tranquilizers

Group		pre-injection	post-injection	significance
Pressor test group				
	Pa_{O_2} (mmHg)	99.1 ± 7.9	79.7 ± 13.2	$P < 0.005$
$F_{0.02}$(p)	Pa_{CO_2} (mmHg)	37.7 ± 2.7	39.7 ± 3.2	$P < 0.05$
(n = 10)	pHa	7.425 ± 2.7	7.397 ± 0.029	$P < 0.01$
	Pa_{O_2} (mmHg)	90.8 ± 7.7	69.1 ± 6.9	$P < 0.001$
$F_{0.04}$(p)	Pa_{CO_2} (mmHg)	39.6 ± 2.5	43.4 ± 3.4	$P < 0.0001$
(n = 10)	pHa	7.421 ± 0.012	7.379 ± 0.016	$P < 0.00001$
	Pa_{O_2} (mmHg)	96.2 ± 9.4	89.4 ± 9.1	$P < 0.05$
$Di_{0.2}$(p)	Pa_{CO_2} (mmHg)	38.4 ± 4.2	39.2 ± 5.1	NS
(n = 10)	pHa	7.415 ± 0.016	7.389 ± 0.012	$P < 0.001$
	Pa_{O_2} (mmHg)	96.5 ± 7.3	86.1 ± 8.1	$P < 0.01$
$Di_{0.4}$(p)	Pa_{CO_2} (mmHg)	38.4 ± 4.8	39.2 ± 4.6	NS
(n = 10)	pHa	7.427 ± 0.021	7.404 ± 0.023	$P < 0.05$
	Pa_{O_2} (mmHg)	97.3 ± 7.7	98.2 ± 10.7	NS
$Dr_{0.2}$(p)	Pa_{CO_2} (mmHg)	39.1 ± 3.6	39.0 ± 3.5	NS
(n = 10)	pHa	7.425 ± 0.014	7.415 ± 0.012	NS
	Pa_{O_2} (mmHg)	97.6 ± 11.4	95.8 ± 12.2	NS
$Dr_{0.4}$(p)	Pa_{CO_2} (mmHg)	39.1 ± 4.6	39.0 ± 2.4	NS
(n = 10)	pHa	7.424 ± 0.046	7.414 ± 0.020	NS
Depressor test group				
	Pa_{O_2} (mmHg)	100.7 ± 10.0	75.5 ± 16.4	$P < 0.005$
$F_{0.02}$(d)	Pa_{CO_2} (mmHg)	38.7 ± 5.4	43.2 ± 3.6	$P < 0.01$
(n = 10)	pHa	7.434 ± 0.039	7.389 ± 0.011	$P < 0.005$
	Pa_{O_2} (mmHg)	96.2 ± 8.4	71.8 ± 13.6	$P < 0.0001$
$F_{0.04}$(d)	Pa_{CO_2} (mmHg)	38.6 ± 3.9	42.2 ± 3.0	$P < 0.005$
(n = 10)	pHa	7.424 ± 0.022	7.383 ± 0.018	$P < 0.0001$
	Pa_{O_2} (mmHg)	93.8 ± 12.9	82.8 ± 9.9	$P < 0.05$
$Di_{0.2}$(d)	Pa_{CO_2} (mmHg)	38.0 ± 4.1	39.6 ± 2.7	NS
(n = 10)	pHa	7.426 ± 0.022	7.408 ± 0.019	$P < 0.05$
	Pa_{O_2} (mmHg)	91.3 ± 4.6	75.1 ± 13.2	$P < 0.01$
$Di_{0.4}$(d)	Pa_{CO_2} (mmHg)	39.3 ± 3.2	41.2 ± 3.3	NS
(n = 10)	pHa	7.416 ± 0.011	7.388 ± 0.018	$P < 0.01$
	Pa_{O_2} (mmHg)	92.1 ± 10.8	89.5 ± 12.7	NS
$Dr_{0.2}$(d)	Pa_{CO_2} (mmHg)	38.9 ± 2.5	37.3 ± 2.0	NS
(n = 10)	pHa	7.422 ± 0.013	7.429 ± 0.016	NS
	Pa_{O_2} (mmHg)	91.9 ± 10.5	98.5 ± 15.0	NS
$Dr_{0.4}$(d)	Pa_{CO_2} (mmHg)	39.6 ± 3.5	37.6 ± 4.5	NS
(n = 10)	pHa	7.413 ± 0.017	7.423 ± 0.024	NS

Values are expressed as mean ± SD NS: Not significant

In group $Di_{0.2}$(p), $Di_{0.4}$(p), $Di_{0.2}$(d) and $Di_{0.4}$(d), Pa_{O_2} and pHa decreased significantly after the administration, but Pa_{CO_2} did not change significantly. In groups $Dr_{0.2}$(p), $Dr_{0.4}$(p), $Dr_{0.2}$(d) and $Dr_{0.4}$(d), there was no change in the parameters after the injection.

Table 3 shows systolic blood pressure, R-

Table 3. Systolic blood pressure, R-R interval, and baroreflex sensitivity of pre-injection and post-injection of tranquilizers

Group		pre-injection	post-injection	significance
Pressor test group				
	Systolic blood pressure (mmHg)	127.4 ± 13.0	105.3 ± 16.4	$P < 0.01$
$F_{0.02}$(p)	R-R interval (msec)	916.0 ± 150.5	807.4 ± 133.7	$P < 0.01$
(n = 10)	Baroreflex sensitivity (ms·mmHg^{-1})	13.6 ± 2.8	13.7 ± 3.0	NS
	Systolic blood pressure (mmHg)	120.7 ± 12.7	98.1 ± 9.4	$P < 0.0001$
$F_{0.04}$(p)	R-R interval (msec)	886.1 ± 110.9	791.9 ± 87.4	$P < 0.01$
(n = 10)	Baroreflex sensitivity (ms·mmHg^{-1})	15.6 ± 5.2	14.7 ± 4.7	NS
	Systolic blood pressure (mmHg)	131.4 ± 17.4	119.0 ± 9.9	$P < 0.01$
$Di_{0.2}$(p)	R-R interval (msec)	912.8 ± 123.4	811.2 ± 118.3	$P < 0.01$
(n = 10)	Baroreflex sensitivity (ms·mmHg^{-1})	14.3 ± 4.9	15.2 ± 3.1	NS
	Systolic blood pressure (mmHg)	133.0 ± 16.8	114.6 ± 17.0	$P < 0.0005$
$Di_{0.4}$(p)	R-R interval (msec)	880.9 ± 91.9	782.3 ± 129.1	$P < 0.05$
(n = 10)	Baroreflex sensitivity (ms·mmHg^{-1})	14.5 ± 2.8	14.3 ± 3.1	NS
	Systolic blood pressure (mmHg)	130.7 ± 19.6	108.1 ± 15.4	$P < 0.01$
$Dr_{0.2}$(p)	R-R interval (msec)	922.3 ± 124.2	857.1 ± 127.8	$P < 0.05$
(n = 10)	Baroreflex sensitivity (ms·mmHg^{-1})	13.2 ± 2.1	13.9 ± 3.2	NS
	Systolic blood pressure (mmHg)	123.4 ± 15.4	108.3 ± 12.8	$P < 0.005$
$Dr_{0.4}$(p)	R-R interval (msec)	985.2 ± 139.7	860.5 ± 134.7	$P < 0.001$
(n = 10)	Baroreflex sensitivity (ms·mmHg^{-1})	13.5 ± 4.3	13.6 ± 3.2	NS
Depressor test group				
	Systolic blood pressure (mmHg)	137.5 ± 14.1	115.3 ± 9.9	$P < 0.0005$
$F_{0.02}$(d)	R-R interval (msec)	940.0 ± 114.6	822.1 ± 90.0	$P < 0.001$
(n = 10)	Baroreflex sensitivity (ms·mmHg^{-1})	10.8 ± 6.1	7.1 ± 9.6	NS
	Systolic blood pressure (mmHg)	127.9 ± 13.1	104.5 ± 10.8	$P < 0.00001$
$F_{0.04}$(d)	R-R interval (msec)	883.2 ± 119.1	752.0 ± 101.5	$P < 0.001$
(n = 10)	Baroreflex sensitivity (ms·mmHg^{-1})	9.7 ± 4.3	5.0 ± 1.9	$P < 0.05$
	Systolic blood pressure (mmHg)	122.8 ± 8.0	112.7 ± 7.2	$P < 0.005$
$Di_{0.2}$(d)	R-R interval (msec)	912.2 ± 163.4	784.4 ± 149.2	$P < 0.01$
(n = 10)	Baroreflex sensitivity (ms·mmHg^{-1})	10.3 ± 3.8	7.8 ± 4.3	NS
	Systolic blood pressure (mmHg)	129.9 ± 14.2	109.8 ± 11.1	$P < 0.00001$
$Di_{0.4}$(d)	R-R interval (msec)	879.3 ± 122.7	783.2 ± 100.0	$P < 0.05$
(n = 10)	Baroreflex sensitivity (ms·mmHg^{-1})	8.7 ± 5.3	6.1 ± 4.0	NS
	Systolic blood pressure (mmHg)	128.6 ± 11.1	119.9 ± 12.9	$P < 0.0005$
$Dr_{0.2}$(d)	R-R interval (msec)	923.2 ± 116.0	760.3 ± 95.9	$P < 0.005$
(n = 10)	Baroreflex sensitivity (ms·mmHg^{-1})	9.9 ± 5.5	8.4 ± 3.8	NS
	Systolic blood pressure (mmHg)	135.7 ± 17.8	121.0 ± 11.6	$P < 0.005$
$Dr_{0.4}$(d)	R-R interval (msec)	921.9 ± 140.7	829.8 ± 103.3	$P < 0.005$
(n = 10)	Baroreflex sensitivity (ms·mmHg^{-1})	9.4 ± 7.8	9.2 ± 7.3	NS

Values are expressed as mean ± SD NS: Not significant

R interval and baroreflex sensitivity before and after the injection of a tranquilizer in all groups. Systolic blood pressure and R-R interval decreased markedly after the injection in all groups. Baroreflex sensitivity decreased only in group $F_{0.04}$(d). In the other groups,

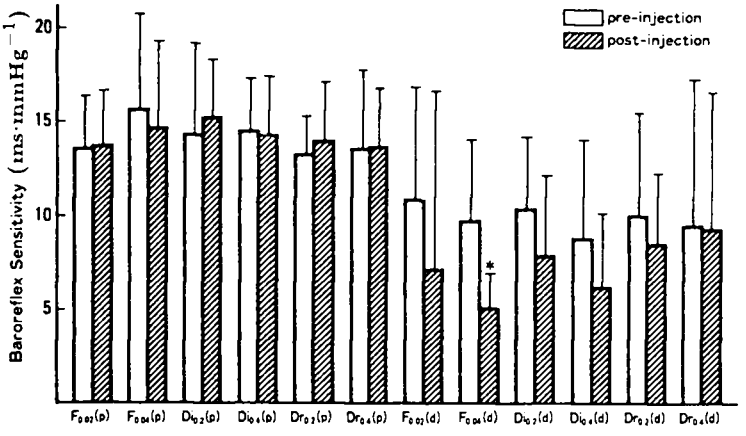

Fig. 1. Comparative changes in baroreflex sensitivity induced by tranquilizers. Only administration of flunitrazepam, 0.04 mg induces a decrease of baroreflex sensitivity ($*P < 0.05$).

there was no significant change (fig. 1).

Discussion

Mediation of the sympathetic nervous system and vagal tone is, in part, under the control of neural impulses arising in the baroreceptors. The baroreceptors play a vital role in rapid correction of blood pressure changes that follow a quick change of heart rate. This response is called the baroreflex.

There are various ways to evaluate baroreflex sensitivity clinically: pressor and depressor tests, the neck-chamber method and the Valsalva maneuver[5]. Pressor and depressor tests were adopted in the present study because they are easily performed, reliable, reproducible[3] and sensitive[5,6].

There are many factors that affect baroreflex response such as aging[7], hypertension[8] and medication. Anesthetics such as thiopental[9], halothane[10], enflurane, enflurane-nitrous oxide[11], isoflurane[12], morphine-diazepam-nitrous oxide[13] and fentanyl-diazepam-nitrous oxide[14] lower baroreflex sensitivity. Cervical epidural block also diminishes it[15]. On the other hand, methoxyflurane does not alter it[16].

No theory has been established on the tranquilizing drugs concerning baroreflex sensitivity. Marty et al.[1] reported a transient reduction in baroreflex sensitivity in adults evaluated by pressor tests after administration of 0.4 mg·kg^{-1} of diazepam. Balagny et al.[2], using pressor test in adults, found that baroreflex sensitivity was depressed for a period of time after droperidol (0.2 mg·kg^{-1}) was administered.

In the present study, three tranquilizers (flunitrazepam, diazepam and droperidol) being utilized for the induction of anesthesia in Japan were evaluated to determine their effects on the baroreflex. The results showed that only a large dosage of flunitrazepam reduces the reflex sensitivity in depressor test.

The present study is the first report on the effects of flunitrazepam on baroreflex control of heart rate. As with diazepam, both pressor and depressor tests indicated that baroreflex response was not altered by a normal dose of flunitrazepam (0.02 mg·kg^{-1}). However, a large dose of flunitrazepam (0.04 mg·kg^{-1}) depressed the sensitivity in the depressor test.

Pa_{CO_2} increased significantly after flunitrazepam administration. Bristow et al.[17] reported inconsistent effects of hypercapnia on the baroreceptor regulation. In the present study, Pa_{CO_2} increased but remained within normal range, suggesting a negative influence on baroreflex through a slight respiratory depression.

Flunitrazepam and diazepam lowered Pa_{O_2} significantly in the present study. Eriksson et al.[18] observed the reduction of Pa_{O_2} by benzodiazepines such as midazolam and diazepam administered intravenously and concluded that airway closure together with shunting of venous blood and regions with low ventilation/perfusion ratios

are probably responsible for the main part of the decrease in Pa_{O_2} . However, since there was only a small reduction in oxygen tension, this might not explain the change of the baroreflex.

Attenuation of baroreflex sensitivity could occur at receptors, the afferent nerve pathway, central nervous system, efferent pathway or the effector organs. It is not easy to determine the precise mechanism of flunitrazepam effects because the present study offers little information on that point. Hockman et al.[19] investigated the effects of diazepam on reflex vagal bradycardia elicited by electrical stimulation of the cartotid sinus nerve in cats and found that reflex vagal bradycardia was inhibited by intravenous administration of diazepam. They reported that the drug had no effect on the cardiac slowing produced by direct electrical stimulation of the peripheral cut-end of the right vagus nerve; however, the inhibitory effect of the drug upon the cardiovascular response elicited by electrical stimulation of the carotid sinus nerve was not observed in the animal decerebrated either at a midcollicular level or in such a way as to leave the diencephalon intact. They concluded that the drug-induced inhibition of the cardiac reflex is of central origin. Since flunitrazepam belongs to the benzodiazepines, as does diazepam, it is likely that flunitrazepam depresses the same part of the baroreflex arc as diazepam.

The results of the present study give us some clinical insight in the use of flunitrazepam. The drug, when given repeatedly, might accelerate hemodynamic derangements induced by acute blood loss, declamping of large arteries, overdoses of anesthetics, and so on. Flunitrazepam might be chosen as an induction agent for the patients with ischemic heart disease to prevent reflex tachycardia induced by hypotension.

In conclusion, baroreflex response was reduced in depressor tests after flunitrazepam administration at double the usual dosage. The results suggest that flunitrazepam should not be used repeatedly in patients with possible circulatory derangement during anesthesia. The results also indicate the usefulness of flunitrazepam for the patient of ischemic heart disease to prevent the increase in heart rate during hypovolemia under anesthesia.

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