The Effect of RO15-1788 on Cardiovascular Depression Caused by Fentanyl and Diazepam

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Cardiovascular depression occuring when diazepam is combined with fentanyl has been investigated using the benzodiazepine antagonist RO15-1788 in the dog.

After the initial administration of fentanyl (40 mcg/kg), the mean arterial pressure (MAP) decreased to 89% of its control value. Following the administration of diazepam (1.2 mg/kg), the MAP and the total peripheral resistance (TPR) decreased significantly, to 75% and 83% of their control values respectively. After the administration of RO15-1788 (0.4 mg/kg), the MAP increased significantly to 90% and the TPR to 102% of their control values and, lastly, the administration of naloxone (40 mcg/kg) increased the MAP to 108% of its control value. No relationship was found between the changes in the catecholamines and the changes in the MAP after the administration of fentanyl, diazepam, and RO15-1788.

The mechanism of circulatory depression when diazepam was used with fentanyl is interpreted as being a peripheral vasodilatory effect of diazepam acting by way of the benzodiazepine receptors since RO15-1788 was found to antagonize this effect. (Key words: RO15-1788, diazepam, fentanyl, naloxone, catecholamine)

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Diazepam, a benzodiazepine group drug, is widely used because it causes limited cardiovascular depression. However, when it is used in conjunction with a narcotic analgesic agent such as fentanyl, the cardiovascular depression is marked[1]. Thus, in order to clarify the mechanism of this cardiovascular depression, we have used the benzodiazepine antagonist RO15-1788 and the narcotic antagonist naloxone, and have investigated its circulatory status together with periodic measurements of plasma catecholamine concentrations, as well as the myocardial and pulmonary extraction of catecholamines.

Materials and Methods

Six mongrel dogs (average weight: 11.7 kg) were used for the experiment. Urethane (600 mg/kg) and α-chloralose (60 mg/kg) were injected intravenously and controlled ventilation was instituted. A left thoracotomy then was performed, and two electromagnetic probes were attached, one at the root of the aorta and the other at the circumflex branch of the left coronary artery. Thus, the blood flow was measured with an electromagnetic flowmeter. The right femoral

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artery and vein, the right atrium, the left atrium, the main pulmonary artery, and the coronary sinus were cannulated. These catheters were used to measure pressures and to obtain blood samples. The catheter in the coronary sinus was placed carefully so that the tip was immediately below the Vieussenns valve. Plasma catecholamine concentrations (CA) were measured by high performance liquid chromatography (HPLC-THI). Derived parameters were calculated from the following equations:

$$TPR = (MAP - RAP)/CC$$
$$SV = CO/HR$$
$$CVR = (DP - RAP)/CBF$$
$$PVR = (PAP - LAP)/CO$$

An explanation of these initials follows: TPR = total peripheral resistance (mmHg·min/l); MAP = mean arterial pressure (mmHg); RAP = mean right atrial pressure (mmHg); CO = cardiac output (l/min); SV = stroke volume (ml); HR = heart rate (beats/min), CVR = coronary vascular resistance (mmHg·min/ml); DP = diastolic pressure (mmHg); CBF = coronary blood flow (ml/min); PVR = pulmonary vascular resistance (mmHg·min/l); PAP = mean pulmonary arterial pressure (mmHg); and, LAP = mean left atrial pressure (mmHg).

After the circulatory status was stabilized, control values were measured. The drugs used in turn were fentanyl (FEN): 40 mcg/kg; diazepam (DIA): 1.2 mg/kg; RO15-1788 (RO): 0.4 mg/kg; and, naloxone (NAL): 40 mcg/kg. Measurements were taken 15 minutes after each intravenous injection. The solvent of RO was 2 ml of propylene glycol.

Hemodynamic parameters were expressed as percentage changes from the control values. The concentrations of plasma norepinephrine (NE) and epinephrine (EPI) in arterial blood were used and were expressed as absolute values. Myocardial and pulmonary extraction ratios of CA were expressed as percentage changes by dividing the arterio-venous differences in the catecholamines of each organ by the relevant arterial blood value. Arterial blood values were used for pulmonary venous blood.

The differences between the control values and the post-administration values of each drug, were analyzed statistically using the paired t-test. A level of $P<0.05$ was taken as significant. The differences between the pre-administration values and the post-administration values of each drug also were analyzed.

Results

The control values were found to be as follows (mean ± standard error): MAP: 99 ± 8 mmHg; HR: 185 ± 13 beats/min, the maximum first derivative of the left ventricular pressure (dp/dt): 2700 ± 490 mmHg/s; TPR: 90 ± 6 mmHg·min/l; CO: 1.1 ± 0.1 l/min; SV: 5.8 ± 0.4 ml; RAP: 4.7 ± 0.5 mmHg; LAP: 6.3 ± 0.4 mmHg; CBF: 20 ± 1 ml/min; CVR: 4.3 ± 0.4 mmHg·min/ml; PAP: 13 ± 2 mmHg; NE: 0.20 ± 0.05 ng/ml; EPI: 0.57 ± 0.11 ng/ml; the myocardial extraction ratio of NE: −70 ± 66%; and, EPI: 75 ± 6%, the pulmonary extraction ratio of NE: 25 ± 16%, and, EPI: 10 ± 8%.

The MAP decreased significantly, to 89% of its control value after the administration of FEN, and to 75% after the administration of DIA. But, with RO, it recovered to 90%, and with NAL it recovered to 108% of its control value.

The HR decreased to 70% with FEN, but increased to 90% with DIA. It decreased to 81% with RO, and recovered to 100% with NAL. The dp/dt decreased with FEN, and recovered with NAL. The CO decreased to 83% with FEN, showed no change with DIA and RO, but recovered almost completely with NAL. The TPR did not change with FEN, but decreased significantly, to 83% with DIA. With RO it recovered markedly to 102%, but showed a tendency to increase with NAL. The SV increased with FEN, but showed no change after that (fig. 1). The RAP and the LAP showed a slight decrease with DIA, which was statistically significant. The CBF showed almost no change. The CVR decreased slightly with DIA and this was statistically significant.

The PVR showed no changes throughout the experiment. Similarly, NE also showed

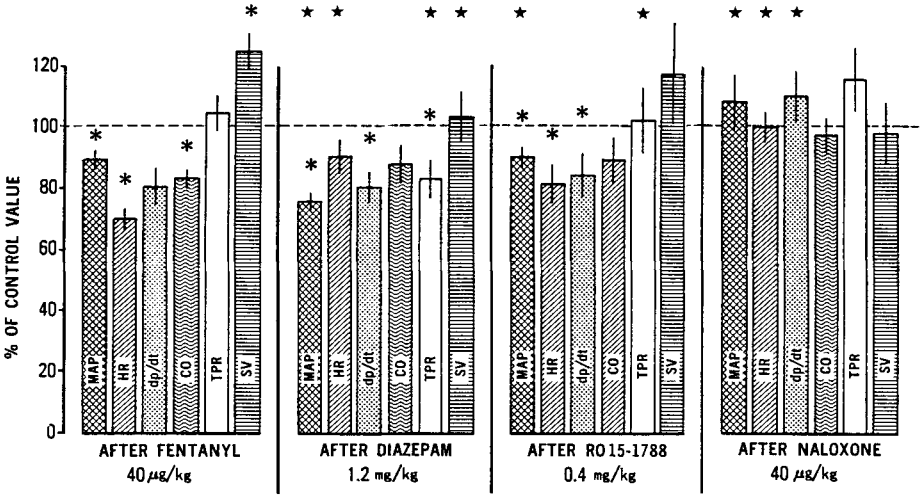

Fig. 1. Changes in hemodynamics after single administration of fentanyl, diazepam, RO15-1788 and naloxone. * represents a significant difference from the control value. ($P<0.05$) ⋆ represents a significant difference from the pre-administration value. ($P<0.05$) For each bar, the vertical line denotes the standard error from the mean.

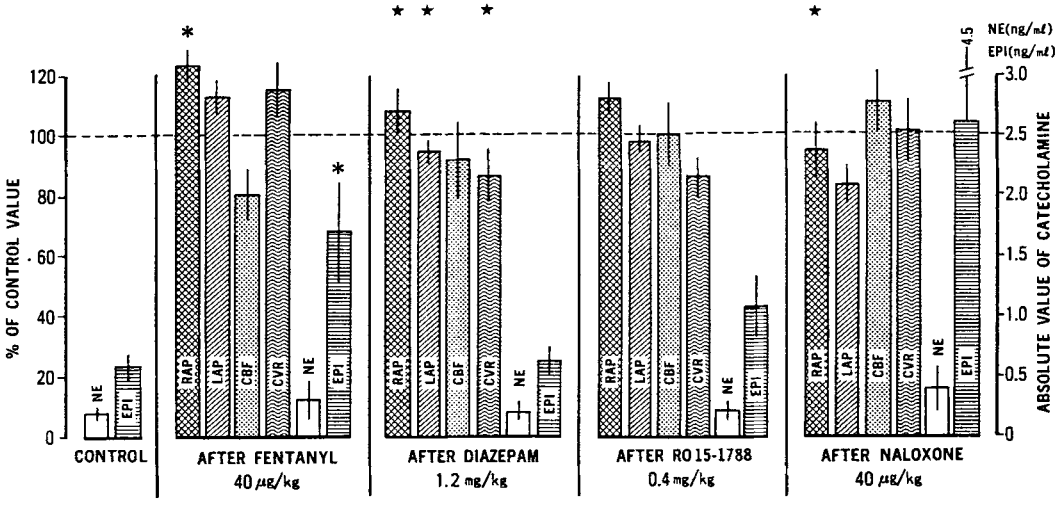

Fig. 2. Changes in hemodynamic and plasma catecholamines after single administration of fentanyl, diazepam, RO15-1788 and naloxone. * represents a significant difference from the control value. ($P<0.05$) ⋆ represents a significant difference from the pre-administration value. ($P<0.05$) For each bar, the vertical line denotes the standard error from the mean.

no significant changes, however there were statistically significant changes in the relationship between the TPR and NE ($r=0.8935$, $P<0.05$) after the administration of NAL. There also were changes in the relationship between the TPR and the MAP ($r=0.9325$, $P<0.01$). Another statistically significant relationship occurred between the EPI and the MAP ($r=0.9972$, $P<0.001$) after the administration of NAL. The EPI tended to increase with FEN, decrease with DIA, and increase with RO and NAL. But, only

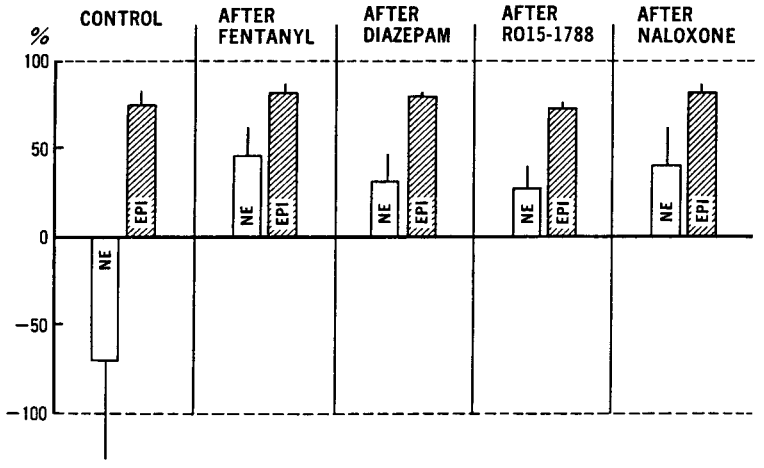

Fig. 3. Changes in the myocardial extraction ratios of catecholamines after single administration of fentanyl, diazepam, RO15-1788 and naloxone. For each bar, the vertical line denotes the standard error from the mean.

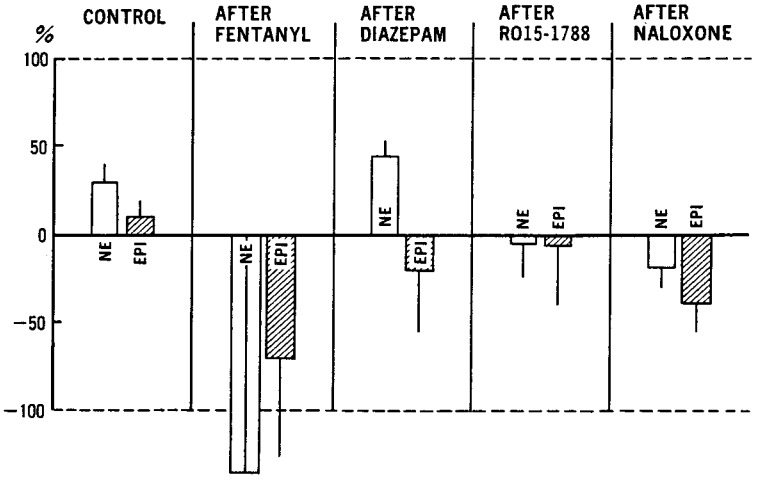

Fig. 4. Changes in the pulmonary extraction ratios of catecholamines after single administration of fentanyl, diazepam, RO15-1788 and naloxone. For each bar, the vertical line denotes a standard error from the mean.

the increase due to FEN was statistically significant (fig. 2). There were, however, no changes in the relationships between EPI and the MAP, or between EPI and the TPR, after the administration of FEN (r=0.6196, r=0.0707), DIA (r=0.4949, r=0.1305), and RO (r=0.0499, r=0.5734), respectively.

Myocardial CA extraction showed no statistically significant differences throughout the entire experiment, but the control values for the myocardium showed a tendency to release NE (fig. 3). Similarly, the pulmonary CA extraction also showed no significant changes, but EPI tended to be released in response to FEN (fig. 4).

Discussion

To date, the cardiovascular depression caused by diazepam in conjunction with the narcotic analgesic fentanyl has been rarely investigated. Stanley et al.[1], who first reported on this, attributed this depression to diazepam's direct inhibitory effect on cardiac contractility. In a recent textbook by Bailey and Stanley[2], they quoted their own work[3] and that of Tomicheck et al.[4], pointing out that the mechanism was not clear but that it might be related to an inhibition of the sympathetic nervous system. (For example, decreases in plasma epinephrine and norepinephrine or decreased peripheral sympathetic nervous activity resulted in vasodilation).

In this experiment, we obtained following results: diazepam used in combination with fentanyl decreased the MAP, and

following the administration of RO15-1788 it increased. In a preliminary experiment, it was confirmed that the administration of diazepam 3 mg/kg followed by the administration of RO15-1788 15 minutes later, or the administration of 2 ml of the propylene glycol, used as the solvent of RO15-1788, did not cause any changes in the MAP. These findings indicate that the decrease in the TPR and the MAP, due to the diazepam used in combination with fentanyl, and the recovery, due to RO15-1788, were not effects due solely to diazepam nor to the solvent.

The fact that the dp/dt, a parameter of myocardial contractility, did not change before or after the administration of diazepam and RO15-1788, rules out the idea that diazepam inhibits myocardial contractility. Reves et al. also could show no additive negative inotropic effect of diazepam and fentanyl in a perfusion sample in rats[5]. Moreover, the changes in the RAP and the LAP in the present experiment were only slight, which do not indicate the effect of diazepam on the capacitance of the vessels. As mentioned previously, the MAP in the present experimental system did not change even with a dose of diazepam as large as 3 mg/kg, showing that diazepam alone does not produce any definite decrease in the MAP. This situation also frequently occurs clinically. The important fact is that diazepam inhibits the increase in the heart rate and blood pressure caused by any electrical stimulus of the hypothalamus, but it has no effect on the blood pressure during quiet, steady-state conditions[6]. Thus, diazepam inhibits the hypothalamus-mediated excitation of the sympathetic nervous system that occurs in unusual conditions such as times of stress.

The present investigation showed an increase in epinephrine following the administratino of fentanyl, indicating that the sympathetic nervous system was, to a certain extent, in an excited state. Fentanyl and morphine, therefore, perhaps maintain a hemodynamically stable state due to compensation by the sympathetic nervous system.

There are several reports of a slight increase in plasma catecholamines due to fentanyl or morphine[7,8], and perhaps one report that a decrease occurred with fentanyl due to the fact that diazepam had been used as a preanesthetic drug[9]. Consequently, the inhibition of the excitation of the sympathetic nervous system (as discussed by Bailey and Stanley) that resulted in a decrease in TPR was probably the cause of the significant diazepam-associated decrease in the MAP from 89% of its control value to 75%.

RO15-1788 restored this decrease in the MAP to the level that existed before the administration of diazepam. This result indicates that RO15-1788 blocked the diazepam-associated decrease in the MAP via the benzodiazepine receptors. At that time, there was little accompanying increase in the plasma catecholamines. Diazepam, therefore, probably does inhibit the sympathetic nervous system, though it also produces peripheral vasodilation by some other mechanism.

The peripheral vasodilation effect of diazepam has been reported previously. Côtē et al. have reported that diazepam, in addition to its central sedative effect, showed a peripheral vasodilation effect similar to nitroglycerin[10]. Abel et al. also have concluded that coronary vasodilation caused by diazepam was due to excitation of the postganglionic sympathetic and parasympathetic vasodilator nerves[11]. Recently, combination sites for benzodiazepines (represented by diazepam) have been discovered in the heart, lung, kidney, liver, the platelets, and in the mast cells, as well as in the brain[12].

The effect of benzodiazepines on these peripheral receptor sites has yet to be clarified. Both Clanachan et al.[13] and Davies et al.[14] feel that diazepam causes coronary vasodilation by the inhibition of tissue absorption of adenosine via the benzodiazepine receptors, in a similar manner to that of the coronary vasodilator dipyridamole. However, others think that these peripheral receptor sites are different in

character from the central receptor sites[15]. Further, RO15-1788 does not antagonize peripheral receptor sites, at least not in the kidney[16].

In the present experiment, the CVR was seen to decrease significantly after the administration of diazepam, and this decrease was not blocked by RO15-1788. Additionally, the PVR showed no change throughout the entire experiment, and was not affected by diazepam or RO15-1788. Thus, the effect that diazepam had on the peripheral, coronary, and pulmonary vascular resistances when it was administered in combination with fentanyl was different in each case. The antagonistic effect of RO15-1788 also was different in each case; it blocked the decrease in peripheral vascular resistance, and it did not block or affect the coronary or pulmonary vascular resistance. If the antagonistic effect of RO15-1788 is interpreted as being only a central block of the inhibition of the autonomic nervous system, then these findings are difficult to explain.

As mentioned previously, the blocking of the peripheral benzodiazepines by RO15-1788 has not been proven, and while the authors do not dispute this, the results of the present experiment strongly suggest the existence of a peripheral vasodilatory effect of diazepam that is blocked by RO15-1788. Perhaps the benzodiazepines act differently in the presence of fentanyl, but the details are not yet clear.

Although RO15-1788 restored the TPR to the control value after the decrease that diazepam had caused, it did not restore the HR or the dp/dt, and recovery to the control value required naloxone. This supports previous reports that fentanyl produced bradycardia and a slight decrease in myocardial contractility which had been antagonized by naloxone[17,18].

No significant changes were seen in myocardial extraction of catecholamines.This means that throughout the entire experiment there was no marked sympathetic nervous stimulation of the myocardium[19]. In general, epinephrine is not released from the myocardium, and norepinephrine has been shown to be released at about 28%[20]. With imposed loads such as pacing, it has been reported that in the failing heart, changes occur in the release of norepinephrine[21,22]. Thus, the myocardial extraction of catecholamine will probably be a useful monitor of the state of the sympathetic nervous system of the heart.

No significant changes were detected in the pulmonary extraction of catecholamines. The lungs are considered capable of yielding a 20% extraction rate of norepinephrine, but not of epinephrine[20,23]. Further, Kim et al. have indicated a correlation between the changes of the MAP, the TPR, and the pulmonary artero-venous difference of norepinephrine at the time of a coronary artery bypass graft operations[24]. In the present experiment, the tendency of fentanyl to release epinephrine from the lungs was of extreme interest. The fact that the PVR did not change and that the epinephrine of the arterial blood significantly increased suggests a release of epinephrine from the lungs. Further investigation as to whether an accumulative release of epinephrine from the lungs occurs is necessary.

RO15-1788 is a selective antagonist of the benzodiazepine group that has been developed in recent years[15,16]. It is considered to be extremely effective in the recovery of consciousness in patients with benzodiazepine poisoning[25], and in patients after anesthetization with benzodiazepines[26]. Any marked action on the cardiovascular system has not been confirmed clinically at the present time[27]. In contrast to this, the results of the present experiment showed a significant reversal of the decrease in the MAP caused by diazepam. However, a marked increase in the MAP that would exceed the value prior to administration of diazepam was not seen.

In conclusion, the mechanism of circulatory depression when diazepam was used with fentanyl has been interpreted as being a peripheral vasodilatory effect of diazepam acting by way of benzodiazepine receptors since RO15-1788 was found to antagonize

this effect. This peripheral vasodilation is interpreted as a partial inhibition of the sympathetic nervous system by diazepam, though diazepam also possesses the ability to act against peripheral resistance vessels via the benzodiazepine receptors.

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