On the Minimal Effective Dose of Noradrenaline for Causing the Blood Pressure Elevation in Non-Anesthetized Dogs

By

Chikamasa Ninagawa

(嵯川 親正)

*From the Department of Physiology, Nagasaki University
School of Medicine, Nagasaki*

(Received for publication, September 14, 1953)

No data are available regarding the minimal effective dose of noradrenaline for the blood pressure elevation in animals under physiological conditions. In order to supply such information, the present investigation was undertaken.

In addition, the pressor effects of L-noradrenaline and DL-noradrenaline were compared with that of L-adrenaline in non-anesthetized dogs.

EXPERIMENTAL

Methods and Results

(I)

Minimal effective dose of noradrenaline was determined in 12 healthy normal dogs weighing 5.0 to 13.8 kg.

The femoral artery was laid bare under local anesthesia with 1% procaine solution and arranged for the blood pressure recording. A small cannula for injection was inserted in the saphenous vein. The blood pressure tracings were taken by means of a mercury manometer. All the experiments were performed without anesthesia.

Synthetic DL-noradrenaline (Sankyo Co.) was dissolved with 1/10 N HCl as a 1:1,000 dilution and just before the injection further diluted with physiological saline solution. Noradrenaline solution was injected intravenously at a uniform rate of 1 cc. per minute for 5 minutes. The amount of noradrenaline injected in the present investigation, was 0.1 μ g., 0.2 μ g., 0.3 μ g., 0.4 μ g., 0.5 μ g., 0.6 μ g., 0.7 μ g. and 1.0 μ g. per kg. of body weight, per minute.

All the data are listed in Table I, and as an example the blood pressure tracings of Exp. 4 are illustrated in Fig. 1.

0.1 μ g. of noradrenaline per kg. per minute was injected in 3 dogs.

TABLE I
Infusion of Dilute DL-Noradrenaline Solution to the Non-
Anesthetized Dogs

No. of Exp.	Body weight and sex	Dose of noradrena- line injected per kg. per min. (μ g.)	Blood pressure (mm. Hg.)		
			Before injection	During injection	Elevation
1	6.8 kg. ♂	0.1	123	119	-4
		0.2	114	117	3
		0.3	113	117	4
2	6.9 kg. ♂	0.1	89	86	-3
		0.2	95	94	-1
		0.3	88	90	2
3	8.2 kg. ♀	0.1	104	104	0
		0.2	105	109	4
		0.3	109	113	4
4	10.7 kg. ♂	0.3	126	132	6
		0.4	117	132	15
		0.5	121	142	21
5	10.2 kg. ♀	0.4	145	153	8
		0.5	138	156	18
		1.0	115	148	33
6	5.0 kg. ♀	0.4	165	170	5
		0.5	141	150	9
		0.6	142	153	11
7	7.0 kg. ♂	0.4	170	170	0
		0.7	157	168	11
8	8.5 kg. ♀	0.4	150	155	5
		0.5	116	132	16
		0.6	146	157	11
		0.7	148	161	13
		1.0	152	169	17
9	8.6 kg. ♀	0.3	130	133	3
		0.4	145	150	5
		0.5	116	129	13
		0.6	131	152	21
10	10.1 kg. ♀	0.5	128	132	4
		0.6	143	151	8
		0.7	142	155	13
11	7.7 kg. ♀	0.4	137	142	5
		0.5	151	161	10
		0.6	140	162	22
12	13.8 kg. ♀	0.2	159	162	3
		0.3	164	171	7
		0.4	158	168	10
		0.5	149	167	18
		0.6	156	172	16

In two cases the blood pressure descended slightly and in one case no change of the blood pressure was observed.

The injection of $0.2 \mu\text{g}$. noradrenaline per kg. per minute was performed in 4 dogs. A very slight fall of the blood pressure was observed in

Fig. 1. Records of the blood pressure in Exp. 4. (Reduced to 2/5).

Dog, 10.7 kg. ♂. Non-anesthetized, non-fasted. A: Injection of DL-noradrenaline in a dose of $0.3 \mu\text{g}$. per kg. per min. B: The same in a dose of $0.5 \mu\text{g}$. per kg. per min. Time in 6 seconds.

one dog, while in other 3 dogs it was raised by 3, 3 and 4 mm. Hg., respectively.

Noradrenaline in a dose of 0.3 μ g. per kg. per minute was injected in 6 dogs, resulting in elevating the blood pressure by 2–7 mm. Hg.

The injection of noradrenaline in a dose of 0.4 μ g. per kg. per minute was performed in 8 dogs. In nearly all the cases the pressor effect was observed. The blood pressure was raised by 5–15 mm. Hg. Only in one dog (Exp. 7) the blood pressure remained unaltered.

The injection of 0.5 μ g. noradrenaline per kg. per minute was attempted in 8 dogs. The blood pressure elevated by 4–21 mm. Hg.

0.6 μ g. (in 6 dogs), 0.7 μ g. (in 3 dogs) and 1.0 μ g. (in 2 dogs) noradrenaline were also tested. In all the cases a more marked rise of the blood pressure was observed.

In order to see the results of all experiments at a glance, the data are summarized in Table II.

The minimal effective dose of DL-noradrenaline for causing the elevation of the blood pressure was thus estimated in the present investigation to be 0.3–0.4 μ g. per kg. of body weight per minute.

TABLE II
Blood Pressure Response to Each Dose of DL-Noradrenaline
in Non-Anesthetized Dogs

Dose of noradrenaline (μ g. per kg. per min.)	Blood pressure elevation (mm. Hg.)							
0.1	–4,	–3,	0.					
0.2	–1,	3,	3,	4.				
0.3	2,	3,	4,	4,	6,	7.		
0.4	0,	5,	5,	5,	5,	8,	10,	15.
0.5	4,	9,	10,	13,	16,	18,	18,	21.
0.6	8,	11,	11,	16,	21,	22.		
0.7	11,	13,	13.					
1.0	17,	33.						

(II)

In 3 healthy normal dogs, weighing 4.6–12.0 kg., the effects of L- and DL-noradrenaline were compared to that of L-adrenaline on the blood pressure. The procedure of experiments was almost the same as that above mentioned.

L-noradrenaline-D-bitartrate-monohydrate (Sterling Winthrop), DL-noradrenaline (Sankyo) and L-adrenaline (Sankyo) were used. The amount of L-noradrenaline in 10 mg. of L-noradrenaline-D-bitartrate-monohydrate was taken as 5 mg. One cc. of the solution, containing nor-

adrenaline or adrenaline in a dose of 2.5–5.0 μg . per kg., was injected intravenously in 10 seconds. Marked elevation of the blood pressure was always observed.

In Exp. 13, the effect of 2.5 μg . L-noradrenaline was almost the same with that of 5.0 μg . DL-noradrenaline and these were far more stronger than 3.0 μg . L-adrenaline. 5.0 μg . DL-noradrenaline was somewhat stronger than 4.0 μg . L-adrenaline and almost as strong as 5.0 μg . L-adrenaline. Thus the activity ratios of L-noradrenaline : DL-noradrenaline : L-adrenaline were estimated in this dog to be 2 : 1 : 1.

In Exp. 14, the effects of 2.5 μg . L-noradrenaline and 5.0 μg . DL-noradrenaline were almost the same. These were weaker than that of 5.0 μg . L-adrenaline and a little weaker than that of 4.5 μg . L-adrenaline. 5.0 μg . DL-noradrenaline was just as strong as 4.0 μg . L-adrenaline. Activity ratios (L-noradrenaline : DL-noradrenaline : L-adrenaline) were determined in this dog to be 1.6 : 0.8 : 1.

Almost the same result was obtained in Exp. 15.

DISCUSSION

The minimal effective dose of DL-noradrenaline for causing the blood pressure elevation was estimated in this investigation to be 0.3–0.4 μg . per kg. per minute. As L-noradrenaline was determined to be about twice as much effective as the racemic one, it may not be unfair to take it that the minimal effective dose of L-noradrenaline is 0.15–0.2 μg . per kg. per minute.

Some reports of the previous investigators (Dragstedt, Wightman and Huffman,¹⁾ Wada and Kanowoka²⁾ and Ooisi³⁾ have indicated that the minimal effective dose of L-adrenaline for raising the blood pressure in non-anesthetized dogs was about 0.2–0.3 μg . per kg. per minute. Comparing these values it may be concluded that the minimal effective dose of L-noradrenaline is somewhat smaller than that of L-adrenaline.

The pressor effect of L-noradrenaline in non-anesthetized dogs was found in the present investigation to be 1.6–2.0 times as much as that of L-adrenaline. This agrees well with the results of previous investigators tested in anesthetized dogs.

In dogs with morphine-ether anesthesia, Schultz⁴⁾ estimated the ratio of pressor activity of DL-noradrenaline to DL-adrenaline to be 1.5 : 1. Tainter, Tullar and Luduena⁵⁾ reported that in dogs under phenobarbital anesthesia, L-noradrenaline was 1.64 ± 0.1 times as much effective as L-adrenaline. Luduena *et al.*⁶⁾ estimated in barbitalized dogs that L-noradrenaline was 1.70 times more active than L-adrenaline in elevating the blood pressure.

I have already studied, in conjunction with Drs. T. Suzuki and T.

Nakamura,⁷⁾ the activity ratio of L-noradrenaline to L-adrenaline on the blood pressure of non-anesthetized dogs, whose spinal cord was sectioned previously at the level of the lowest cervical segment. L-noradrenaline was found in that time to be 2.1 times more effective than L-adrenaline in the average value.

SUMMARY

Injecting intravenously DL-noradrenaline at the uniform rate during 5 minutes, the minimal effective dose for causing the blood pressure elevation was determined in non-anesthetized normal dogs. It was estimated to be 0.3–0.4 μ g. per kg. per minute.

In addition, the pressor effects of L-noradrenaline, DL-noradrenaline and L-adrenaline were compared in non-anesthetized normal dogs. L-noradrenaline was double as much effective as DL-noradrenaline and 1.6–2.0 times as much active as L-adrenaline.

As the pressor effect of L-noradrenaline is twice as much as that of DL-noradrenaline, the minimal effective doses of L-noradrenaline for causing the elevation of the blood pressure in non-anesthetized normal dogs will be 0.15–0.2 μ g. per kg. per minute.

My thanks are due to Prof. T. Suzuki for his helpful advice.

References

- 1) Dragstedt, Wightman, & Huffman, Amer. J. Physiol., 1928, **84**, 307.
 - 2) Wada, & Kanowoka, Tohoku J. Exp. Med., 1935, **27**, 9.
 - 3) Oosi, *ibid.*, 1942, **44**, 329.
 - 4) Schultz, Hygienic Lab. Bull., 1909, No. 55, 31 ff.
 - 5) Tainter, Tullar, & Luduena, Science, 1948, **107**, 39.
 - 6) Luduena, Ananenko, Siegmund, & Miller, J. Pharmacol., 1949, **95**, 155.
 - 7) Suzuki, Nakamura, & Ninagawa, Jap. J. Physiol., 1953, **3**, 170.
-