THE EFFECT OF REPEATED ADMINISTRATION OF EPHEDRINE[1]

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In our previous communication, there were reported the results of a single toxic dose of ephedrine (2). The drug is possibly of clinical importance, especially in the treatment of asthma and hypotension, such as is seen in Addison's disease. In these cases ephedrine is administered in repeated dosage. The study of the effects of repeated administration of small doses, therefore, assumes importance to determine whether it produces pathological changes and whether it is a habit forming drug. In an earlier report (3) it was stated that a rabbit injected daily with 20 mgm. of ephedrine for nine days did not show any pathological effect except some renal degeneration. This paper deals with an investigation of this phase of the problem in a more extensive way.

I. METHODS

Ephedrine sulphate in 5 per cent solution was used in every case. The solution was measured with a 1 cc. tuberculin syringe or a pipette, each graduated to 0.01 cc. For oral administration, the solution diluted with ten volumes of water was given by stomach tube.

Three series of young healthy, white rabbits of 1 to 1.5 kilos were selected for experimentation. One series of ten was given intravenous injections daily of 25 mgm. of ephedrine sulphate irrespective of their body weight for four weeks except Sundays;

[1] A preliminary report of this work was presented before the Peking Branch of the Society for Experimental Biology and Medicine on April 2, 1925 (1).

another series was given intramuscular injections daily of the same dose and for the same length of time, still another series was administered orally the same dose for the same length of time. Practically all of these animals were kept alive for about one-hundred forty days and then sacrificed by a sudden blow in the neck. Autopsy was performed immediately after death and specimens of visceral organs, such as lungs, spleen, liver, kidney, pancreas and adrenal body were fixed in Zenker's solution and stained by eosin and hemotoxylin for microscopic examination. As ephedrine raises the blood pressure much more persistently than epinephrine, our attention was attracted to the question of hypertension which might cause arteriosclerosis. In fact, it has been reported (4) that repeated intravenous injections of ephedrine in rabbits produced arteriosclerosis chiefly in aorta especially in old or pregnant animals. In our investigation, the whole heart, aortic arch, thoracic aorta, abdominal aorta, and subclavian, carotid, brachial, cerebral, retinal, splenic, superior mesenteric, inferior mesenteric, renal, femoral and popliteal arteries, were examined both grossly and microscopically. As soon as it was found how rarely arteriosclerosis occurred, this systematic observation was not made any further than the aorta, and sections of the arteries were fixed in formalin.

In a series of white rats, we injected large doses of ephedrine intravenously about every other day with the hope of producing severe lesions. The animals were, however, heavily infected with the cysticercus of Taenia crassicollis in the liver, and many of them died spontaneously of the infection, which prevented our further investigation. They were autopsied and the visceral organs of a few of them were removed and sectioned for study. No extensive work was done upon the surviving animals.

II. RESULTS IN WHITE RABBITS

1. Local effects

In the intravenous injections there was development of thrombosis in the vein after three or four injections, especially those locally sterilized with tincture of iodine, which was soon replaced

by 70 per cent alcohol. By intramuscular administration there was fibrosis at the site of injection after four or five doses, which disappeared in course of time, for at the end of the experiment it was impossible to locate the point of injection. When given by mouth, ephedrine did not produce any lesion in the gastrointestinal tract, that could be grossly detected in the postmortem examination.

2. Effects on the body weight and general condition

Immediately after each intravenous injection the animal showed mydriasis, stretched its legs and lay still, and showed no inclination to eat when offered food. By other routes of administration (intramuscular and oral), the only sign observed was mydriasis which disappeared in a few hours. The total amount of the drug used and the difference between the initial and final body weights after administration by different methods are summarized in tables 1, 2 and 3. It will be seen that ephedrine in the doses given did not prevent the animals from gaining weight except in one instance (table 3, no. E 178), the reason for which was not clear. There does not seem to be any relation between the gain in weight and the route of administration. The greatest increase was 61.47 per cent (table 1, no. E 152). The majority of the animals gained over 25 per cent, while only two gained less than 10 per cent The two control animals (table 1, nos. E 150 and E 151) did not gain in weight as fast as the treated animals although their living conditions were exactly the same.

The total dose of intravenous injection varied from 130.5 to 817.2 per cent of the M.L.D. with reference to the initial body weight (table 1). The total dose by intramuscular injection varied from 13.25 to 174.8 per cent (table 2), and that per os from 57.54 to 90.0 per cent (table 3), of the M.L.D., all calculated on the basis of the initial body weight. Rabbit number E 179 (table 3) was accidentally killed, while rabbit number E 153 (table 1) and E 170 (table 2) died of unknown cause. It was not certain if this was due to their hypersusceptibility to the drug; this seemed unlikely because no convulsions were observed in

TABLE 1.

Daily injections of 25 mgm. of ephedrine sulphate in white rabbits by the ear vein for four weeks except Sundays

RABBIT NUMBER	SEX	INITIAL BODY WEIGHT	FINAL BODY WEIGHT	DIFFERENCE OF BODY WEIGHT	DURATION OF EXPERIMENT	TOTAL DOSE OF EPHEDRINE SULPHATE	TOTAL DOSE GIVEN IN PERCENTAGE OF M.L.D.
		kilos	*kilos*	*per cent*	*days*	*mgm.*	*per cent*
E 150, Control.	Male	1.54	1.65	+7.144	145	0	0
E 151, Control.....	Male	1.33	1.40	+5.263	144	0	0
E 152.....	Female	1.09	1.76	+61.470	109	587.8	817.2
E 153.....	Male	1.60			7	137.8	130.5
E 154.....	Female	1.41	1.76	+24.820	145	587.8	631.6
E 155.....	Female	1.36	1.60	+17.650	145	587.8	659.3
E 156.....	Male	1.33	1.63	+22.560	146	587.8	669.6
E 157.....	Female	1.16	1.56	+34.480	146	587.8	767.7
E 158.....	Female	1.15	1.70	+47.830	139	600.0	790.8
E 159.....	Female	1.12	1.67	+49 110	139	587.8	795.2
E 160.....	Female	1.35	1.69	+25.120	138	600.0	673.5
E 161.....	Male	1.35	1.41	+4.445	32	600.0	673.5

TABLE 2

Daily injections of 25 mgm. of ephedrine sulphate in white rabbits intramuscularly for four weeks except Sundays

RABBIT NUMBER	SEX	INITIAL BODY WEIGHT	FINAL BODY WEIGHT	DIFFERENCE OF BODY WEIGHT	DURATION OF EXPERIMENT	TOTAL DOSE OF EPHEDRINE SULPHATE	TOTAL DOSE GIVEN IN PERCENTAGE OF M.L.D.
		kilos	*kilos*	*per cent*	*days*	*mgm.*	*per cent*
E 162.....	Female	1.42	1.86	+30.985	135	600.0	124.3
E 163	Female	1.29	1.37	+6.202	28	600.0	136.8
E 164.....	Female	1.42	1.72	+21.125	142	600.0	124.3
E 165.....	Male	1.01	1.46	+44.550	142	600.0	174.8
E 166.....	Female	1.20	1.40	+16.665	142	600.0	147.1
E 167.....	Female	1.20	1.55	+29.170	142	600.0	147.1
E 168.....	Female	1.63	1.81	+11.045	140	600.0	108.3
E 169.....	Female	1.55	1 77	+14.195	140	600.0	113.9
E 170.....	Female	1.11			3	50.0	13.25
E 171.....	Female	1.16	1.78	+53.450	139	600.0	152.2

either case. The general health of other surviving animals remained excellent both during and after the course of treatment. Rabbit number E 168 (table 2) gave birth to eight young ones all of which lived and were normal.

3. Gross examination of the viscera at autopsy

With only few exceptions all of the animals of the three series presented no gross pathology. One rabbit (E 155, table 1) had chronic appendicitis which was confirmed microscopically. One

TABLE 3

Daily administration of 25 mgm. of ephedrine sulphate to white rabbits per os for four weeks except Sundays

RABBIT NUMBER	SEX	INITIAL BODY WEIGHT	FINAL BODY WEIGHT	DIFFERENCE OF BODY WEIGHT	DURATION OF EXPERIMENT	TOTAL DOSE OF EPHEDRINE SULPHATE	TOTAL DOSE GIVEN IN PERCENTAGE OF M.L.D.
		kilos	*kilos*	*per cent*	*days*	*mgm.*	*per cent*
E 172	Female	1.40	1.98	+41.430	140	600.0	72.65
E 173	Male	1.13	1.49	+31.860	140	600.0	90.00
E 174	Male	1.61	1.61	0	135	600.0	63.18
E 175	Female	1.17	1.54	+31.620	135	600.0	86.98
E 176	Female	1.23	1.81	+47.150	141	600.0	82.70
E 177	Male	1.24	1.71	+37.890	141	600.0	77.78
E 178	Female	1.14	1.08	−5.556	32	600.0	89.20
E 179	Female	1.62			26	550.0	57.54
E 180	Male	1.18	1.48	+25.425	137	600.0	86.20
E 181	Female	1.28	1.87	+46.100	137	600.0	79.48

of the control animals (E 150) developed bulging of the aortic arch resembling an aneurysm. Only two animals (E 159 and E 160) in the series with intravenous injection showed the presence of plaques in the inner surface of the aorta. None of the animals showed hypertrophy of the heart.

4. Microscopic examination

a. Kidney. Of 30 kidneys from different animals in the three series, 15 showed some parenchymatous degeneration. Two of

the control animals also showed parenchymatous degeneration. One animal (E 172, table 3) developed a focus of interglomerulonephritis, another (E 176, table 3) a small chronic abscess, and still another (E 179, table 3) had bilateral congenital cysts in the cortex. It appears obvious that no rabbit in our series developed any lesion that can be definitely attributed to the effect of repeated administration of ephedrine.

b. Cardio-vascular system. Of 24 hearts examined including those from the two control animals, none had any abnormality either in the myocardium or in the valves. Of 25 aortas studied, one showed definite thickening of the intima, while another had definite calcification of the media resembling sclerosis of Mönckeberg's type. Both of them were in the series with intravenous injections. A control animal (E 150, table 1) also presented signs of degeneration of the media in the aortic arch, thoracic and abdominal aorta. Other arteries from 9 rabbits including the two control ones were all free from sclerotic changes, except the renal artery of the same animal that had intimal thickening in the aorta as mentioned above. Its intima was also thickened. Although the ages of these experimental rabbits were not known, it is probable that the two cases of sclerosis in the series with intravenous injections were due to spontaneous development, especially so when compared with the degenerative changes of the aortic media in one of the control animals. Therefore, it can be safely said that ephedrine does not produce arteriosclerosis, although it raises the blood pressure persistently, as illustrated in figure 1.

c. Other organs. The lungs, liver and speen of all the rabbits were carefully examined. One animal (E 179, table 3) showed bronchopneumonia, and two (E 158, table 1; E 179, table 3) small abscess formation in the liver. All the rest were normal. There was no abnormality found in 21 adrenal bodies and 18 pancreas of different animals including the two controls. Thus ephedrine cannot be said to have done any damage to these organs.

5. The development of tolerance to ephedrine

In our previous communication (2), evidence has been presented that most animals who received repeated doses are still susceptible to a M.L.D. by any particular route. In this investigation, we never failed to find mydriasis after administration of the drug. In anesthetized rabbits ephedrine still retains its

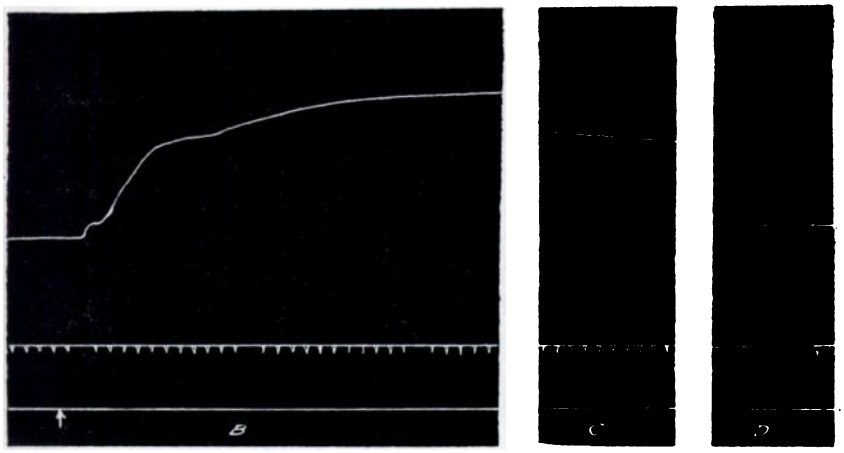

FIG. 1. EFFECT OF EPHEDRINE ON BLOOD PRESSURE AFTER ITS REPEATED ADMINISTRATION

Rabbit E 155, female, 1.6 kilos, injected intravenously 25 mgm. of ephedrine sulphate daily for four weeks except Sundays, anesthetized with urethane (0.75 gram per kilo intraperitoneally).

Records from above down are: carotid blood pressure, time in five seconds, and signal line.

B, at arrow, 25 mgm. of ephedrine sulphate were injected intravenously, blood pressure rising from 86 to 157 mm. Hg.

C, ten minutes after injection of ephedrine, blood pressure at 133 mm. Hg.

D, twenty minutes after injection of ephedrine, blood pressure at 92 mm. Hg, returning to 86 mm. Hg twenty-five minutes after the injection.

blood pressure raising property both in regard to extent and duration. Figure 1 was obtained from a rabbit (E 155, table 1) that was injected daily with 25 mgm. of ephedrine sulphate intravenously for four weeks except Sundays. It will be seen that 25 mgm. of the drug in the animal anesthetized with urethane raised the blood pressure from 86 to 157 mm. Hg which did not fall

to the former level until twenty-five minutes after. This is the usual picture seen in normal animals. These facts show clearly that rabbits do not develop a tolerance to the blood pressure raising property of ephedrine.

III. RESULTS IN WHITE RATS

As mentioned above, a series of white rats was administered large doses of ephedrine intravenously every other day for seven days. Each dose (100 mgm. per kilo) amounted to 74 per cent of the M.L.D., and the total dose to 700 mgm. per kilo, being 5.2 times the M.L.D. presented in the last publication (2). The animals were weighed daily. Although our results were complicated by a cestodal infection of the liver resulting in many deaths, our general impression was that ephedrine even in such large doses did not do much damage, if any, for several animals were still living after a period over seven and a half months. During the course of treatment, the body weight decreased by 2 to 12 grams, but towards the end it increased over the initial weight in nearly all cases. Of the organs removed from the animals dying of the fore-mentioned infection, on microscopic examination, the liver showed the presence of cysts containing the cysticercus of Taenia crassicollis, and a certain amount of congestion and necrosis; the lungs oedema and broncho-pneumonia; the spleen extensive congestion; and the kidney tubular nephritis. These lesions can be logically explained by the Taenia infection.

IV. DISCUSSION

From our results in rabbits, it looks fairly obvious that ephedrine in small doses can be given indefinitely, either by mouth, or intravenously, or intramuscularly. The total dose given over a period of time may far exceed the single M.L.D. as shown in the series with intravenous injections, without producing any toxic signs. Apparently the drug is gradually excreted or destroyed in the body. The increase in body weight is not prevented and the general health not impaired. None of the visceral organs undergo any changes that can be referred to the effect of the drug.

Although each dose raises blood pressure to a high level for over twenty minutes as seen in anesthetized animals (fig. 1), it does not appear to produce any sclerotic changes in the vascular system. The two instances of aortic sclerosis observed in the series with intravenous injections were in all probability due to spontaneous development which is very apt to occur in rabbits. Thus, one of the two control animals showed degenerative changes in the media of the aorta also. The question of tolerance can be dismissed on the ground that (1) a rabbit treated repeatedly with ephedrine is still susceptible to a M.L.D.; (2) mydriasis occurs after each injection; and (3) there is no lessening of blood pressure raising effect after repeated doses.

In white rats, repeated use of large doses intravenously does not seem to injure the visceral organs. The abnormality observed in our series may be entirely referred to the infection of cysticercus of Taenia crassicollis in the liver.

SUMMARY

1. Ephedrine administered either intravenously, intramuscularly or per os, to small white rabbits in doses of 25 milligrams, daily for four weeks except Sundays, does not produce any observable toxic effects.

2. The total amount of ephedrine given by intravenous injection was as great as 8 times the M.L.D. calculated for the initial body weight of the animal.

3. All of the animals, with few exceptions, show a large gain in body weight, after a period of about one hundred forty days.

4. The visceral organs from treated animals by gross and microscopic examination do not show any definite or uniform lesion that can be attributed to the effect of ephedrine.

5. No tolerance is developed in rabbits to the mydriadic or pressor action of ephedrine by repeated administration nor is there any change in the dose required to cause death.

6. In white rats, ephedrine given in doses of 100 mgm. per kilo every other day for seven days, does not produce any damage to the visceral organs which cannot be explained by other causes.

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