274 (2797)

The effect of repeated administration of ephedrine.

By K. K. CHEN.

[*From the Laboratory of Pharmacology of Peking Union Medical College, Peking, China.*]

In our preliminary report,[1] the results from a rabbit with daily injections of 20 mg. of ephedrine per kilo intravenously for nine days were mentioned. Our present paper deals with a study of the same nature, but much more extensively.

Three series of young, healthy rabbits were selected for experimentation. One series of ten was given intravenous injections of 25 mg. of ephedrine sulphate, irrespective of their body weight, daily for four weeks except Sundays. The total dose amounted to as high as 8.172 times the M. L. D. with reference to the initial body weight, or 817.2 per cent of the M. L. D. Another series of ten was given daily intramuscular injections of 25 mg. of ephedrine sulphate for four weeks except Sundays. Still another series of ten was administered orally 25 mg. of the drug for the same length of time. The total dose in the former exceeded a little the intramuscular M. L. D., while that in the latter was slightly below the oral M. L. D. In all cases with one exception, the body weight was increased, and some animals gained as much as 61 per cent of the initial body weight. Practically all of them were kept alive for about 140 days, and then sacrificed.

Locally, in the intravenous injection, there was development of thrombosis which was gradually absorbed. In the intramuscular administration there was fibrosis at the site of injection, which also disappeared in course of time, for at the end of experiment it was impossible to locate the point of injection. When given by mouth ephedrine did not produce any detectable lesion in the gastro-intestinal tract that could be seen in the postmortem examination.

In these animals, a physiological dose of ephedrine still produced usual effects such as mydriasis, rise in blood pressure and acceleration of heart rate when they were anesthetized. They could still be killed by a M. L. D. The question of habit forma-

[1] Chen, K. K., and Schmidt, Carl F., *J. Pharmacol. and Exper. Therap.*, 1924, xxiv, 339.

tion can apparently be eliminated in so far, at least, as the rabbits are concerned.

At the time when the animals were sacrificed, autopsy was done in every case. Sections were made from lungs, liver, spleen, adrenal body and kidney. While the examination of these sections has not yet been completed, it suffices here to say that no gross pathology can be made out; and that, as far as we have gone, there has not been any demonstrable abnormality in the structures of these visceral organs. There was some cloudy swelling in most of the kidneys, but that was shared by the control animals also.

As ephedrine is a drug that raises blood pressure, it is interesting to study whether there is any development of arteriosclerosis due to hypertension, as many investigators have shown with injection of adrenaline. In one of our several rabbits under anesthesia, an intravenous injection of 0.5 cc. of adrenaline (1-100,000) raised the blood pressure from 96 to 150 mm. Hg., which came back to normal within three minutes; while a similar injection of 25 mg. of ephedrine sulphate (the dose used for daily injection of our animals) in the same animal raised the pressure from 86 to 157 mm. Hg., which did not fall to the former level until twenty-five minutes after. If hypertension were a predisposing factor of arteriosclerosis, we would expect ephedrine to be a more potent drug for the production of such a disease. In fact, it has been reported[2] that repeated intravenous injections of ephedrine in rabbits caused arteriosclerosis chiefly in the aorta, especially in old or pregnant animals. For the same purpose, we examined in some of our experimental rabbits both grossly and microscopically the heart, aortic arch, thoracic aorta, abdominal aorta, and subclavin, crotid, brachial, cerebral, retinal, splenic, superior mesenteric, inferior mesenteric, renal, femoral, and popliteal arteries. As far as it can be said at present there was only one animal in the series by intravenous injections, none in the other two series, which could be suspected of arteriosclerosis. But it happened that one of our control animals showed the same lesion. So it is quite probable that it was due to spontaneous development.

In a series of white rats, we injected intravenously large doses of ephedrine every other day for seven days. Each dose

[2] Kiyono, K., and Higashihara, K., Kyoto Igaku Zasshi, 1919, xv, 154.

amounted to 74 per cent of M. L. D. Their body weight was constant or somewhat decreased two to three days after the injection, but in all cases it subsequently increased. There were no marked pathological lesions that could be attributed to the effect of the drug.

275 (2798)

The effect of ephedrine on digestive secretions.

By K. K. CHEN.

[*From the Laboratory of Pharmacology and Physiology of Peking Union Medical College, Peking, China.*]

In our preliminary report,[1] a very brief mention was made of the action of ephedrine on the submaxillary gland. In this investigation, the whole system of digestive secretions was studied, including the salivary, gastric, pancreatic, bile and intestinal secretions.

Of nine anesthetized dogs whose Wharton's duct was exposed and canulated, ephedrine increased the submaxillary flow only in two cases, but had no effect in others. The increase in flow in both animals took place after atropinization when chorda stimulation was ineffective, an evidence that the parasympathetic system has no relation to the action of ephedrine. The dose given did not seem to play any part, for in one animal we injected as much as 40 mg. per kilo in contrast to an ordinary effective dose (1-2 mg. per kilo), and we failed to notice any change in secretion. The increase in submaxillary secretion in dogs by ephedrine is therefore rather an exception than a rule.

In non-anesthetized animals, however, an intravenous injection of large doses of ephedrine usually gives rise to increase of saliva, especially in dogs. Thus in one animal a dose of 25 mg. per kilo produced profuse salivation. When a dose slightly below the M. L. D. was administered, the increase in salivary flow was a constant feature.

[1] Chen, K. K., and Schmidt, Carl F., *J. Pharmacol. and Exper. Therap.*, 1924, xxiv, 339.