PEKING BRANCH

University of Peking Medical School, February 25, 1925.

193 (2716)

The acute toxicity of ephedrine.

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In our preliminary report,[1, 2] mention was made concerning the toxicity of ephedrine in rats and rabbits. As the drug is possibly of clinical importance in the treatment of asthma and hypotension as demonstrated in the Peking Union Medical College Hospital, it is thought desirable to study its toxicity more in detail.

Ephedrine sulphate was used in all our experiments.

In frogs, the M.L.D. by injection into the anterior lymph sac varies from 530 to 680 mg. per kilo of body weight. The animal shows weakness in the legs half an hour after the injection of such a dose, and dies in 2 to 3 hours without any noticeable convulsions.

Of the mammals investigated, the white rat appears to be most tolerant to the drug. By intravenous injection, the M.L.D. in mg. per kilo of body weight in rabbits is 66-70, in dogs 70, in cats 75, and in white rats 135-140. It appears that animals weighing over a kilo have their M.L.D. approximating 70 mg. per kilo. Death is almost immediate and follows clonic convulsions. If the chest is opened when the animal is apparently dead, the heart is seen either in fibrillation or in incomplete block. The skin and the mucous membrane do not appear to be blanched. In anesthetised animals, the M.L.D. causes an immediate and permanent fall in blood pressure to 10-15 mm. Hg, accom-

1 Chen, K. K., and Schmidt, Carl F., PROC. SOC. EXP. BIOL. AND MED., 1924, xxi, 351.

2 Chen, K. K., and Schmidt, Carl F., *J. Pharm. Exp. Ther.*, 1924, xxiv, 339.

panied by a tremendous decrease of intestinal and kidney volumes. The respiratory movements may persist for a short time after the blood pressure has reached the lowest level. The fall of pressure is not prevented by artificial respiration after the destruction of the brain and the cord. Death is therefore least likely due to the failure of the respiratory center. The cardiac changes are worthy of notice. Rabbit's heart perfused by Langendorff-Locke's apparatus shows auricular and ventricular fibrillation after a large dose of ephedrine, which cannot be attributed to the slight change, if any, in the coronary outflow of H-ion concentration. The action is obviously not of central origin. Electrocardiographic studies reveal very prompt alterations in the curves after the intravenous injections of a M.L.D. There is disappearance of sinus rhythm, with the occurrence of bundle-branch-block which is finally followed by ventricular fibrillation. These changes are not due to vagal effect because they are not prevented by complete atropinization.

Recovery from sublethal doses is always complete. Repeated injections of small amounts in the same animal do not raise its M.L.D, showing that a tolerance is not developed.

By different methods of administration, the M.L.D in mg. per kilo varies; thus, in rabbits, it is 590-600 per os, 340 by intramuscular injection, 320-360 by subcutaneous injection, 310-390 by intraperitoneal injection, and 66-70 by intravenous injection. Ephedrine given other than by intravenous injection does not produce convulsions until 1 to 2½ hours after, and death in 2 to 7 hours. These convulsions are not due to cortical stimulation because they are not abolished by decerebration. There is definite change in the electrocardiogram during the convulsive stage, as illustrated by prolongation of P-R interval, widening of Q-R-S waves, and the occurrence of bigeminal rhythm due to ventricular extrasystoles.