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Synthetic Ephedrine.*

K. K. CHEN.

From the Department of Pharmacology, Johns Hopkins University.

Ephedrine was successively synthesized by Nagai,¹ Späth and Göhring,² and Eberhard.³ The chemical difference between the ephedrine occurring naturally and that prepared synthetically lies in their optical activity, the natural being laevo-rotatory while the synthetic is optically inactive. From the pharmacological point of view, one would expect synthetic ephedrine to possess an action similar to that of the natural product but to be less potent; for it is known that the racemic form of several well known substances, notably hyoscyamine, hyoscine, homatropine, and epinephrine is weaker than the *l*-form.⁴ After the recent demonstration of the action and clinical uses of the ephedrine isolated from the Chinese medicinal herb Ma Huang, investigators studied the synthetic ephedrine, and showed its comparable effects to those of the natural product.^{5, 6, 7, 8, 9, 10, 11}

The present work consists of a comparison, both qualitative and quantitative, of the natural ephedrine prepared under the supervision of the author in 1924, and the synthetic ephedrine courteously supplied by E. Merck of Darmstadt, Germany. Its trade name is ephetonine. A preliminary clinical trial is also included. The hydrochloride of the synthetic compound melts at 187° C., is optically inactive, in aqueous solution at 21° C., and gives with cupric hydroxide a purple color extractable by ether,¹² It is apparently stable to light, air and heat.

When applied locally to the conjunctival sac of rabbits and man, synthetic ephedrine produces mydriasis with the preservation of the light reflex. An intravenous injection of the solution in the dosage of 2 mg. per kg. in anesthetized dogs, cats, or rabbits, results in a prolonged rise of arterial blood pressure, lasting for 25 to 30 minutes or longer, much the same as that seen after a similar injection of the natural ephedrine. It accelerates the pulse rate, especially after atropinization, and constricts the vessels of the kidney, the nasal mucous membrane and accessory nasal sinuses in dogs. Ergotamine reduces its pressor action, but does not invert it to a depressor action as it does with epinephrine. The synthetic ephedrine restores the respiration and blood pressure after large doses of morphine in

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anesthetized animals, and relieves bronchial spasm artificially induced by the intravenous injection of arecoline or physostigmine. It contracts the isolated guinea pig's uterus. It appears clear, therefore, that qualitatively it is similar in all respects to the natural ephedrine.

Quantitatively, the pressor action of the natural and the synthetic ephedrine cannot be compared in the same anesthetized animal, for the initial injection of the one always overpowers the subsequent injection of the other. In man, a dose of 50 to 100 mg. of the synthetic ephedrine *per os* sometimes raises the systolic blood pressure by a few mm. of mercury, but is much less effective than an equal dose of the natural ephedrine given to the same subject on a different day. In Caucasians, the synthetic ephedrine appears to be a less powerful mydriatic than the natural, but the ratio of the increase of the transverse diameter of the pupil caused by a 10% solution of the former to that caused by a 10% solution of the latter in the same subject, calculated from a limited number of observations, has not exceeded 1.0:1.1. The M. L. D. of each drug in the form of the hydrochloride in white rabbits is 60 mg. per kilogram. Aside from the inequality of the pressor action in man after oral administration the difference of activity between the natural and the synthetic ephedrine does not seem to be great.

Clinically, the synthetic drug was given in 50 mg. dosage *per os* to several cases of bronchial asthma of mild or moderate severity. Most of the patients had relief from their attacks. In 4 cases of hypertrophied turbinates and 3 cases of acute rhinitis, a 5% solution of the synthetic ephedrine hydrochloride, applied locally, definitely caused a constriction lasting for 2 to 3½ hours. There were no signs of irritation or secondary congestion. It is hoped that by further comparative study, the synthetic drug may be proven to be clinically as useful as the natural ephedrine.

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⁴ Cushny, A. R., Biological Relations of Optically Isomeric Substances (Dohme Lectures), Baltimore, Williams and Wilkins Company, 1926.

⁵ Kreitmair, H., *Münch. med. Wchnschr.*, 1927, lxxiv, 190; Merck's Annual Report, 1927, Part III, 238.

⁶ Hess, F. O., *Münch. med. Wchnschr.*, 1927, lxxiv, 565.

⁷ Petow, H., and Wittkower, E., *Münch. med. Wchnschr.*, 1927, lxxiv, 767.

⁸ Saxl, S., *Wien. klin. Wchnschr.*, 1927, xl, 754.

⁹ Fischer, W., *Münch. med. Wchnschr.*, 1927, lxxiv, 1047.

¹⁰ Berger, W., and Ebster, H., *Münch. med. Wchnschr.*, 1927, lxxiv, 1083.

¹¹ Berger, W., Ebster, H., and Heuer, M., *Münch. med. Wchnschr.*, 1927, lxxiv, 1317.

¹² Chen, K. K., and Kao, C. H., *J. Am. Phar. Assn.*, 1926, xv, 629.

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The Racial Difference of the Mydriatic Action of Ephedrine, Cocaine, and Euphthalmine.*

K. K. CHEN AND EDGAR J. POTH.

From the Department of Pharmacology, Johns Hopkins University.

In the continuation of the study of ephedrine as a mydriatic,¹ it was found that in Caucasians a 10% solution uniformly produces mydriasis by local application, and that its mydriatic action is further strengthened if it contains, in addition, 0.1% of homatropine hydrobromide, or 1.0% of euphthalmine hydrochloride. These solutions are useful in ophthalmoscopic examination, especially from the patients' point of view, because they cause almost no change in accommodation. There were no untoward symptoms or signs noted. Only in iritis and uveitis do they fail to dilate the pupil.

TABLE I.

A comparison of mydriasis occurring in different races, 1 hour after an instillation of 2 drops of the solution, observed in diffuse daylight.

Hydrochloride of	Strength of solution in per cent	Race	Number of observations	Mean increase† of transverse diameter of the pupil in mm.
Ephedrine	10	Caucasian	21	2.0+
		Chinese	5	0.5+
		Negro	21	0.5
Pseudo-ephedrine	10	Caucasian	20	1.0
		Negro	21	0.0
Synthetic Ephedrine	10	Caucasian	19	1.5
		Negro	21	0.0
Cocaine	4	Caucasian	20	2.0—
		Negro	21	0.0
Euphthalmine	5	Caucasian	20	2.5+
		Negro	21	1.0

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† Mean increase is the average of the central 3 or 4 figures of the data arranged numerically.