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The Persistence of Effect of Thevetin.

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Thevetin is a glucoside obtained from the kernels of the "bestill" tree; *Thevetia neriifolia* (Jussieu) family Apocynaceae. Chen and his associates[1, 2, 3] have discussed the bibliography and described the various constituents of these nuts. They have also studied experimentally and clinically the biological potency and characteristic digitalis effect of thevetin.[1-6]

A limited number of experiments concerned with the persistence of effect of thevetin in the cat has been reported by Chen and Chen,[2] the results of which indicate that the physiological effect of thevetin endures only for a relatively short period of time, approaching ouabain in this respect.

In view of recent observations which we have made on the persistence of effect of several digitalis substances in the pigeon,[7] it was of interest to extend our studies to include thevetin for purposes of comparison. About 130 pigeons were employed in the present observations.

The thevetin* was standardized by the intravenous pigeon fatal dose method as described previously.[8] A 1-10,000 thevetin solution was injected into the alar vein of etherized pigeons, 0.5 cc. every 10 minutes. The minimum lethal dose (M.L.D.), *i. e.*, weight of bird under amount of drug, was determined for 24 pigeons. The average M.L.D. was 1.95 mg. per kg. Thevetin was also standardized upon 10 cats according to the technic of Hatcher and Brody[9] and in conformity with experiments of Chen and Chen.[2] The cat unit was 1.0 mg. Chen and Chen[1] originally obtained a slightly higher

1 Chen, K. K., and Chen, A. Ling, *J. Pharm. and Exp. Therap.*, 1933, **48**, 270. (Proceedings).

2 Chen, K. K., and Chen, A. Ling, *J. Pharm. and Exp. Therap.*, 1934, **51**, 23.

3 Chen, K. K., and Chen, A. Ling, *J. Biol. Chem.*, 1934, **105**, 231.

4 Arnold, Harry L., Middleton, William S., and Chen, K. K., *Am. J. Med. Sci.*, 1935, **189**, 193.

5 Middleton, William S., and Chen, K. K., *Am. Heart J.*, 1936, **11**, 75.

6 Noble, Thomas B., and Chen, K. K., *Am. J. Med. Sci.*, 1936, **192**, 639.

7 Haag, H. B., *J. Pharm. and Exp. Therap.*, 1936, **58**, 42.

* We wish to thank Eli Lilly & Company for their kindness in supplying the sample of thevetin used in these studies.

8 Haag, H. B., and Woodley, J. D., *J. Pharm. and Exp. Therap.*, 1934, **51**, 360.

9 Hatcher, R. A., and Brody, L. G., *Am. J. Pharm.*, 1910, **82**, 360.

figure: 1.24 mg., but subsequently,[2] with a more purified product, they found the cat unit to be 0.85 mg. From our studies upon pigeons and cats thevetin appears to be about 1/10 as active as ouabain, U.S.P. XI. Chen and Chen[2] found that purified thevetin was about 1/8 as toxic for frogs, and 1/7 as toxic for cats as ouabain.

In performing the persistence studies, 60% of the average M.L.D. of thevetin was injected intravenously into a series of pigeons, and then at various intervals the amount of thevetin necessary to produce death was ascertained by slow intravenous injection (0.5 cc. of a 1-10,000 solution every 10 minutes). Obviously, then, the difference between this fatal dose and that previously established for normal controls would represent the thevetin effectiveness still remaining. The average value secured from 11 to 20 birds was used for determining the degree of persistence at each time interval studied. As has been noted for other digitalis substances,[7] there were extremely wide individual variations in the degree of continuance of action exhibited.

Following the injection of 60% of the average M.L.D. of thevetin into the 110 birds used for the actual persistence studies 35, or 31.8%, died within several hours. This necessitated a recalculation of the lethal dose for the surviving animals, which was done in the manner previously described,[7] with the result that the "compensated" average M.L.D for these tolerant birds was raised from 1.95 mg. to 2.18 mg. Initial doses of 75% of the average M.L.D.

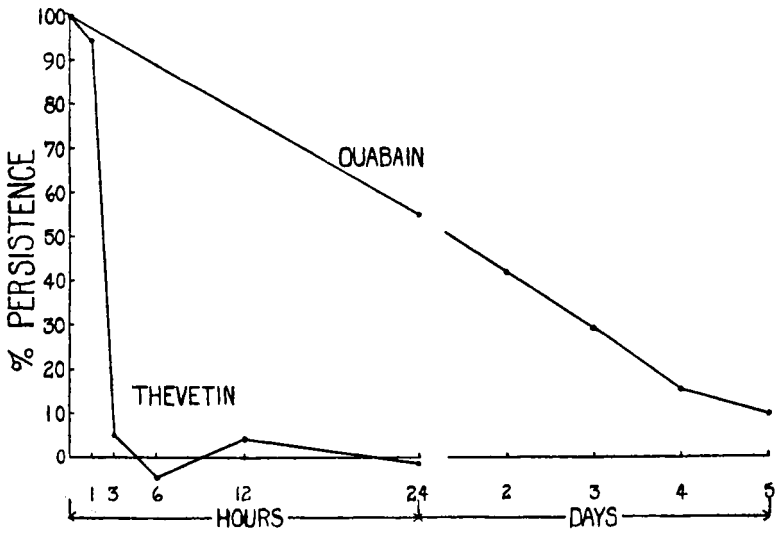

FIG. 1.
Persistence of Action of Thevetin and Ouabain in Pigeons.

resulted in such a high mortality that they could not be used in these studies.

Graph 1 depicts the results obtained in these persistence studies on thevetin as compared with a previously established curve for ouabain.[9] We were astounded by the relative evanescence of the thevetin action, finding practically no persistence of effect in the pigeon after 3 hours. Similar experiments on 8 cats (employing an initial dose of 75% of the average M.L.D.) showed about 15% of its effectiveness remaining after 24 hours. This figure approaches the limit of error for this method of bioassay. These experiments upon pigeons and cats indicate that thevetin is one of the most rapidly eliminated (physiologically) digitaloids yet described.

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Ureteral Pain as Determined by Faradic Stimulation in Man.

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In studying the ureteral contractions by the electrical method as described by Paladini,[1] it occurred to us that the localization of ureteral pain could be studied by applying a stimulus to the electrode and having the patient describe the area in which the pain was felt. Experiments of this kind have been extensively done on the pleura, pericardium and peritoneum by Capps[2] and more recently by Boyden and Rigler[3] on the gastrointestinal tract.

Since the electrodes used in the contraction studies were not quite suitable for pain distribution studies, a special electrode with a single metal contact at the tip was manufactured for this purpose by the American Cystoscope Makers, Inc. A Harvard inductorium was used for the source of current with 6 volts on the primary circuit. The inactive electrode was applied to the chest.

The patient was cystoscoped, the ureteral catheter electrode was introduced into the ureter and stimulation was made at various

1 Paladini, A., *Arch. ital. di urologia*, 1934, **11**, 211.

2 Capps, J. A., An Experimental and Clinical Study of Pain in the Pleura, Pericardium and Peritoneum, Macmillan Company, New York, 1932.

3 Boyden, E. A., and Rigler, L., *J. Clin. Invest.*, 1934, **13**, 833.