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CROSS TOLERANCE: DECREASED RENAL RESPONSE TO THEOBROMIN AND THEOPHYLLIN IN RABBITS TOLERANT TOWARD CAFFEIN

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The close chemical relationship of the methylated xanthines used in therapeutics, suggests, in view of their similarity in action, the possibility of crossed tolerance existing between the different members. A fact that adds further to the possibility of crossed tolerance existing between these methylated xanthines is the common fate of demethylization occurring in the body.

To determine the presence or absence of crossed toleration it is necessary to study the comparative response to a common action. Caffein, theobromin and theophyllin share most equally in the power to cause increased formation of urine. This action offers a rather definite means of determining comparative tissue response and becomes the action of choice for study.

It has been shown (1) that the toleration of caffein developed in rabbits includes a decreased renal response toward the drug. It remains to determine the minimal effective diuretic doses of theobromin and theophyllin in caffein tolerant rabbits and compare them with the doses required to produce similar results in control rabbits.

EXPERIMENTAL METHOD

Rabbits were made tolerant toward caffein by giving subcutaneous injections of the drug, six days each week, with doses increasing from 50 to 90 mgm. per kilogram. After a period of approximately four months of such injections a rabbit requires somewhat more than double the dose necessary in a control rabbit to produce an increased flow of urine (1). Renal

response to theobromin and theophyllin was determined according to the method described in a previous paper (1). The drug under study was injected into a lateral ear vein at a slow rate in order to minimize endocardial irritation and temporary fluctuations in blood pressure.

RENAL RESPONSE TO THEOBROMIN

The normal rabbit requires about 1.5 mgm. of theobromin per kilogram, intravenously, to respond with a minimal increase in urine flow. Figure 1 illustrates such a response to 1.5 mgm. dosage. Figure 2 shows the response to an interrupted injection of the same amount, the second segment of the curve showing the failure of the kidney to respond to an intravenous injection of 1 mgm. theobromin per kilogram, the third segment showing an increased secretion of urine following an added 0.5 mgm. per kilogram given a few minutes later. No diuresis occurs in rabbits given 1.25 mgm of theobromin per kilogram. Any amount over 1.5 mgm. produces a more copious and long continued flow of urine than is shown in figures 1 and 2.

A rabbit tolerant toward the action of caffein does not show any change in rate of urine flow when injected intravenously with 2.1 mgm. of theobromin per kilogram. The majority of tolerant rabbits injected with 2.2 mgm. of theobromin exhibit suggestive but uncertain fluctuations in rate of renal secretion. Each tolerant rabbit injected with 2.3 mgm. of theobromin gave a definite, usually moderate increased rate of urine flow. Figure 3 illustrates the type of response obtained with 2.2 mgm. doses; figure 4 shows the curve of renal secretion following 2.3 mgm. amounts. Similar results were obtained with these doses in rabbits with cannulized ureters and in those with retained catheters in the bladder.

One may reasonably conclude from these results that rabbits tolerant toward caffein, in which a diminished renal response to the drug exists, exhibit a crossed toleration toward theobromin in so far as renal action is concerned. No difference in degree of crossed toleration was found in those animals that

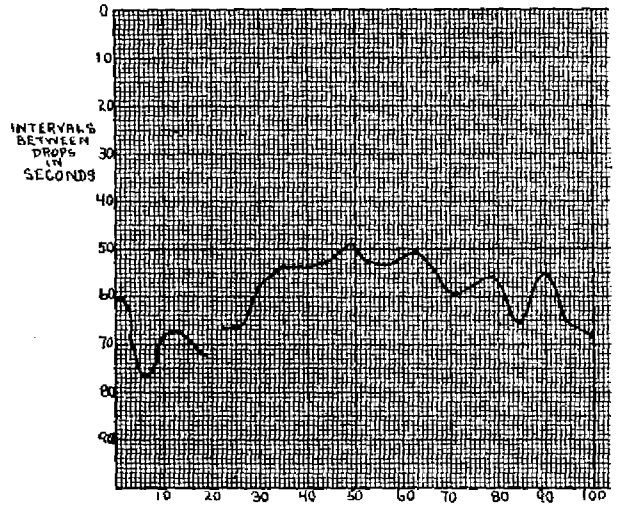

FIG. 1. THEOBROMIN, 1.5 MGM. PER KILOGRAM, INJECTED INTRAVENOUSLY IN CONTROL RABBIT DURING THE BREAK IN THE CURVE

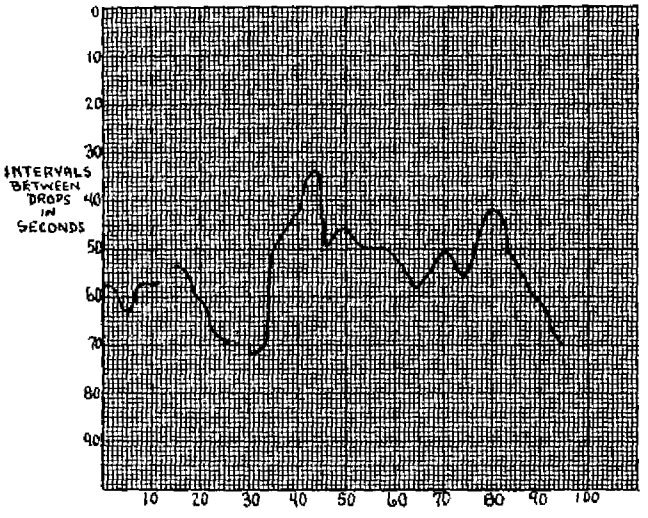

FIG. 2. THEOBROMIN, 1 MGM. PER KILOGRAM WEIGHT, INJECTED INTRAVENOUSLY IN CONTROL RABBIT DURING THE FIRST BREAK IN THE CURVE; FOLLOWED BY A SECOND INJECTION OF 0.5 MGM. PER KILOGRAM DURING THE SECOND BREAK

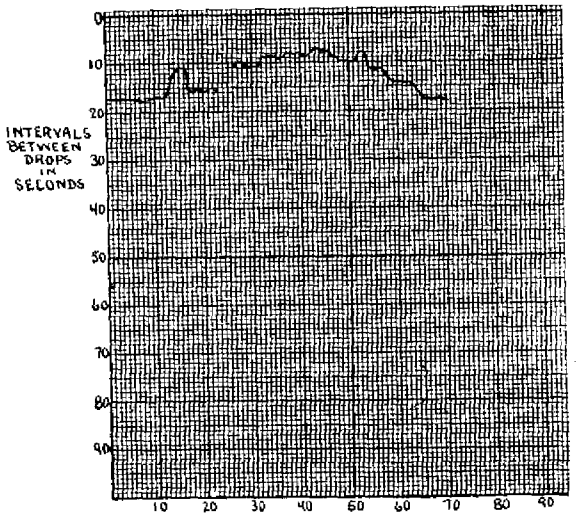

FIG. 3. THEOBROMIN, 2.2 MGM. PER KILOGRAM WEIGHT, INJECTED INTRAVENOUSLY IN A CAFFEIN TOLERANT RABBIT DURING THE BREAK IN THE CURVE

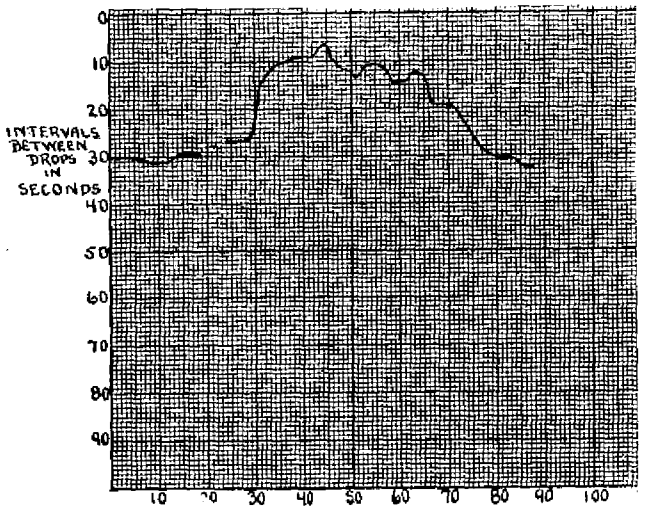

FIG. 4. THEOBROMIN, 2.3 MGM. PER KILOGRAM WEIGHT, INJECTED INTRAVENOUSLY INTO A CAFFEIN TOLERANT RABBIT DURING THE BREAK IN THE CURVE

had received caffein for one year as compared with those that had been injected with the drug but one-half that length of time.

RENAL RESPONSE TO THEOPHYLLIN

The minimal intravenous dose of theophyllin required to produce an increase in urine flow in a control rabbit is 0.2 mgm. of the drug per kilogram weight of rabbit. No change in rate of urine secretion follows the intravenous injection of 0.1 mgm. theophyllin per kilogram. A curve illustrative of the slight

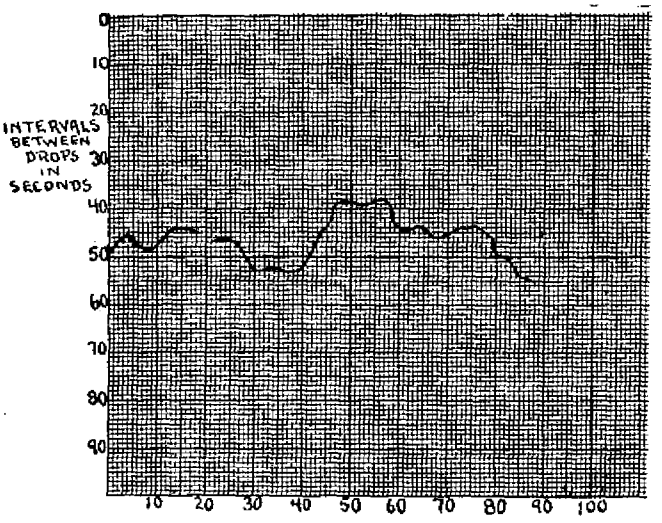

FIG. 5. THEOPHYLLIN, 0.2 MGM. PER KILOGRAM WEIGHT, INJECTED DURING THE BREAK IN THE CURVE, IN EAR VEIN OF CONTROL RABBIT

Illustrating minimal renal response

renal action following a dose of 0.2 mgm. theophyllin is shown in figure 5. A more marked increase in rate of secretion follows 0.3 mgm. theophyllin in control rabbits.

A rabbit tolerant toward caffein does not show any alteration in rate of urine flow when 0.3 mgm. theophyllin per kilogram weight is injected intravenously. With 0.4 mgm. doses, caffein tolerant rabbits exhibit minimal to moderate increases in rate of secretion of urine. The most marked response to this dosage

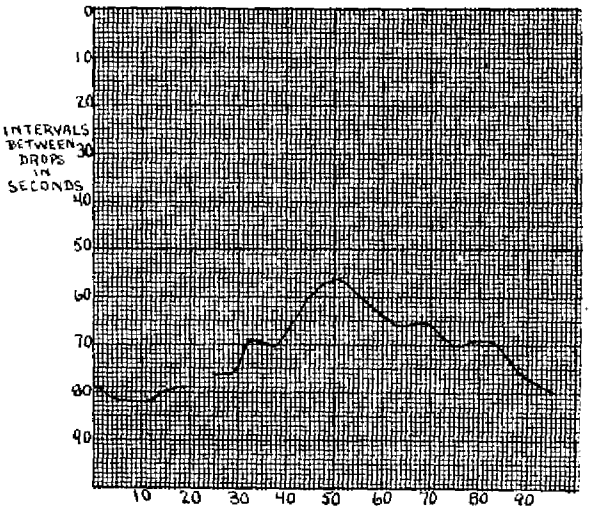

FIG. 6. THEOPHYLLIN, 0.4 MGM. PER KILOGRAM WEIGHT, INJECTED DURING THE BREAK IN THE CURVE INTO AN EAR VEIN OF A CAFFEIN TOLERANT RABBIT

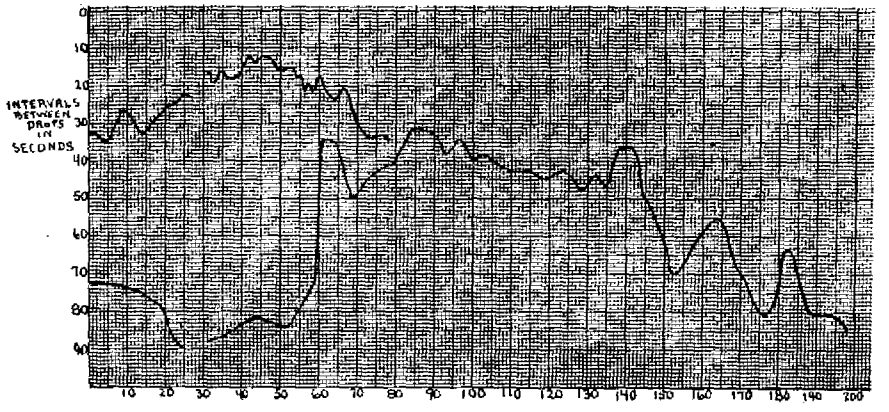

FIG. 7. THEOPHYLLIN, 0.5 MGM. PER KILOGRAM WEIGHT, INJECTED INTRAVENOUSLY DURING THE BREAK IN EACH CURVE

Illustrating comparative renal response in caffein tolerant versus control rabbits.

obtained in several caffein tolerant rabbits is shown in figure 6. Figure 7 shows two curves illustrating urine flows obtained with 0.5 mgm. theophyllin per kilogram in caffein tolerant and in control rabbits. The comparative responses with a dose active in each type is shown, the lesser reaction obtained with the caffein tolerant rabbit illustrating the degree of crossed toleration toward theophyllin developed in caffein tolerant rabbits.

CONCLUSION

Rabbits tolerant toward the action of caffein exhibit a decreased response toward the diuretic action of theobromin and theophyllin.

REFERENCE

(1) MYERS, H. B.: Jour. Pharm. and Exper. Therap., vol. xxiii, no. 6, 1924, p. 465.