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A COMPARATIVE STUDY OF TWO XANTHINE DIURETICS.*

THEOPHYLLINE SODIUM ACETATE AND THEOBROMINE SODIUM SALICYLATE.

BY A. RICHARD BLISS, JR.,[1] AND ROBERT W. MORRISON.[2]

INTRODUCTION.

No reliable quantitative clinical experiments on the comparative diuretic effects of the various Xanthine derivatives in graduated doses have been reported in the literature, and, with the exception of one quantitative report in German and the reports of the authors of this paper, there are no published reports concerning the actions produced in laboratory animals by graduated doses of the newer Theobromine and Theophylline derivatives. This investigation was prompted by numerous inquiries concerning the diuretic powers of these agents, and this paper is the second of a series of reports concerning comparative studies of Theobromine and its derivatives "Theocalcin" (Theobromine Calcium Salicylate) and "Diuretin" (Theobromine Sodium Salicylate), and Theophylline and its derivatives "Phyllicin" (Theophylline Calcium Salicylate) and "Theocin Soluble" (Theophylline Sodium Acetate).

Although Xanthine possesses very little diuretic power, certain derivatives containing the Xanthine nucleus are among the most powerful of the diuretics. Of the dimethylxanthines Theophylline and Theobromine are the most active, while Caffeine is the most active of the trimethylxanthines.

Because of its pronounced central effects, Caffeine has been more or less supplanted as a diuretic by Theophylline and Theobromine which have not its strong central effects, and which are credited generally with more powerful diuretic actions. Some writers consider Theobromine to be more reliable in action and less prone to

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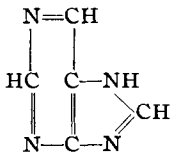
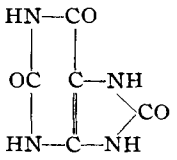
excite disagreeable nervous symptoms, although many claim that it is apt to be irritating to the kidneys. Theophylline is credited with being more prompt in producing diuresis, and its action is supposedly of shorter duration. It has little, if any, central stimulating action in the dosage usually employed, but the drug is said to be more irritating to the gastrointestinal tract and to the kidneys.

Theobromine, Theophylline and Caffeine may fail to produce a diuresis if there is no excess of water in the tissues, as with rabbits which have been kept for a long period on a dry diet. Apparently, these agents hasten the excretion of excess water (6). However, it has been found that Caffeine may fail to increase the secretion of urine even when water is at the disposal of the animal. Schroeder (12) in 1886 demonstrated that Caffeine invariably acts as a diuretic in rabbits providing the nerves going to the kidneys are first sectioned, or Chloral Hydrate or Paraldehyde are administered first to the animals, measures thought to prevent an interfering vasomotor stimulation. Diuresis is always obtained in the dog if the kidneys are first denervated or the vasomotors paralyzed, and section of the vagus nerves results in increased diuresis, or induces it when absent. These results have led to the conclusion that the vagus nerves carry inhibitory fibres to the secretory cells of the dog's kidneys, and that these fibres are stimulated by Caffeine (1). Theobromine, however, does not stimulate these vagus fibres, and this drug produces diuretic effects even when the nerves are intact (14).

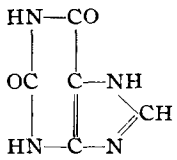
FORMULAS.



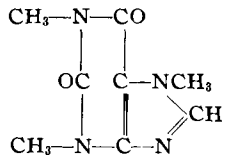
Purin, $C_5H_4N_4$.



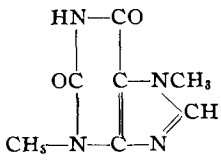
Uric Acid, $C_5H_4N_4O_3$.



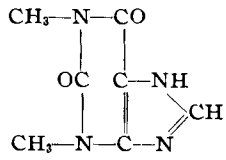
Xanthine, $C_5H_4N_4O_2$.



Caffeine, Trimethylxanthine.



Theobromine.



Theophylline.

Wallace and Pellini (19) demonstrated that Theophylline, Theobromine, Caffeine and "Diuretin" not only failed to produce a diuretic action in dogs kept on a fixed food and water intake, but instead showed a decided decrease in the daily output of urine which often amounted to 50% of the normal volume. Further, that the Sodium Chloride content was diminished also. These investigators suggested that there is a shift of water and Sodium Chloride from the circulating

blood into the tissues, and that Caffeine and its allies bring this about through the production of a dilatation and an increased permeability of the capillaries in the splanchnic organs and muscles, these effects overshadowing the kidney action in animals which are in water balance. The diuretic effect, then, appears when there is an excess of water in the body or when the tissues give off some of their stored water.

The effects of Theobromine on the kidneys are stated generally as being practically identical with those of Caffeine. Solis-Cohen and Githens (15) claim that Theobromine differs from Caffeine in not stimulating the vasomotor and the inhibitosecretory nerves of the kidney, and that it consequently produces diuresis constantly in rabbits and dogs. Sasaki (10) found that the continued administration of Theobromine increased water excretion in rabbits only when these animals were kept on a wet diet; but that chloride excretion is increased also on a dry diet, *i. e.*, independently of a diuretic action. "Diuretin" (Theobromine Sodium Salicylate), "Agurin" (Theobromine Sodium Acetate) and other double salts of Theobromine have been widely employed in the place of the free substance itself because of their greater solubility in water.

Hellin and Spiro (5) found that Caffeine is effective in pure tubular nephritis but that it fails in glomerular and general nephritis. They reported that Theophylline and Theobromine are more effective. Pearce, Hill and Eisenbrey (8) and Schlayer and Hedinger (11) have confirmed these observations. Some consider these findings as important evidence that the diuretic effect of Caffeine is exerted on the glomerular circulation and filtration, and not on the tubular epithelium.

Sollmann and McComb (16) report that Caffeine in ordinary doses does not appear to produce any demonstrable injury even in nephritic subjects, but that in larger doses it may increase albuminuria. They advise against the continued use of Theophylline even in moderate doses. Miller (7) is of the opinion that Theophylline and Theobromine may cause gastric and renal irritation. Chevalier (3) reports the presence of toxic impurities in commercial samples of Theobromine. Emerson (4) observed no increased albuminuria in acute or chronic nephritis following the administration of Theobromine. Pouchét and Chevalier (9) claim that the Theophylline in large doses will injure glomerular and tubular epithelia.

Vieth and Leube (18) determined the most effective daily doses of Theobromine, "Diuretin," "Phyllicin," "Theocalcin," et cetera, in rabbits. These investigators concluded that of the acid groups introduced in position 1 of the Theobromine molecule only the acetyl group increased diuresis. Bürgi's (2) assumption that the diuretic powers of the Xanthine derivatives are enhanced by salts was confirmed by these investigators in their experimental work with certain salicylates. They demonstrated that the Calcium salts of the Xanthine derivatives may influence diuresis in rabbits if this metal is combined with Salicylic Acid.

In human patients, Stewart (17) observed that Theobromine Calcium Salicylate was less irritating to the stomach than Theophylline and Theobromine Sodium Salicylate; and that this drug may be administered daily for months without untoward symptoms. Selig (13) is the only writer who has reported the effect of Theobromine Calcium Salicylate on the volume of urine excreted by man. He observed that this agent induces diuresis.

ANIMAL EXPERIMENTATION.

The series of experiments herewith reported were carried out on adult rabbits which were kept on a complete and balanced diet determined for the individual animal. The daily water-intake was carefully controlled. The animals were housed in individual metabolic cages. New animals were used for each dose series. Before beginning the administration of the drugs, the animals were observed over a period of days to establish whether they were in a state of metabolic equilibrium. The drugs, in aqueous solution or mixed with water, were administered three times a day (morning, noon and evening) by stomach tube over a period of four days and the observations continued thereafter until the daily output approached that of the premedication period. The daily observations included the total volume of urine voided, the determination of the physical characteristics of the urine, reaction, specific gravity, total solids, uric acid, urea, albumin, sugar and microscopic examination.

RESULTS.

The tables which follow give the observations made and the results obtained in this series of experiments with Theophylline Sodium Acetate ("Theocin Soluble") and Theobromine Sodium Salicylate ("Diuretin").

The first table (Table I) represents the type of daily record which was kept for the individual animal.

Tables II and III present the average percentages of increase and decrease in the urine volume output for the medication periods, the average percentages of increase calculated from the maximum 24-hour urine output during the medication periods, the average percentages of increase in solids, also in uric acid, the increase in albumin, also in sugar, the duration of diuresis, and the days during which the higher 24-hour output occurred.

DISCUSSION.

It should be stressed that the drugs were not administered until long observation had established that the rabbits were in good balance as determined by intake, output and weight, and that the animals were kept on a fixed daily food and water intake.

A study of the tables makes it obvious that in rabbits:

First: Relatively small doses of "Theocin Soluble" and "Diuretin" are capable of producing a good diuresis, an appreciable increase in the solids and the uric acid outputs, and a diuresis of fair duration.

Second: Thirty (30) mg. per Kilo three times a day is the most efficient dose of "Theocin Soluble," if judged from the standpoint of the increased volume of urine output during the medication period, the increase in solids, the increase in uric acid eliminated, and the duration of the diuretic action. The average duration of the diuresis for the various doses listed is 6.35 days, the minimum being 5 and the maximum 7.25.

Third: No evidence of local irritation was obtained with "Theocin Soluble" until doses of 50 mg. or more per Kilo three times a day were reached. Gastroenteritis and renal irritation were observed in the animals that died.

TABLE I.—DIURETIC EFFECTS OF CERTAIN XANTHINES ON RABBITS.

Uniform Fluid Intake: 150 Cc. Daily. Drug Given on 5th through 8th Days.

Animal.	Drug and Dose Gm. T. i. d.	Day.	Total Daily Output.	Color Turb. React.	S./G.	Total Solids Gm. p. Cc.	Uric Acid Gm. p. L.	Urea Gm. p. Cc.	Album Gm. p. L.	Sugar %.	Microscopic.	Other Abnormalities.
1	Normal Pre-med.	1	42	y/s/al	1.012	0.027	0.18	0.015	0.20	Neg.	Neg.	Neg.
		2	44	y/s/al	1.010	0.022	0.18	0.010	0.30	Neg.	Neg.	Neg.
		3	45	y/s/al	1.012	0.027	0.18	0.020	0.20	Neg.	Neg.	Neg.
		4	40	y/s/al	1.010	0.022	0.18	0.010	0.20	Neg.	Neg.	Neg.
	Averages		43	y/s/al	1.011	0.025	0.18	0.014	0.23	Neg.	Neg.	Neg.
	Diuretin 0.030 Gm.	5	80	y/m/ac	1.018	0.042	0.16	0.014	0.40	Neg.	Neg.	Neg.
	per Kilo	6	56	y/m/ac	1.014	0.033	0.18	0.014	0.30	Neg.	Neg.	Neg.
		7	62	y/m/ac	1.018	0.042	0.22	0.012	0.30	Neg.	Neg.	Neg.
		8	55	y/m/ac	1.010	0.022	0.25	0.010	0.20	Neg.	Neg.	Neg.
	Averages		63	y/m/ac	1.015	0.035	0.20	0.012	0.30	Neg.	Neg.	Neg.
	Post-medication	9	52	y/m/al	1.012	0.027	0.22	0.010	0.50	Neg.	Neg.	Neg.
		10	62	y/m/al	1.010	0.022	0.17	0.010	0.15	Neg.	Neg.	Neg.
		11	42	y/m/al	1.010	0.022	0.17	0.010	0.20	Neg.	Neg.	Neg.
		12	45	y/m/al	1.010	0.022	0.14	0.010	0.20	Neg.	Neg.	Neg.
	Averages		50	y/m/al	1.011	0.023	0.18	0.010	0.26	Neg.	Neg.	Neg.

y = yellow. s = slight turbidity. al = alkaline reaction.
m = moderate turbidity. ac = acid reaction. Pre-med. = pre-medication period.

Fourth: In the case of "Diuretin," 50 mg. per Kilo three times a day appears to be the most efficient dose from the standpoint of increased urine output, in increase in solids eliminated, and the increase in the elimination of uric acid. The percentage of uric acid eliminated was in direct ratio to the dose of the drug. The maximum uric acid output was obtained with 100 mg. doses. The average duration of diuretic action for the doses listed was 7.3 days, the minimum being 7 days and the maximum 8.25 days. Thus "Diuretin" shows a slight advantage over "Theocin Soluble." In promptness of diuretic action these two drugs appear to be about equal, action being observed in each case on the first drug day.

TABLE II.—EFFECTS OF VARIOUS DOSES OF THEOCIN SOL. ON RABBITS.

Dose Mg. per K. T. i. d.	Ave. % Increased Output.	Ave. % Increased Max. Op.	Ave. % Increased Solids.	Ave. % Increased Uric A.	Increased Albumin.	Increased Sugar.	Duration Diuresis through	Day(s) Maxim. Output.
10	33	72½	48	154½	..	..	6½ days	1, 3 drug; 1, 2 post
30	49	88	58½	189	..	..	6½ days	1, 3 drug; 2 post
50	35	96	34	164	Plus	..	5 days	1, 3 drug
75	64	120	36	260	Plus	..	7¼ days	1, 3 drug; 3, 4 post
			One animal died third drug day. Two animals lost weight during drug period.					
100	131	100	90	267	Plus	..	6½ days	1 drug; 2 post
			Two animals died during second drug day. All animals that died showed casts in urine, and gastroenteritis.					

NOTE: Columns one and two refer to the volume of urine. In the last column "drug" = medication day; "post" = post-medication day.

Fifth: Irritation was manifested with "Theocin Soluble" when this drug was administered in doses of 50 mg. or more per Kilo three times a day. "Diuretin," in doses up to and including 100 mg. per Kilo three times a day, did not produce any demonstrable irritation of the kidneys or of the gastrointestinal tract.

Sixth: No deaths occurred with "Theocin Soluble" until doses of 75 mg. or more per Kilo three times a day were administered.

Seventh: Both drugs produce an increase in the volume of urine voided, the amount of uric acid eliminated, and the quantity of solids in the urine. Within

TABLE III.—EFFECTS OF VARIOUS DOSES OF DIURETIN ON RABBITS.

Dose Mg. per K. t. i. d.	Ave. % Increased Output.	Ave. % Increased Max. Op.	Ave. % Increased Solids.	Ave. % Increased Uric A.	Increased Albumin.	Increased Sugar.	Duration Diuresis through	Day(s) Maxim. Output.
10	50	92	45	72	..	..	7 days	3, 4 drug; 1, 6 post
30	44	94	51	88½	..	..	8 days	1, 4 drug; 2, 4 post
50	57	97	52½	158	..	..	7½ days	3, 4 drug; 1 post
75	26	108	34½	215	..	..	7¾ days	1 drug; 2, 3 post
100	46	115	53	262	..	..	8¼ days	1 drug; 3, 4 post

what appear to be the more efficient safe doses in rabbits, "Theocin Soluble" seems to yield a higher uric acid output than "Diuretin;" but "Diuretin" is apparently more safe, as evidenced by the facts that there were no deaths among the "Diuretin" animals, and no evidence of renal or gastrointestinal irritation was observed. What proportion of the uric acid eliminated is derived from the drugs themselves, and the extent of the possible rôle of the Salicylic and Acetic Acid groups in the production of the diuresis have not been determined as yet.

The results obtained with Theophylline Calcium Salicylate, Theobromine Calcium Salicylate, Theophylline and Theobromine will be presented in other papers.

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MANGANESE PREPARATIONS FOR THE TREATMENT OF FUNGOUS INFECTIONS.*

BY F. A. TAYLOR.

Potassium permanganate has long enjoyed a vogue in the treatment of ring worm infections. As early as 1822 (1) manganese dioxide was introduced into therapeutics and since that time the number and uses of manganese compounds have steadily increased. In 1843 (2) the dioxide was prescribed in the treatment of herpes and scabies. It was said to be of value in the healing of old ulcers, as a depilatory and as a remedy for skin diseases, especially itch and porrigo. It was applied as an ointment.

From this beginning, stimulated by the anticipated value of permanganate as an antiseptic, the modern use of the salt in fungous infections may be said to have arisen.

Some of the considerations which have limited the use of permanganate as a

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