JCI The Journal of Clinical Investigation

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J Clin Invest. 1959;38(10):1778-1781. https://doi.org/10.1172/JCI103956.

Research Article

TUBULAR SECRETION OF URATE IN MAN *

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(Submitted for publication May 28, 1959; accepted June 19, 1959)

In normal man, the renal clearance of urate is only a small fraction, some 5 to 10 per cent, of the inulin clearance. The prevailing interpretation of this low urate/inulin clearance ratio assumes complete filtrability of the plasma urate at the glomerulus, an assumption supported by several lines of evidence (1–7); reabsorption of 90 to 95 per cent of the filtered urate; and excretion of that 5 to 10 per cent which has escaped reabsorption. The renal regulation of urate excretion in man is thus considered to be limited to the processes of glomerular filtration and tubular reabsorption.

There are some difficulties with this concept. Berliner, Hilton, Yü and Kennedy (2), in demonstrating a Tm urate for normal man of the order of 15 mg. per minute, pointed out that this reabsorptive capacity is far greater than any filtered urate load normally imposed upon it. Consequently, the Tm for urate cannot be considered directly to determine the quantity of urate excreted, which is regulated by a proximate mechanism as yet undefined. Not easily reconciled with the current concept is the striking dissociation between filtered urate loads and excreted urate noted over a wide range of glomerular filtration rate in clearance studies of 150 gouty subjects (8). Further, the marked suppression of renal excretion of urate in man after administration of pyrazinamide (9) or lactate (10) would, in the conventional view, require the rather awkward assumption that tubular reabsorption of urate is stimulated by these compounds. Finally, the paradoxical effect of salicylate and other drugs on urate excretion in man (11) would, according to the conventional concept, necessitate the presumption that small doses stimulate, and large doses of the same drug suppress, tubular reabsorption of urate; moreover, that intermediate doses (which have little or no net effect on urate excretion) simultaneously stimulate and suppress the tubular reabsorptive transport system (12).

The present study is concerned with an alternative interpretation of the overall urate clearance data in man which would seem largely to resolve these difficulties, namely that the plasma urate is virtually wholly filtrable at the glomerulus; the filtered urate is then practically completely reabsorbed by the tubules; and tubular secretion of urate constitutes the proximate mechanism largely responsible, under ordinary circumstances, for the excretion of urate in the urine (11, 13). Support for these assumptions is provided by the clearance data to be presented which indicate that, under appropriate experimental conditions, the quantity of uric acid excreted in the urine of man can be demonstrated to exceed the quantity calculated to be filtered at the glomerulus.

METHODS

The subjects studied, seven with intercritical gout and five nongouty, none with overt cardiovascular disease, were given 400 to 600 mg. per day of a potent uricosuric agent, G-28315 (sulfinpyrazone) (14) for a day or two. The clearance studies were then begun, with the patients in the postabsorptive state, by infusing 1 per cent inulin in saline solution and, simultaneously, 0.2 per cent uric acid in 15 per cent mannitol at a rate of 9 ml. per minute (later increased to 17 ml. per minute). Shortly after the infusions were started the first of four doses (each 375 mg.) of the sodium salt of sulfinpyrazone was injected intravenously; this was repeated at intervals of 40 to 60 minutes for a total of 1.5 Gm. to ensure the greatest obtainable suppression of tubular reabsorption of urate throughout the experiment. After allowing for equilibration, urine samples were collected at 15 to 20 minute periods by indwelling catheter, with bladder air wash at the end of each collection period. Venous blood samples were procured at the midpoint of each period, using heparin as anticoagulant.

The uric acid-mannitol infusate was prepared by dissolving 5.0 Gm. uric acid in 1 L. of hot 0.15 per cent lithium carbonate solution; this was then added to 1.5 L. of 25 per cent mannitol in water to give 2.5 L. of 15 per

* This study was supported by a grant-in-aid (A-162) from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, United States Public Health Service, Bethesda, Md.

cent mannitol containing 0.2 per cent uric acid and 0.06 per cent lithium carbonate. The total uric acid delivered in the course of any one experiment varied from 3.0 to 4.8 Gm. The total quantity of lithium given as Li, 0.2 to 0.3 Gm., is well below the toxic level in patients not receiving salt poor diets (15). No untoward reactions were noted except for transient water emesis in three patients shortly after termination of the experiment. Neither gouty nor nongouty subjects developed any acute arthritis in association with the uric acid infusion.

Inulin was determined in plasma and urine, immediately upon procurement of the specimens, by the resorcinol method of Schreiner (16). Uric acid in plasma and urine was determined by a modification (17) of the colorimetric method of Buchanan, Block and Christman (18) incorporating the use of crude uricase, urea cyanide carbonate, and arsenophosphotungstic acid. As indicated elsewhere (17) the results obtained by this method are in satisfactory agreement with spectrophotometric analysis, which was employed for spot checks.

In making the calculations, the plasma urate was assumed to be completely diffusible in both gouty and nongouty subjects (4). Corrections for plasma protein content or Donnan effect were not made; such corrections, it is estimated, would increase the figures for filtered urate something less than 10 per cent.

RESULTS

Table I summarizes the results of six experiments in which the ratio, excreted urate/filtered urate, exceeded 1.0 in at least two consecutive periods. Ratios > 1.10 were attained in five of these experiments, two reaching 1.20 and 1.23. Of the six similar studies not included in Table I, all yielded ratios of 0.90 to 1.0, and two rose to 1.05 for a single period.

Suppression of tubular reabsorption of urate is required for such demonstration of tubular secretion of urate in man, since the quantity of urate filtered and reabsorbed otherwise is many times greater than that excreted. For this purpose G-28315, which as previously reported (14) markedly increases C_{urate}, was employed. The uricosuric effect was further augmented, about 20 per cent, by vigorous mannitol diuresis to 20 to 40 ml. urine flow per minute, as established in preliminary experiments. Despite these measures, however, it is highly improbable that tubular reabsorption of urate was completely suppressed, even when the excreted urate exceeded the filtered urate. This is unlikely not only on *a priori* but also on experimental grounds; in studies carried out as described under Methods, but omitting uric acid from the infusion, the highest urate/inulin clearance ratio attained was 0.73. It may therefore be presumed that the quantity of urate excreted throughout the experiments, summarized in Table I, was appreciably lessened by persistent tubular reabsorption of substantial amounts of urate.

When the plasma urate was increased by sustained infusion of uric acid to levels of 13 to 22 mg. per 100 ml. (Table I), the filtered urate load of course increased within the limits of the reduced glomerular filtration rates of the subjects studied, but there was a disproportionate increase in excreted urate, the net effect being higher excreted urate/filtered urate ratios. It is presumed that the higher plasma urate levels enhanced the tubular secretion of urate. Moreover, it is likely that the reabsorptive Tm for urate, which was markedly reduced by the G-28315 administered, was exceeded in some experiments by the large filtered urate loads presented to the tubules.

A prerequisite for the demonstration of urate/inulin clearance ratios > 1.0 in these studies was a reduced glomerular filtration rate, of the order of 40 to 80 ml. per minute. This requirement was fulfilled by selection of subjects known through prior clearance studies or suspected by virtue of age to qualify. As indicated in Table I, the experimental conditions employed did not effect any significant change in inulin clearance. It was not necessary to resort to positional changes or use of ganglionic blocking agents to bring about any further reduction in the glomerular filtration rate.

DISCUSSION

The data summarized in Table I offer direct testimony for tubular secretion of urate in normal and gouty man. It should be emphasized that the excreted urate/filtered urate ratios cited were procured in the face of probable incomplete suppression of tubular reabsorption of urate, and therefore should be regarded as minimal figures. Although quantitative data thus are not available, it may be inferred that under ordinary circumstances the excreted urate is very largely derived by tubular secretion (8). Indeed it is possible that larger quantities of urate are secreted by the tubules than are excreted in the urine, since the sites of secretion and reabsorption of urate in the

TABLE I

Experiments demonstrating tubular secretion of urate in gouty and nongouty subjects

Name Age B.S.A.	Time	Urine flow	C_{inulin}*	P_{urate}†	F_{urate}‡	UV_{urate}§	C_{urate}‖	Excreted urate / Filtered urate
	min.	*ml./min.*	*ml./min.*	*mg./100 ml.*	*mg./min.*	*mg./min.*	*ml./min.*	
1. M. H.	−42	Infusions started: inulin; uric acid-mannitol, 9 ml./min.; G-28315¶						
49	0–99	11.1	68.9	14.0	9.65	7.53	53.7	0.78
1.85	99–134	16.9	75.7	16.5	12.5	9.79	59.3	0.78
Gout	134	Uric acid-mannitol infusion rate increased to 17 ml./min.						
	134–149	21.3	68.8	18.8	13.0	12.2	65.0	0.94
	149–159	24.5	64.5	19.2	12.4	14.0	73.0	1.13
	159–174	28.3	67.0	20.4	13.7	15.8	77.3	1.15
	174–184	30.0	66.3	22.0	14.6	17.4	79.3	1.19
	184–189	30.0	66.3	22.3	14.8	17.4	78.0	1.18
2. I. K.	−42	Infusions started: inulin; uric acid-mannitol, 9 ml./min.; G-28315¶						
65	0–61	13.2	44.3	10.2	4.52	3.67	36.0	0.81
1.73	61	Uric acid-mannitol infusion rate increased to 17 ml./min.						
Gout	61–94	21.1	43.0	13.6	5.85	6.22	45.7	1.06
	94–107	23.5	40.5	15.7	6.35	7.20	46.0	1.13
	107–121	25.4	39.3	17.0	6.70	8.20	48.3	1.23
	121–138	28.0	46.4	18.6	8.60	9.40	50.5	1.10
	138–146	29.7	48.0	18.6	8.90	10.0	53.8	1.12
3. H. G.	−32	Infusions started: inulin; uric acid-mannitol, 9 ml./min.; G-28315¶						
68	0–63	20.5	54.0	8.5	4.60	2.09	24.3	0.46
1.51	63–103	22.5	58.7	13.8	8.10	4.78	34.7	0.59
Gout	103–123	23.1	62.0	13.0	8.06	6.65	48.2	0.83
	123–143	23.9	60.2	13.4	8.05	8.01	58.0	0.99
	143–162	27.5	60.3	13.6	8.20	9.15	67.3	1.12
	162–173	28.6	62.2	13.8	8.60	9.68	70.3	1.13
4. J. R.	−38	Infusions started: inulin; uric acid-mannitol, 9 ml./min.; G-28315¶						
47	0–98	8.6	86.4	11.1	9.60	5.98	53.8	0.62
1.83	98–160	13.0	82.7	13.6	11.3	8.82	64.9	0.78
Gout	160	Uric acid-mannitol infusion rate increased to 17 ml./min.						
	160–180	17.8	69.0	15.1	10.4	11.3	74.8	1.09
	180–195	18.3	69.5	15.8	11.0	11.4	72.2	1.04
	195–207	21.3	72.8	16.3	11.9	12.4	76.0	1.04
5. H. M.	−51	Infusions started: inulin; uric acid-mannitol, 9 ml./min.; G-28315¶						
65	0–59	17.7	81.4	8.0	6.50	5.48	68.5	0.84
1.74	59	Uric acid-mannitol infusion rate increased to 17 ml./min.						
Nongouty	59–74	22.3	86.0	10.0	8.60	8.04	80.4	0.93
	74–89	29.3	81.3	11.7	9.50	10.6	90.7	1.12
	89–104	33.3	84.2	12.7	10.7	12.0	94.5	1.12
	104–119	37.3	87.0	13.9	12.1	13.5	97.2	1.11
	119–134	42.7	85.0	15.2	12.9	15.5	102	1.20
6. L. W.	−45	Infusions started: inulin; uric acid-mannitol, 9 ml./min.; G-28315¶						
72	0–57	8.5	49.2	11.3	5.55	4.72	41.8	0.85
1.60	57	Uric acid-mannitol infusion rate increased to 17 ml./min.						
Nongouty	57–72	13.0	53.0	12.9	6.85	6.15	47.7	0.90
	72–84	16.3	48.3	13.7	6.60	7.59	55.3	1.15
	84–94	18.0	51.7	14.7	7.60	8.19	55.8	1.08
	94–100	20.8	52.0	15.7	8.15	9.03	57.5	1.11

* Inulin clearance.
† Plasma urate concentration.
‡ Filtered urate.
§ Urinary urate excretion.
‖ Urate clearance.
¶ Injection of G-28315 repeated every 40 to 60 minutes three times during the course of the experiment.

tubules have not been established, and reabsorption of some secreted as well as filtered urate is not precluded by the overall clearance data. In special circumstances (inborn or acquired defects in tubular reabsorption of urate, use of uricosuric drugs) a substantial proportion of the excreted urate would include filtered urate which has escaped reabsorption.

Praetorius and Kirk (19) previously demonstrated tubular secretion of urate in a young man with striking hypouricemia but in good health. This represents a special case, however, since the clearance data disclosed a marked intrinsic deficiency in tubular reabsorption of urate, the human equivalent of the Dalmatian coach hound.

In the present study, tubular secretion of urate could be as readily demonstrated in gouty as in nongouty subjects, and no gross differences were disclosed. Although these data do not, of course, exclude the possibility of deficient tubular secretion of urate in gout, this is considered unlikely for reasons discussed elsewhere (8). The data do make clear, however, that the tubular reabsorption of urate in gouty or nongouty subjects cannot be estimated indirectly by clearance calculations which assume no tubular secretion of urate, hence comparisons on this basis are invalid (8).

SUMMARY

Excreted urate/filtered urate ratios > 1.0 were demonstrated by appropriate clearance techniques in gouty and nongouty man, implying tubular secretion of urate. The results support the hypothesis that the renal regulation of urate excretion in man involves glomerular filtration, tubular reabsorption and tubular secretion.

REFERENCES

1. Bordley, J., 3rd, and Richards, A. N. Quantitative studies of the composition of glomerular urine. VIII. The concentration of uric acid in glomerular urine of snakes and frogs, determined by an ultramicroadaptation of Folin's method. J. biol. Chem. 1933, **101**, 193.
2. Berliner, R. W., Hilton, J. G., Yü, T. F., and Kennedy, T. J., Jr. The renal mechanism for urate excretion in man. J. clin. Invest. 1950, **29**, 396.
3. Bene, E., and Kersley, G. D. Technical methods. Ultrafiltration of plasma uric acid. J. clin. Path. 1951, **4**, 366.
4. Yü, T. F., and Gutman, A. B. Ultrafiltrability of plasma urate in man. Proc. Soc. exp. Biol. (N. Y.) 1953, **84**, 21.
5. Wyngaarden, J. B. Uric acid *in* Cyclopedia of Medicine, Surgery, Specialties. Philadelphia, F. A. Davis Co., 1955, vol. 6, p. 344.
6. Salteri, F., Cirla, E., and Fasoli, A. Electromigration on filter paper of uric acid from serum and synovial fluid. Science 1958, **127**, 85.
7. Villa, L., Robecchi, A., and Ballabio, C. B. Physiopathology, clinical manifestations, and treatment of gout. Part 1. Physiopathology and pathogenesis. Ann. rheum. Dis. 1958, **17**, 9.
8. Gutman, A. B., and Yü, T. F. Renal function in gout, with a commentary on the renal regulation of urate excretion, and the role of the kidney in the pathogenesis of gout. Amer. J. Med. 1957, **23**, 600.
9. Yü, T. F., Berger, L., Stone, D. J., Wolf, J., and Gutman, A. B. Effect of pyrazinamide and pyrazinoic acid on urate clearance and other discrete renal functions. Proc. Soc. exp. Biol. (N. Y.) 1957, **96**, 264.
10. Yü, T. F., Sirota, J. H., Berger, L., Halpern, M., and Gutman, A. B. Effect of sodium lactate infusion on urate clearance in man. Proc. Soc. exp. Biol. (N. Y.) 1957, **96**, 809.
11. Yü, T. F., and Gutman, A. B. Paradoxical retention of uric acid by uricosuric drugs in low dosage. Proc. Soc. exp. Biol. (N. Y.) 1955, **90**, 542.
12. Yü, T. F., and Gutman, A. B. A study of the paradoxical effects of salicylate in low, intermediate and high dosage on the renal mechanisms for excretion of urate in man. J. clin. Invest. 1959, **38**, 1298.
13. Gutman, A. B., and Yü, T. F. Renal regulation of uric acid excretion in normal and gouty man: Modification by uricosuric agents. Bull. N. Y. Acad. Med. 1958, **34**, 287.
14. Burns, J. J., Yü, T. F., Ritterband, A., Perel, J. M., Gutman, A. B., and Brodie, B. B. A potent new uricosuric agent, the sulfoxide metabolite of the phenylbutazone analogue, G-25671. J. Pharmacol. exp. Ther. 1957, **119**, 418.
15. Schou, M. Biology and pharmacology of the lithium ion. Pharmacol. Rev. 1957, **9**, 17.
16. Schreiner, G. E. Determination of inulin by means of resorcinol. Proc. Soc. exp. Biol. (N. Y.) 1950, **74**, 117.
17. Yü, T. F., and Gutman, A. B. Quantitative analysis of uric acid in blood and urine. Methods and interpretation. Bull. rheum. Dis. 1957, **7**, Suppl. S-17.
18. Buchanan, O. H., Block, W. D., and Christman, A. A. The metabolism of the methylated purines. I. The enzymatic determination of urinary uric acid. J. biol. Chem. 1945, **157**, 181.
19. Praetorius, E., and Kirk, J. E. Hypouricemia: With evidence for tubular elimination of uric acid. J. Lab. clin. Med. 1950, **35**, 865.