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Received July 6, 1954. P.S.E.B.M., 1954, v86.

Isotopic Uric Acid in Gouty and Rheumatoid Arthritis Patients Treated with Probenecid and Phenylbutazone.* (21225)

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(Introduced by Fred R. Griffith, Jr.)

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There has been a clinical impression, not very well documented, that phenylbutazone (Butazolidin;† 3, 5-dioxo-1,2,-diphenyl-4-n-butylpyrazolidine) can lower the serum urate concentration markedly without causing a comparable excretion of "extra" uric acid. It was reported that both phenylbutazone and probenecid (Benemid;‡ p(di-n-propyl sulfamyl)benzoic acid) caused a significant increase in urinary uric acid output in 2 gouty subjects but failed to do so in 3 patients with rheumatoid arthritis(1). Both drugs tended to cause a decrease in the serum urate levels although the effect was less regular in the gouty subjects than in the subjects with rheumatoid arthritis. In an attempt to elucidate the mechanism involved, isotope studies were carried out on 3 more gouty patients and 4 more patients with rheumatoid arthritis. The body uric acid pool size and turnover rate were determined during control and drug periods, and urinary uric acid excretion was determined by the isotope dilution method. The results indicate that within the experimental design used, both drugs cause statistically significant uricosuria only in subjects with increased body stores of uric acid.

* These studies supported by grants from the National Institutes of Health, Bethesda, Md., and the Buffalo Chapter of the Arthritis and Rheumatism Foundation.

† Butazolidin was kindly supplied by Geigy Pharmaceuticals, Division of Geigy Co.

‡ Benemid was kindly supplied by Sharp and Dohme, Philadelphia, Pa.

Experimental. All patients were hospitalized and were kept under close observation. Their diet was uniformly low in purines and constant in calories, carbohydrate, fat and protein. The only medications allowed in addition to the test drugs were codeine (P.R.N. for pain) and non-barbiturate hypnotics. All urine was collected *ad libitum* and pooled into convenient samples. Uric acid was isolated from one aliquot of each pool for N^{15} determination and another aliquot was taken for uric acid determination by the isotope dilution method(2). The uric acid pool size and turnover rate were determined during the control period as previously described(2) and each patient was then placed on one of the test drugs for approximately one week. The uric acid pool size and turnover rate were determined in the second week of that period, during which the patient continued the same therapeutic regimen. The first drug was then discontinued and the second one given for approximately one week. During the second week of this therapeutic period the uric acid pool size and turnover rate were again determined. The daily dose schedule for probenecid was 3 tablets of 0.5 g each, and for phenylbutazone was 2 tablets of 200 mg each.

Results. The pool of miscible uric acid in normal individuals as determined in this and other laboratories(3) is usually not greater than 1200 mg (29 mMols U A nitrogen), and may be less in women. From Tables I and II it is apparent that only 2 patients, D. W., and A. B., were within normal limits. The other

TABLE I. Uric Acid Pool Size, Turnover Rate, Turnover, Excretion and Serum Concentration in 4 Rheumatoid Arthritis Patients after Treatment with Probenecid and Phenylbutazone.

	Age, yr		Pool size, mMol UAN	Turnover rate, pools/day	Turnover, mMol UAN /day	Mean excretion, mMol UAN/day	Significance, p below‡	Serum UA, mg %
							%	
D.W.	74	C*	13.4	.94	12.6	9.95 ± .69†		4.3
♀		Pr	8.0	1.63	13.0	10.95 ± 2.56	not	1.6–2.0
		Ph	8.5	1.71	14.5	10.24 ± 1.47	"	1.7–2.7
A.B.	59	C	15.2	1.04	15.9	10.33 ± 1.09		4.1
♀		Ph	8.5	1.77	15.0	10.32 ± 1.57	"	1.6–2.2
		Pr	6.7	2.08	13.8	10.78 ± 1.59	"	1.4–1.8
L.F.	58	C	36.9	.40	14.7	7.51 ± 2.32		6.2
♀		Ph	36.4	.42	15.4	10.03 ± 2.74	2.5	5.8
		Pr	27.1	.59	16.0	12.14 ± 2.94	.5	5.3
J.S.	67	C	39.0	.64	25.2	13.10 ± 1.83		5.4
♂		Pr	20.6	1.05	21.6	15.31 ± 3.57	10	3.1–3.4
		Ph	30.0	.73	22.0	12.79 ± 2.35	not	3.6–4.6

* C = Control; Ph = Phenylbutazone; Pr = Probenecid.
† Stand. dev.
‡ t test(6).

5 patients had enlarged uric acid pools.

In the 2 patients, D. W., and A. B., both phenylbutazone and probenecid caused a marked reduction in the pool size and increase in the turnover rate. The turnover remained essentially constant. Yet despite this pronounced decrease in the pool size there was no significant increase in the urinary uric acid output. This is shown by the fact that the t tests between the means of the control and experimental periods were not significant.

The 3 gouty patients and one rheumatoid arthritis patient, L. F., demonstrated essentially the reverse of this situation, *i.e.*, a significant uricosuria with either drug and a less marked reduction in the pool size. The case of J. S. is equivocal and does not clearly fit into either category. Probenecid was more potent as a uricosuric drug than phenylbutazone. A t test between the means of the drug periods revealed significance below the 5% level in the rheumatoid arthritic patients L. F. and J. S. and on all gouty patients except D. F.

Perhaps the most striking feature of all these studies is that the turnover remains relatively constant in each individual even though the pool size, turnover rate, serum urate concentration, or urinary uric acid excretion may have been markedly affected by the drugs. On this basis one might reason that the rate of loss of uric acid through the kidney is determined by the serum urate level and the percent of tubular resorption. Lowering the resorption rate(4,5) would immediately start to lower the serum urate level, and eventually equilibrium would set in at a lower serum urate and resorption level. If the body is not building up uric acid stores then the output at this new level must be the same as before, since the output of uric acid from the body must equal the rate of synthesis of uric acid in the body. The situation in the gouty individual is different in that he is building up uric acid stores and may be depositing uric acid in the solid phase. By drawing upon these stores he may keep his serum urate level elevated even though tubular resorption rate has decreased. Thus "extra" uric acid can be excreted and the miscible pool of uric acid will not necessarily be markedly affected. In this study the one rheumatoid arthritis patient (L. F.) that behaved like the gouty subjects did have an elevated serum urate level and an enlarged pool size.

The 2 cases, D. W. and A. B., demonstrate that uricosuric drugs can decrease the body uric acid pool size and serum urate concentration without causing statistically significant uricosuria. All the details of the mechanism cannot be elucidated by the present experimental design since in this procedure many days are grouped statistically to measure long range effects. To complement this data we need excretion data for the first few hours or

TABLE II. Uric Acid Pool Size, Turnover Rate, Turnover, Excretion and Serum Concentration in 3 Gouty Patients after Treatment with Probenecid and Phenylbutazone.

	Age, yr		Pool size, mMol UAN	Turnover rate, pools/day	Turnover, mMol UAN /day	Mean excretion, mMol UAN/day	Significance, p below‡	Serum UA, mg %
							%	
D.F.	40	C*	60.8	.30	18.4	11.80 ± 3.48†		8.3
♂		Ph	55.5	.47	25.9	16.32 ± 4.99	5	4.7–7.9
		Pr	62.7	.32	20.2	18.94 ± 5.07	1	5.8–8.0
M.B.	53	C	54.6	.41	22.6	7.71 ± .59		11.1
♂		Pr	41.2	.51	21.0	14.92 ± 2.02	.5	7.9
		Ph	40.5	.54	21.8	10.14 ± 1.84	.5	10.3–11.5
M.F.	37	C	56.5	.70	34.1	16.58 ± 2.52		10.4–11.7
♂		Ph	34.5	.92	31.6	13.05 ± 3.29	2.5	6.3– 9.7
		Pr	36.0	.98	35.1	30.72 ± 5.24	.5	5.3

* C = Control; Ph = Phenylbutazone; Pr = Probenecid.
† Stand. dev.
‡ t test(6).

days after the administration of these uricosuric drugs. Such studies are now under way in this laboratory and may explain what happens to the "extra" uric acid when the serum rate level decreases after drug administration.

Conclusion. Neither phenylbutazone nor probenecid caused a statistically significant uricosuria in 2 patients with rheumatoid arthritis, even though these drugs decreased the pool size of uric acid, increased the turnover rate, and decreased the serum urate level. In 3 gouty patients and 1 rheumatoid arthritis patient with an elevated serum urate concentration the drugs caused statistically significant uricosuria but variable effects on the pool size, turnover rate and serum urate concentration. In 1 patient with rheumatoid arthritis the results were equivocal. In 4 of these 5 cases the uricosuric effect of probenecid was statistically greater than that of phenylbutazone. It is postulated that the uricosuric drugs such as phenylbutazone and probenecid will produce statistically significant uricosuria only in those cases in which increased body stores of uric acid are present. The present studies are based on experimental periods of 1-2 weeks for each regimen and the data do not indicate what happens in the first few hours of drug administration.

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Received July 8, 1954. P.S.E.B.M., 1954, v86.