EFFECT OF A PHENYLBUTAZONE ANALOG (4-[PHENYLTHIOETHYL]-1,2-DIPHENYL 3,5-PYRAZOLIDINEDIONE) ON URATE CLEARANCE AND OTHER DISCRETE RENAL FUNCTIONS IN GOUTY SUBJECTS. EVALUATION AS URICOSURIC AGENT [1]

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A number of phenylbutazone derivatives and metabolites are under study (1–4) in a joint effort to develop an analog possessing the marked anti-rheumatic properties but not the undesirable side effects of the parent compound. In the course of testing the anti-rheumatic effects in acute gouty arthritis of one of these compounds, G–25671, in which a phenylthioethyl group replaces the butyl side chain of phenylbutazone, marked uricosuric activity was noted (1, 2). The interesting properties of this substance suggested further study and a clinical trial in the management of gout.
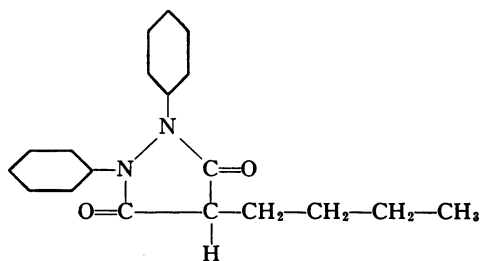

Phenylbutazone

G-25671
4-(phenylthioethyl)-1,2-diphenyl
3,5-pyrazolidinedione

The present report deals with the effect of G–25671 on the simultaneous renal clearances of inulin, para-aminohippurate, urate, sodium, potassium and chloride. More protracted urate and electrolyte balance studies are included. Our clinical experience with G-25671 in gouty subjects also is briefly summarized.

METHODS

Renal clearance studies were carried out in 12 gouty subjects, all males 33 to 62 years of age, and in the intercritical phase of the disorder. These subjects had been maintained on a low purine, low fat, restricted protein (60 to 75 gm. per day) diet and were in the postabsorptive state at the time of study. Standard clearance techniques (5) were employed, with slight modifications described elsewhere (6).

To ensure adequate urine flow throughout the experiments, liberal quantities of water were administered orally. Urine and blood collections were initiated in three premedication control periods, each of 20 to 30 minutes duration. Then G–25671 was injected intravenously, the rate of injection being varied according to the design of the experiment, and appropriate urine and blood collections were made.

In 7 subjects the total drug dosage, 0.90 to 1.54 gm. of the sodium salt (16 mg. per Kg. body weight) dissolved in 100 to 150 ml. isotonic saline solution, was delivered within a period of approximately 20 minutes to attain high blood levels of G–25671 rapidly. Injection of the drug was then discontinued and 4 to 6 urine collections were obtained, each comprising a period of 20 to 30 minutes. Three blood samples were procured during these collection periods. The respective plasma concentrations of inulin, PAH, urate, Na, K and Cl were obtained by plotting the concentrations semilogarithmically against time and by extrapolating back to 2.5 minutes (approximate urine delay time) from the mid-time of each urine collection period. In three of these subjects, A. R., M. C., and L. W., parallel clearance studies with phenylbutazone,
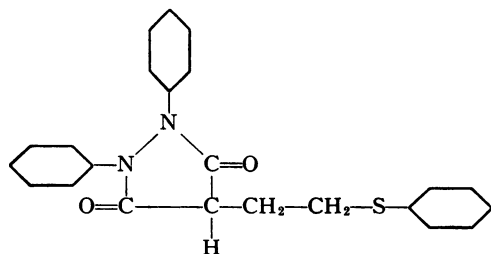
as the sodium salt, were made. In Cases A. R. and L. W. the effects of injection of 100 ml. saline solution alone also were determined.

Five experiments were designed to study the effects of slowly rising drug levels to determine the order of effects on specific renal clearances. In Cases J. S. and L. L., G-25671 as the sodium salt was dissolved in 5 per cent glucose in water to make a 0.14 per cent solution of the drug which was then delivered by sustained intravenous injection. The initial rate of infusion was 1 ml. per minute; this was increased by an increment of approximately 1 ml. per minute at the beginning of each 20-minute urine collection period to make a total drug

dosage of 0.80 gm. for Case J. S. and 0.86 gm. for Case L. L. Seven such collections were made in each experiment. Blood samples were procured at the mid-point of each clearance period. Parallel experiments were carried out in Cases N. P., J. B., and L. O., in which phenylbutazone as the sodium salt dissolved in 5 per cent glucose in water to make a 0.14 per cent solution of the drug, was delivered by slow infusion.

To obtain information as to the more protracted effects of G-25671, particularly on the renal excretion of sodium, potassium, chloride and inorganic phosphate, two gouty subjects were hospitalized for two weeks during which they were maintained on constant weighed diets

TABLE I

Effect of rapid infusion of G-25671 (in isotonic saline solution) on renal clearances of inulin, PAH and urate—Three analogous experiments with phenylbutazone are included

Case Age B.S.A.	Period	$P_{G-25671}$ or P_{Pb}	C_{In}	C_{PAH}	P_{Urate}	C_{Urate}	$\dfrac{C_{Urate}}{C_{In}}$	Remarks
		mg. %	ml./min.	ml./min.	mg. %	ml./min.	%	
1. A. R.	Control	0	132	511	8.7	7.84	5.93	Non-tophaceous gout, 11 years; no clinical evidence of cardiorenal disease.
44	G-25671: 1.4 gm. in 150 ml. isotonic saline solution							
(2.05 M²)	0–39 min.	19.0	106	355	8.4	17.6	16.6	
	39–67 min.		119	407	7.8	47.0	39.5	
	67–92 min.	13.4	115	397	7.5	45.5	39.6	
	92–122 min.		134	421	7.0	50.7	37.8	
	122–152 min.	11.2	104	356	6.4	41.2	39.6	
	Control	0	117	551	7.9	6.35	5.30	
	Phenylbutazone: 1.4 gm. in 150 ml. isotonic saline solution							
	0–34 min.	11.2	122	445	7.8	13.1	10.8	
	34–62 min.		103	417	7.8	22.5	21.8	
	62–90 min.		102	398	7.7	14.0	13.7	
	90–113 min.	9.9	129	465	7.6	15.8	12.3	
	113–127 min.	9.7	137	515	7.4	15.6	11.4	
2. L. W.	Control	0	104	529	8.6	3.38	3.25	Non-tophaceous gout, 12 years; no clinical evidence of cardiorenal disease.
46	G-25671: 1.2 gm. in 100 ml. isotonic saline solution							
(1.93 M²)	0–32 min.	22.7	72.0	287	8.2	10.1	14.0	
	32–50 min.		81.2	375	7.5	26.3	32.4	
	50–73 min.		119	493	7.0	47.8	40.1	
	73–92 min.		103	507	6.6	50.8	49.3	
	90–107 min.	15.7	97.0	500	6.3	47.5	49.0	
	Control	0	109	404	7.0	3.92	3.60	
	Phenylbutazone: 1.2 gm. in 100 ml. isotonic saline solution							
	0–33 min.	13.8	119	293	6.7	10.3	8.70	
	33–61 min.		112	356	6.6	19.9	17.8	
	61–88 min.		107	325	6.6	12.1	11.3	
	88–109 min.	12.0	110	332	6.6	11.2	10.2	
	109–133 min.	11.5	101	294	6.4	11.4	11.3	
3. M. C.	Control		124	590	8.6	7.62	6.14	Non-tophaceous gout, 1 year; no clinical evidence of cardiorenal disease.
33	G-25671: 1.3 gm. in 100 ml. isotonic saline solution							
(1.93 M²)	0–25 min.		118	451	8.5	18.3	15.5	
	25–48 min.		125	462	8.3	36.5	29.2	
	48–71 min.		115	517	8.2	36.2	31.5	
	71–100 min.		122	531	8.1	35.6	29.2	
	100–122 min.		117	474	7.9	32.9	28.1	
	122–143 min.		130	493	7.7	35.2	27.1	
	Control	0	119	600	9.8	6.55	5.00	
	Phenylbutazone: 1.3 gm. in 100 ml. isotonic saline solution							
	0–35 min.	13.6	114	440	9.8	9.28	8.10	
	35–77 min.		145	538	9.3	8.62	6.00	
	77–107 min.		141	608	9.0	10.2	7.20	
	107–130 min.	11.5	149	564	9.0	13.4	9.00	
	130–151 min.	11.0	122	450	9.1	9.42	7.70	

TABLE I—*Continued*

Case Age B.S.A.	Period	P$_{G-25671}$	C$_{In}$	C$_{PAH}$	P$_{Urate}$	C$_{Urate}$	$\frac{C_{Urate}}{C_{In}}$	Remarks
		mg. %	ml./min.	ml./min.	mg. %	ml./min.	%	
4. M. H.	Control	0	92.4	416	9.9	4.88	5.28	Tophaceous gout, 17 years; no clinical evidence of cardiorenal disease.
45	G-25671: 0.95 gm. in 100 ml. isotonic saline solution							
(1.68 M²)	0–34 min.	12.3	93.4	334	9.6	11.5	12.3	
	34–54 min.		96.0	337	9.3	28.8	30.0	
	54–79 min.	10.7	99.0	343	9.0	29.6	29.9	
	79–104 min.		104	337	8.6	*32.9*	*31.7*	
	104–130 min.	8.4	96.3	275	8.4	22.1	23.0	
	130–152 min.		92.0	*223*	8.3	25.2	27.4	
5. S. S.	Control	0	86.0	453	9.7	6.14	7.13	Non-tophaceous atypical gout; no clinical evidence of cardiorenal disease.
38	G-25671: 1.0 gm. in 100 ml. isotonic saline solution							
(1.66 M²)	0–35 min.	16.7	90.2	424	9.0	4.90	5.43	
	35–59 min.		88.4	*413*	8.4	8.60	9.73	
	59–90 min.		78.9	429	8.2	14.3	18.1	
	90–120 min.	12.0	82.0	473	7.9	*17.8*	*21.7*	
6. H. G.	Control	0	83.7	290	11.5	6.68	7.97	Tophaceous gout, 11 years; post-scarlatina nephritis for more than 20 years; albuminuria and cylindruria, serum NPN 34 mg. %, PSP excretion 50% in 2 hours.
44	G-25671: 1.5 gm. in 150 ml. isotonic saline solution							
(2.08 M²)	0–43 min.	19.1	83.6	*165*	11.1	*13.8*	*16.5*	
	43–75 min.		75.2	183	10.8	9.40	12.5	
	75–100 min.		74.8	183	10.5	10.3	13.8	
	100–123 min.		72.9	362	10.2	10.8	14.8	
	123–153 min.	11.1	68.0	333	10.2	11.0	16.2	
7. I. K.	Control		64.9	202	8.7	4.76	7.34	Non-tophaceous gout 32 years; nephrosclerosis; albuminuria and cylindruria, serum NPN 60 mg. %, PSP excretion 50% in 2 hours; post-gastrectomy refractory anemia, 15 years.
62	G-25671: 0.9 gm. in 100 ml. isotonic saline solution							
(1.65 M²)	0–37 min.		64.3	*147*	8.4	9.63	15.0	
	37–62 min.		66.7	156	8.2	11.5	17.3	
	62–88 min.		80.0	198	8.2	15.5	19.3	
	88–115 min.		79.4	208	8.2	*18.7*	*23.6*	

* Figures italicized indicate maximal changes.

and controlled salt and water intake. The daily caloric intake for subject O. G. was 1600 (protein, 60 gm. per day), with 2.5 gm. of sodium chloride added; subject L. W. received 1800 calories per day (protein, 60 gm. per day) with 3.5 gm. sodium chloride added. On the seventh day of hospitalization, G-25671 administration was begun: O. G. received 1.2 gm. intravenously every day for four consecutive days, delivered in three divided doses of 0.4 gm. (in 100 ml. 5 per cent glucose in distilled water) at 9:00 A.M., 3:00 P.M., and 9:00 P.M.; L. W. received 1.6 gm. intravenously for four consecutive days, similarly delivered daily in three divided doses of 0.4 gm. (9:00 A.M.), 0.4 gm. (3:00 P.M.) and 0.8 gm. (9:00 P.M.). Blood samples were secured just prior to each infusion. Urine collections, obtained by spontaneous voidings, were spaced to comprise the periods from 9:00 A.M. to 3:00 P.M., then to 9:00 P.M., and overnight to 9:00 A.M. The urine was collected over the three days immediately preceding medication, the four days of G-25671 administration, and three days thereafter. The body weight was recorded each morning. Parallel studies with phenylbutazone had previously been made in these two subjects (7).

The analytical methods for the determination of urate, inulin, creatinine, para-aminohippurate, sodium, potassium, chloride, and inorganic phosphate were the same as previously employed (6). Plasma concentrations of G-25671 were measured by the method previously de-scribed (8) for phenylbutazone except that 3 per cent isoamyl alcohol was added to the petroleum ether used for extraction of the drug and the optical densities were measured at 255 mμ.

RESULTS

Plasma levels of G–25671 after intravenous injection

The plasma levels of G–25671 obtained when the total dosage of drug (16 mg. per Kg. body weight) was delivered in one rapid injection varied from 22.7 to 12.3 mg. per cent at the mid-point of the first post-medication collection period (Table I). In every instance the plasma concentration of the drug declined in the course of the experiment, the final concentrations ranging from 15.7 to 8.4 mg. per cent. This is in contrast to the very slow disappearance of phenylbutazone from the plasma (7).

In two experiments involving sustained infusion of the drug at increasing rates (Table II), the plasma concentration of G–25671 was slowly

increased from initial trace levels to 9.5 and 5.4 mg. per cent, respectively, in Cases J. S. and L. L.

Effects of G–25671 on C_{In} and C_{PAH}

In Cases A. R., L. W., and M. C., the values for C_{In} and C_{PAH} prior to injection of G–25671 were within the normal range (Table I). The remaining six subjects were found to have significant reductions in glomerular filtration rate and/or renal plasma flow (Tables I and II), as commonly observed in older patients with a long history of overt gout. Cases J. S. and I. K. exhibited the most marked impairment of renal hemodynamics (C_{In} 54.4 and 64.9 ml. per min., C_{PAH} 242 and 202 ml. per min., respectively).

Infusion of G–25671 in the dosage employed did not significantly affect the glomerular filtration rate in five subjects (Tables I and II). In three instances C_{In} was appreciably although transitorily depressed, to a maximum of -30 per cent in

TABLE II

Effect of slow, sustained infusion of G-25671 and of phenylbutazone (in glucose solution) on renal clearances of inulin, urate, sodium, potassium and chloride

Case Age B.S.A.	Period	$P_{G-25671}$ or P_{Pb}	C_{In}	P_{Urate}	C_{Urate}	$\frac{C_{Urate}}{C_{In}}$	UV_{Na}	C_{Na}	UV_K	C_K	UV_{Cl}	C_{Cl}
		mg. %	ml./ min.	mg. %	ml./ min.	%	mEq./ min.	ml./ min.	mEq./ min.	ml./ min.	mEq./ min.	ml./ min.
1. J. S. 60 (1.98 M²)	Control	0	54.4	11.0	4.81	8.91	0.42	3.01	0.062	18.2	0.21	2.00
	G-25671: 0.80 gm. (9.5 mg./Kg. body weight) in 5% glucose/water											
	0–25 min.	Trace	47.0	11.0	3.51	7.47	0.39	2.76	0.060	14.6	0.18	1.64
	25–45 min.	0.6	49.2	11.0	3.84	7.80	0.40	2.84	0.050	12.6	0.18	1.69
	45–68 min.	1.3	60.5	11.0	8.22	13.6	0.39	2.77	0.049	12.5	0.21	2.01
	68–90 min.	4.0	60.5	11.0	8.86	14.7	0.38	2.70	0.043	11.0	0.19	1.81
	90–109 min.	5.2	63.9	10.7	11.8	18.5	0.33	2.37	0.039	10.0	0.18	1.68
	109–128 min.	7.3	60.3	10.3	16.0	26.6	0.33	2.34	0.033	9.4	0.15	1.40
	128–145 min.	9.5	56.5	10.3	16.8	29.7	0.29	2.10	0.029	8.6	0.12	1.13
2. L. L. 60 (1.87 M²)	Control	0	89.1	7.5	9.54	10.7	0.28	2.07	0.082	20.6	0.27	2.62
	G-25671: 0.86 gm. (11.5 mg./Kg. body weight) in 5% glucose/water											
	0–24 min.	Trace	82.3	8.0	9.60	11.7	0.24	1.78	0.064	15.9	0.24	2.34
	24–45 min.	0.2	82.3	7.8	9.28	11.3	0.28	2.06	0.079	19.7	0.28	2.72
	45–66 min.	1.0	92.8	7.6	11.4	12.3	0.29	2.12	0.081	20.2	0.29	2.82
	66–89 min.	1.2	90.0	7.3	12.6	14.0	0.30	2.16	0.073	18.2	0.28	2.78
	89–109 min.	2.7	92.8	7.4	16.3	17.6	0.30	2.18	0.067	16.6	0.28	2.72
	109–130 min.	3.7	91.1	8.1	19.5	21.4	0.31	2.27	0.064	16.0	0.27	2.62
	130–153 min.	5.4	92.5	8.0	23.0	24.8	0.31	2.25	0.058	14.5	0.26	2.52
3. N. P. 43 (2.13 M²)	Control	0	81.3	10.6	1.52	1.87	0.10	0.71	0.021	5.53	0.072	0.74
	Phenylbutazone: 0.46 gm. (5.1 mg./Kg. body weight) in 5% glucose/water											
	0–36 min.	Trace	88.0	10.5	1.24	1.41	0.10	0.70	0.023	6.05	0.073	0.75
	36–57 min.	0.5	75.0	10.1	1.07	1.43	0.082	0.57	0.022	5.80	0.060	0.62
	57–80 min.	0.8	88.9	10.5	1.12	1.26	0.082	0.57	0.024	6.32	0.057	0.59
	80–99 min.	2.3	99.3	10.5	1.38	1.39	0.084	0.59	0.027	7.11	0.056	0.57
	99–120 min.	4.0	89.4	10.5	1.09	1.22	0.069	0.48	0.026	6.86	0.043	0.44
	120–135 min.	3.5*	89.4	10.5	1.26	1.41	0.081	0.56	0.026	6.86	0.050	0.51
4. J. B. 56 (1.74 M²)	Control	0	127	8.5	6.67	5.22	0.21	1.45	—	—	0.17	1.62
	Phenylbutazone: 0.56 gm. (8.2 mg./Kg. body weight) in 5% glucose/water											
	0–26 min.	Trace	119	8.4	5.83	4.89	0.19	1.30	—	—	0.16	1.53
	26–51 min.	0.4	130	8.4	6.40	4.92	0.19	1.30	—	—	0.18	1.70
	51–85 min.	0.8	127	8.4	6.39	5.03	0.16	1.10	—	—	0.13	1.22
	85–106 min.	1.3	120	8.2	6.66	4.72	0.12	0.86	—	—	0.077	0.73
	106–128 min.	—	109	8.2	6.25	5.73	0.12	0.85	—	—	0.076	0.72
	128–176 min.	4.9	118	8.0	6.85	5.80	0.12	0.84	—	—	0.059	0.56
5. L. O. 37 (1.90 M²)	Control	0	129	9.4	7.40	5.73	0.26	1.81	0.093	22.1	0.28	2.78
	Phenylbutazone: 0.82 gm. (11.0 mg./Kg. body weight) in 5% glucose/water											
	0–25 min.	0.3	108	9.3	5.99	4.47	0.22	1.52	0.085	20.2	0.27	2.67
	25–47 min.	1.2	116	9.1	5.30	4.17	0.17	1.21	0.083	19.8	0.19	2.00
	47–68 min.	2.1	116	9.2	4.43	3.48	0.12	0.83	0.065	15.5	0.13	1.36
	68–90 min.	3.7	116	9.1	4.98	3.92	0.12	0.83	0.064	15.2	0.11	1.21
	90–122 min.	5.5	106	9.3	4.58	3.94	0.10	0.72	0.045	10.7	0.086	0.93
	122–154 min.	8.7	115	9.4	6.70	5.32	0.11	0.76	0.042	10.0	0.087	0.94

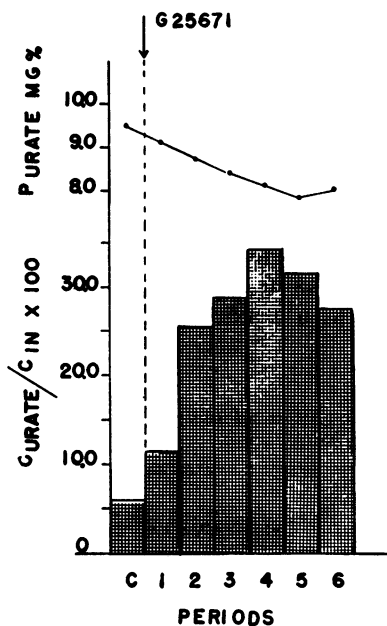* Phenylbutazone stopped after 120 minutes.

FIG. 1. EFFECT OF RAPID INTRAVENOUS INFUSION OF
G-25671, IN 16 MG. PER KG. BODY WEIGHT DOSAGE, ON
URATE CLEARANCE AND SERUM URATE LEVELS

The bars represent the means of seven urate/inulin
clearance ratio determinations before injection (C) and
in six post-injection collection periods. The line above
represents the concomitant mean serum urate response
in these seven experiments.

Case L. W., − 20 per cent in Cases A. R. and
H. G. A pyrogenic reaction to the infusion in
Case I. K. was associated with a transient rise
in C_{In}. The overall change in C_{In} following
G-25671 infusion was negligible in most instances.
Phenylbutazone in comparable dosage likewise
usually has little or no effect on the glomerular
filtration rate but may depress C_{In} in some in-
stances, more consistently when larger doses are
employed (7).

C_{PAH} was rapidly and consistently depressed
by G-25671 (Table I), the mean control value of
402 ml. per min. falling to a mean minimum of 284
ml. per min., an average decline approximating
30 per cent. This effect is presumed to be due
to decreased renal extraction of PAH rather than
to reduction in renal blood flow, since phenylbu-
tazone (7) markedly depresses Tm_{PAH}. Both
drugs significantly suppress the rate of phenol-
sulfonphthalein excretion (1), another indication
of depression of tubular excretory mechanisms.

Effect of G-25671 on urate clearance

A marked increase in urate clearance occurred
in every instance upon exhibition of the drug and
was invariably apparent in the first collection pe-
riod (Table I). The mean C_{urate}/C_{In} ratio rose
from a pre-medication value of 6.15 per cent to a
five-fold peak of 30.6 per cent. This effect was
more pronounced in the subjects with normal
renal hemodynamics (Cases A. R., L. W., and
M. C.) whose C_{urate}/C_{In} ratio rose from a mean
of 5.11 per cent to a mean peak of 40.1 per cent but
was readily demonstrable also in those with de-
pressed C_{In} and C_{PAH}, whose mean pre-medication
C_{urate}/C_{In} ratio of 6.93 per cent increased to 23.4
per cent (Table I). The uricosuria induced by
injection of G-25671 was associated invariably
and roughly proportionately with a progressive
decline in serum urate concentration, from a mean
initial level of 9.3 mg. per cent to a mean minimum
of 8.0 mg. per cent at the end of the period of ob-
servation (Figure 1). The fall in serum urate in
individual patients ranged from 2.3 to 0.5 mg. per
cent.

The data in Table II indicate that G-25671 be-
gins to exert its uricosuric effect at low plasma
concentrations of the drug, approximating 1 mg.
per cent, and that this action is progressively en-
hanced as the drug levels rise.

The uricosuric action of G-25671 is attributable
to suppression of tubular reabsorption of urate.
The percentage of filtered urate which was reab-
sorbed (i.e., filtered − UV/filtered) was calculated
to fall, under the influence of the drug, from a
mean pre-medication value of 93.9 per cent to a
mean minimum of 70.2 per cent (in Case L. W., to
as low as 50.8 per cent). As already implied, the
quantity of urate filtered at the glomerulus was
not significantly altered by the drug; no significant
change in the proportion of plasma urate which is
filtrable need be assumed (9); and the rapidity
of the uricosuric action precluded any appreciable
urate moiety due to augmented metabolic degrada-
tion of nucleic acids.

Effect of G-25671 on clearance and excretion (UV) of sodium, potassium and chloride

The experiments summarized in Table I in-
cluded simultaneous determinations of C_{Na}, C_K
and C_{Cl}. The results (data not included in Table

I) indicated an increase in sodium clearance in four of the seven subjects studied, no significant change in two, and a decrease in one; these alterations did not correlate with any changes in glomerular filtration rate. C_{Cl} paralleled C_{Na} throughout. C_K/C_{In} ratios were not significantly altered.

The increased sodium and chloride excretion noted in four subjects does not, under the conditions of these experiments, demonstrate that G–25671 may elicit sodium chloride diuresis since 14.2 to 24.0 mEq. of sodium, as sodium chloride solution and sodium salt of G–25671, were infused concomitantly with the drug. Calculation of the net electrolyte balance in fact revealed some retention of sodium, from 12.1 to 26.7 mEq. over the approximately 2-hour period of the experiment, in every patient except I. K. who developed a pyrogenic reaction. In Cases A. R. and L. W. (who received equivalent infusions of sodium chloride with and without the drug) 26.7 and 6.0 mEq. sodium, respectively, were retained when the drug, in saline solution, was infused, and 14.7 and − 1.6 mEq. sodium when sodium chloride alone was injected.

In two clearance experiments summarized in Table II, G–25671 was infused in a 5 per cent solution of glucose in water. Case J. S. shows retention of sodium chloride, Case L. L. does not. In both instances UV_K and C_K fell significantly; this result, which was not obtained in any experiments involving saline solution as a vehicle for G–25671, is attributed to the infusion of glucose and the utilization of potassium for glycogen formation.

Balance studies: G–25671 given by repeated intravenous injection

The observations made by the use of clearance techniques were supplemented by more protracted urate and electrolyte balance studies. In two such experiments G–25671 was administered intravenously in daily doses of 1.2 gm. (Case O.G.) and 1.6 gm. (Case L. W.), given in three divided doses, over a four-day period (Figure 2). These doses brought the plasma drug level in Case O. G. to 6.0 mg. per cent after 24 hrs. and to 11.8 mg. per cent on the fourth day of medication. In Case

L. W. the plasma drug levels were 4.0 mg. per cent and 9.7 mg. per cent, respectively.

Patient O. G., whose mean urinary urate excretion was 408 mg. per 24 hrs. in the 3-day control period, increased his mean daily output to 626 mg. per 24 hrs. during the period of drug injection, a total excess urinary urate excretion of 872 mg. for the 4-day period of drug administration. This was associated with a sharp fall in serum urate, from 9.7 mg. per cent to 2.6 mg. per cent. Upon discontinuance of medication the urinary urate excretion fell below pre-medication levels to a mean of 270 mg. per 24 hrs.; this period of urate retention was associated with a slow rise in serum urate level to 6.7 mg. per cent after 3 days. Patient L. W. excreted a mean of 454 mg. urate per 24 hrs. in the control period. On the first day of drug injection the urinary urate output rose to
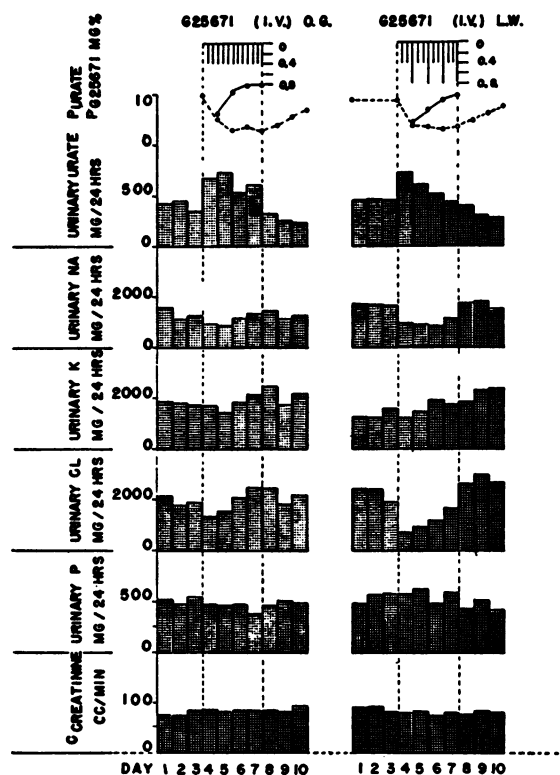

FIG. 2. CASES O. G. AND L. W. URINARY EXCRETION PER 24 HRS. OF URATE, SODIUM, POTASSIUM, CHLORIDE AND INORGANIC PHOSPHATE BEFORE, DURING, AND AFTER DAILY INTRAVENOUS INJECTION OF G–25671 IN THE DOSAGE INDICATED AT THE TOP

The effect on "endogenous" creatinine clearance is indicated at the bottom of the figure, the serum urate levels (hollow dots) and serum G–25671 (solid dots) above.

TABLE III

Effect of G-25671 on serum and urinary urate in five gouty subjects
(Dosage 1.0 gm. per day)

Case	Uric acid	Pre-medication	Day of medication							Day of post-medication	
			1	2	3	4	5	6	7	1	2
1. J. Z.	Serum (mg./100 ml.)	9.1	6.6	4.3	3.0	3.0		3.7	3.4	5.0	5.7
	Urine (mg./24 hrs.)	604	1,250	1,337	1,095	818	717	785	805	560	393
2. R. C.	Serum	11.3	10.0	7.8	7.9	7.8	7.1		7.3	9.8	12.0
	Urine	852	975	1,597	1,476	1,133	1,158	1,409	1,450	848	654
3. A. K.	Serum	12.6	10.6	5.8	5.4		5.6			7.6	11.4
	Urine	493	911	1,268	910		922			576	512
4. R. E.	Serum	11.1	9.6	6.5	7.5	5.4				6.2	7.1
	Urine	424	606	866	702	531				316	487
5. L. C.	Serum	9.2	7.4	5.6	4.8					5.8	7.1
	Urine	671	972	938	938					605	487

736 mg. per 24 hrs., then declined to 596 mg. per 24 hrs. and thereafter to control levels—a temporary uricosuria often encountered when the quantity of mobilizable urate deposit is small and readily depleted, as in this instance. The serum urate level, initially 8.7 mg. per cent, fell to approximately 3.0 mg. per cent and remained there throughout the period of drug administration. This is an indication of continued suppression of tubular reabsorption of urate, despite the return of urinary urate excretion levels to pre-medication values. Discontinuance of the drug was followed by urinary urate retention and slow rise of the serum urate level.

In Case O. G. the mean control level of urinary sodium excretion, 1.32 gm. per 24 hrs., was reduced to a mean of 0.95 gm. per 24 hrs. for the first two days of drug administration, then reverted to the control figures; the urinary chloride excretion closely paralleled these changes. Case L. W., whose sodium chloride intake and drug dosage were greater than in Case O. G., showed more marked and sustained sodium chloride retention. The mean urinary sodium excretion in the control period, 1.69 gm. per 24 hrs., fell to a mean of 0.96 gm. per 24 hrs. during the 4-day period of drug administration. The urinary chloride excretion fell concomitantly to a mean of approximately 50 per cent of the mean control period levels. The urinary excretion of potassium, inorganic phosphate and creatinine was not significantly altered by G–25671.

The serum levels of sodium, potassium, chloride and inorganic phosphate remained essentially unchanged throughout the experiments. There was no significant decrease in the hematocrit in either patient although Case L. W. gained two pounds in weight.

Effect of oral administration of G–25671 on urinary urate excretion and serum urate levels

Table III records the day-by-day uricosuric response to daily doses of 1.0 gm. G–25671, given in five divided doses of 0.2 gm., in 5 gouty subjects maintained on a constant diet low in purines and fats, and containing 60 to 80 gm. protein per day. The mean increase in urinary urate excretion with this dosage was 55 per cent at the end of the first 24-hours of medication, reached a peak of 97 per cent after 48 hours, and continued to be augmented so long as the drug was administered. There was a concomitant sharp and sustained fall in serum urate. Cessation of medication was invariably followed by a period of urate retention.

Data on the response of the serum urate level are available in 13 gouty subjects, free of significant impairment of renal function, after oral administration of G–25671 in 1.0 gm. daily dosage. The mean pre-medication figure of 9.6 mg. per cent was reduced to a mean minimum of 4.7 mg. per cent.

A special study was made of the uricosuric response to G–25671 of gouty subjects with marked renal damage, since it is this category

which is most apt to be refractory to uricosuric agents, even in doses larger than ordinarily employed. Observations were made in five such patients after 1.0-gm. daily dosage and, in all but one, subsequently after 2.0-gm. daily dosage. In Case J. D., the initial urinary urate excretion of 656 mg. per 24 hrs. and serum urate level of 10.8 mg. per cent changed, with 1.2 gm. G–25671 daily, to 834 mg. per 24 hrs. and 7.7 mg. per cent, respectively, and then to 1140 mg. per 24 hrs. and 5.9 mg. per cent with 2.0-gm. daily dosage. In Case S. R., the respective figures were 968 mg. per 24 hrs. and 14.7 mg. per cent before medication; 1332 mg. per 24 hrs. and 7.2 mg. per cent with 1.2 gm. drug daily; 1145 mg. per 24 hrs. and 5.2 mg. per cent with 2.0 gm. drug daily. In Case S. T., the initial serum urate level of 10.6 mg. per cent fell to 9.7 mg. per cent on 1.2-gm. daily dosage and to 7.6 mg. per cent on 2.0-gm. daily dosage. In Case L. M., the response was altogether unsatisfactory: With 1.2 gm. G–25671 daily both urinary urate excretion and serum urate level were essentially unchanged from the initial figures of 805 mg. per 24 hrs., and 12.6 mg. per cent, respectively, and an attempt to increase the dosage had to be discontinued because of the appearance of a drug rash. Case G. S., who gave a typical history of chronic glomerulonephritis (with serum NPN 91 mg. per cent, PSP excretion 20 per cent in 2 hours) as well as gout, also responded unsatisfactorily. The pre-medication urinary urate excretion of 288 mg. per 24 hrs. was unchanged with 1.2-gm. daily dosage although the serum urate level fell from 11.1 to 9.4 mg. per cent; on 2.0-gm. daily dosage the urinary urate excretion was 228 mg. per 24 hrs. and the serum urate 7.7 mg. per cent.

Anti-rheumatic action

Animal screening tests indicate that G–25671 possesses marked anti-inflammatory properties in experimental inflammations.[2] This action is demonstrable also in man but the effects are distinctly less marked and less consistent than with phenylbutazone (1). Thus of 10 acute gouty attacks treated with 1.0 gm. G–25671 daily, only three

[2] We are indebted to R. Domenjoz and G. Wilhelmi of Geigy Pharmaceuticals for this information.

remitted completely within 24 to 48 hours, two within 72 hours, four improved temporarily but recurred promptly upon discontinuance of the drug, and in one instance the dosage had to be increased to 2.0 gm. per day because of inadequate response. All these patients showed the usual prompt and marked uricosuria, with decline in serum urate levels.

These results discouraged further trial of G–25671 in the termination of severe attacks of acute gouty arthritis but suggested that, apart from its uricosuric action, the drug might be useful in the control of pain and stiffness associated with chronic gouty arthritis. Of six such cases studied, four were promptly relieved of pain and stiffness with doses of 1.2 gm. daily, two only when the dosage was increased to 2.0 gm. daily. One of the patients, who received the drug in 2.0-gm. daily dosage continuously for 10 months, shows definite reduction in the size of tophi.

Despite relief of chronic joint symptoms, however, G–25671 in 1.0-gm. or 2.0-gm. daily dosage proved to be ineffective as a prophylactic agent in preventing recurrence of acute gouty arthritis in 4 of 7 patients receiving the drug for protracted periods.

Toxic reactions to G–25671

The drug was administered to 28 gouty subjects in all, 21 for studies of less than one week's duration, 7 continuously and without adverse effects for periods of 3 to 10 months. Three patients developed a rash (one urticarial, one erythematous, 1 purpuric), in every instance within a day or two of initiation of medication; one had reacted similarly to phenylbutazone. One patient developed a renal calculus, another noted "sand" in the urine, a third complained of renal colic. One patient complained of anorexia, one of marked constipation, the only gastro-intestinal complications encountered. The drug did not appear to precipitate acute gouty arthritis when first administered but, as already mentioned, did not prevent recurrence of acute seizures in the course of protracted usage. Careful checks at regular intervals in the 7 patients receiving the drug for 3 to 10 months failed to reveal any indication of bone marrow depression, hepatotoxicity or neurotoxicity.

DISCUSSION

The effects of G–25671 on discrete renal functions, as described in the preceding section, differ in significant respects from those observed with equivalent dosages of phenylbutazone, notably in relation to tubular reabsorption of urate and of salt and water. These differences, brought about by substitution of a phenylthioethyl group for the butyl side chain of the parent compound, appear to be quantitative rather than qualitative in nature, as will be made evident in detailed comparisons to follow. Nevertheless they are of such order of magnitude as to impart potential clinical usefulness to G–25671 as a uricosuric drug in the management of gout (1), phenylbutazone not being serviceable for this purpose (7). The data now at hand make possible a provisional assessment of G–25671 as a uricosuric agent.

Comparison of uricosuric effects of phenylbutazone and G–25671

It was found in a prior study (7) of ten gouty subjects that intravenous injection of phenylbutazone in dosages ranging from 12 to 27 mg. per Kg. body weight caused a rise in C_{urate}/C_{In} ratios from a mean control value of 6.04 per cent to a mean peak of 19.5 per cent, an approximately three-fold increase. The data of the present analogous study with G–25671, given intravenously in a dosage of 16 mg. per Kg. body, indicate an approximately five-fold mean peak rise in C_{urate}/C_{In}, from a premedication value of 6.15 per cent to 30.6 per cent. Direct comparisons, made in the same patient, more convincingly demonstrate the greater uricosuric efficacy of G–25671 (Table I). In Case A. R., the C_{urate}/C_{In} ratio rose from 5.9 per cent to a peak of 39.6 per cent with G–25671 whereas with the same dosage of phenylbutazone the rise was from 5.3 per cent to 21.8 per cent; in Case L. W., the respective increases were from 3.3 per cent to 49.3 per cent with G–25671 and from 3.6 per cent to 17.8 per cent with phenylbutazone; in Case M. C., from 6.1 per cent to 31.5 per cent and from 5.0 per cent to 9.0 per cent, respectively. Since these and similar comparisons of the two drugs were made with dosages equivalent on a drug-weight basis, the actual dosage of G–25671 administered was approximately 25 per cent less

than that of phenylbutazone when calculated on an equi-molecular basis (molecular weight of phenylbutazone, 298; of G–25671, 384).[8]

There has been some difference of opinion as to whether phenylbutazone, when administered orally, exerts any uricosuric action in the usual dosage, 400 to 800 mg. daily. The preponderance of evidence (7, 10, 11 and others) clearly indicates that phenylbutazone increases urinary urate excretion when plasma drug concentrations approximating 10 mg. per cent or more are attained, for which regular oral doses of at least 600 mg. per day ordinarily are required (10). A decline in serum urate concentration may precede distinct uricosuria but this appears to be largely factitious, usually the result of hemodilution due to marked salt and water retention.

The available data on G–25671 indicate that this drug, when given orally, elicits increases in urinary urate excretion and associated falls in serum urate concentration at least as great as probenecid in equivalent dosage (12). The uricosuric action begins at plasma drug levels approximating 1 mg. per cent, and effective blood levels are readily achieved when the drug is given orally in the daily dosage we have ordinarily employed, 1.0 gm. per day. Because of the short biologic half-life of G–25671 (about 3 hours compared to 70 hours for phenylbutazone) (1) maintenance of effective plasma drug levels throughout the day requires distribution in divided doses. We give 0.2 gm. every 4 hours from 7:00 A.M. to 11:00 P.M.

Comparison of effects of phenylbutazone and G–25671 on salt and water retention

It is well known that phenylbutazone may cause marked retention of salt and water; indeed, the

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[8] Several additional phenylbutazone analogs, representing other substitutions in the side chain, have been tested in respect to their uricosuric action. G–25903, in which a phenylthiopropyl side chain replaces the phenylthioethyl group of G-25671, has much less uricosuric effect than G–25671 or phenylbutazone; 2 gm. per day by mouth elicits only a 25 per cent increase in urinary urate excretion. On the other hand, G–25669 (isopropylthioethyl analog) and G–25921 (p-chlorophenylthioethyl analog) are both very potent uricosuric agents. All three of these compounds undergo rapid biotransformation and have a half-life approximating that of G–25671.

clinical consequences thereof, in particular expansion of the intravascular fluid compartment, represent a hazard in the use of the drug. In our own experience (7), the urinary excretion of sodium in one patient studied, Case O. G., fell from 0.81 gm. per 24 hrs. to 0.37 gm. per 24 hrs. when 0.8 gm. phenylbutazone was infused daily; the corresponding figures for urinary chloride excretion were 1.63 and 0.92 gm. per 24 hrs., respectively. This patient was maintained throughout the experiment on a constant low-sodium diet to which 2.5 gm. sodium chloride a day was added. In another instance (7), Case L. W., who also received 0.8 gm. phenylbutazone by intravenous injection, the urinary excretion of sodium fell from 2.20 to 1.13 gm. per 24 hrs., the urinary chloride excretion concomitantly from 3.61 to 1.80 gm. per 24 hrs. Case L. W.'s low salt diet was supplemented with 3.5 gm. sodium chloride daily. In both instances retention of sodium was associated with a rise in serum sodium levels, in Case O. G. from 141 to 150 mEq. per L, in Case L. W. from 145 to 156 mEq. per L.

These same patients were subjected to analogous experiments with G–25671 which, as indicated by the data of this study already presented, also causes some retention of sodium chloride (Figure 2); in equivalent dosage and plasma drug levels, however, significantly less than does phenylbutazone. Thus the urinary sodium excretion in Case O. G. fell from 1.32 gm. per 24 hrs. to a mean of 0.95 gm. per 24 hrs. for the first two days of intravenous injection of 1.2 gm. G–25671 daily (50 per cent higher dosage than in the corresponding phenylbutazone experiment) but returned to the control level, 1.25 gm. per 24 hrs., as the drug infusion was continued. The corresponding figures for urinary chloride excretion were closely parallel: 1.94 gm. per 24 hrs. control level, 1.47 gm. per 24 hrs. for the first two days, and 2.28 gm. per 24 hrs. for the last two days of injection. The constant low sodium diet in this instance was supplemented with 2.5 gm. sodium chloride daily, as in the corresponding phenylbutazone experiment. Case L. W. received 1.6 gm. G–25671 daily by intravenous injection. At this dosage retention of sodium was about as marked as was obtained with 0.8 gm. of phenylbutazone: The premedication uri-

nary excretion of sodium, 1.69 gm. per 24 hrs., fell to a mean of 0.96 gm. per 24 hrs., the urinary chloride excretion fell from 2.26 to 1.14 gm. per 24 hrs. The low sodium diet in this instance was supplemented with 3.5 gm. sodium chloride, as in the prior phenylbutazone experiment.

Owing to the rapid metabolic degradation of G–25671, the tendency to retain sodium chloride was no longer apparent even on the first day of discontinuance of medication whereas the sodium-retaining effect of phenylbutazone was still in evidence 24 to 72 hours thereafter. G–25671 did not cause any hypernatremia, such as was noted with phenylbutazone, and hemodilution was not significant in ordinary clinical dosage.

Another relevant point in this connection was brought out by slow infusion experiments in which the plasma concentration of phenylbutazone or G–25671 was raised gradually in order to determine the relative drug levels required to effect uricosuria and/or sodium retention (Table II). These experiments demonstrate that plasma phenylbutazone levels of 1 to 2 mg. per cent are associated with distinct sodium retention (Table II) whereas no increase in urinary urate excretion occurs until plasma drug concentrations of approximately 10 mg. per cent are reached (7, 10). On the other hand, G–25671 causes distinct uricosuria at plasma drug concentrations of 1 mg. per cent, which appear to be insufficient to elicit significant sodium retention. In Case L. O., the plasma phenylbutazone level was slowly raised to 8.7 mg. per cent at which point UV_{Na} was decreased 58 per cent and UV_{Cl} declined 66 per cent, yet C_{urate}/C_{In} approximated the pre-medication ratio.[4] Case J. B. exhibited the same phenomenon, although not so markedly, at lower plasma phenylbutazone concentrations. In contrast, C_{urate}/C_{In} increased 130 per cent at a plasma G–25671 concentration of 5.4 mg. per cent in Case L. L., without any decline whatsoever in UV_{Na} or UV_{Cl}. In Case J. S., C_{urate}/C_{In} increased 35 per cent at a plasma G–25671 concentration of 1.3 mg. per cent at which point UV_{Na} and UV_{Cl} were unchanged.

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[4] It will be noted that in this and other instances, very low plasma phenylbutazone and G–25671 levels may be associated with *reduction* in C_{urate}/C_{Inulin}. The significance of this phenomenon is discussed elsewhere (13).

*Comparison of clinical usefulness of phenylbuta-
zone and G–25671 in the management of acute
and chronic gouty arthritis*

The potent anti-rheumatic properties of phenyl-
butazone have established a limited but definite
place for it in the current management of various
arthritic disorders, notably in the short-term treat-
ment of acute gouty arthritis. Our own data in
this connection conform to the favorable general
experience. Of 103 acute gouty seizures in 61
patients, treatment with 800 mg. phenylbutazone
a day gave complete remission within 24 to 48
hours in 76 (74 per cent) and within two days
to one week in 14 (14 per cent). Five patients
(5 per cent) showed a partial response, three (3
per cent) did not respond at all and five (5 per
cent) improved but this was followed by disturb-
ing side effects of the drug. In contrast to these
good results with phenylbutazone, only 30 per
cent of 10 acute gouty attacks treated with
G–25671 (1 gm. daily) remitted completely within
24 to 48 hours, an experience which does not
justify use of this drug for termination of acute
gouty arthritis. Our experience with G–25671 in
protracted daily usage as a prophylactic agent to
prevent recurrence of acute gouty seizures also
has been discouraging, certainly less satisfactory
than with the daily prophylactic use of small doses
of colchicine for the purpose (14).

The experience herein described suggests, how-
ever, that G–25671 may have potential clinical
usefulness as a uricosuric agent in the prevention
and treatment of chronic gouty arthritis; it has
potent uricosuric and mild anti-rheumatic prop-
erties, and causes negligible retention of sodium
and water. Since administration as a uricosuric
agent would require daily dosage for months or
years, the limiting factor in use of the drug for
this purpose would appear to be its hazard of
significant toxicity. In our own small experience
thus far, this hazard does not appear to be exces-
sive. Of 28 gouty subjects treated with the drug,
three developed significant side reactions (drug
rash, which disappeared promptly upon discon-
tinuance of medication), three had complications
referable to excessive uricosuria (a hazard com-
mon to all uricosuric agents which can usually be
circumvented), none gave evidence of bone mar-
row depression, hepatotoxicity or neurotoxicity.

The similarity in chemical structure to phenylbu-
tazone, however, suggests caution in the protracted
administration of G–25671, and much more ex-
tensive and prolonged experience will be necessary
to permit conclusions as to its safety for use in the
management of chronic gouty arthritis.

Phenylbutazone has been recommended for pro-
tracted daily use in gouty subjects (15) but we
consider that the toxic hazards entailed do not
justify its employment for this purpose (7).

SUMMARY

1. G–25671 is a phenylbutazone derivative in
which a phenylthioethyl group replaces the butyl
side chain. The effects of G–25671 on the simul-
taneous renal clearances of inulin, para-aminohip-
purate, urate, sodium, potassium and chloride are
reported, and the results compared with those
obtained with phenylbutazone.

2. Like phenylbutazone, G–25671 usually does
not significantly affect the inulin clearance but
may lower it in some instances. Both drugs sig-
nificantly depress C_{PAH}, apparently as a result of
decreased renal extraction of PAH.

3. In seven rapid infusion experiments, G–25671
caused a mean five-fold increase in C_{urate}/C_{In}, from
a mean pre-medication value of 6.15 per cent to a
mean peak of 30.6 per cent. This uricosuric effect,
which is much more pronounced than that of
phenylbutazone, is attributable to suppression of
tubular reabsorption of urate.

4. G–25671 causes distinctly less sodium and
water retention than phenylbutazone in comparable
dosage, and exerts its uricosuric action at low
plasma drug levels (approximately 1 mg. per cent)
which are not associated with any discernible ef-
fects on tubular transport of electrolytes. Phenyl-
butazone, in contrast, causes sodium and water
retention at low plasma drug levels and uricosuria
only in plasma drug levels of approximately 10
mg. per cent or more. Neither drug significantly
affects potassium or phosphate excretion.

5. Administered orally to gouty subjects, in 1.0
to 2.0-gm. daily dosage, G–25671 is a potent uri-
cosuric agent. In 13 such patients, free of sig-
nificant renal damage, the serum urate level was
reduced from a mean pre-medication figure of 9.6
mg. per cent to a mean minimum of 4.7 mg. per
cent; the effect in patients with renal damage was

less satisfactory. G–25671 also possesses antirheumatic properties sufficient to control pain and stiffness in chronic gouty arthritis but these are distinctly less pronounced than phenylbutazone and the drug is of little or no value in terminating acute gouty attacks.

6. The limiting factor in clinical use of G–25671 as a uricosuric agent in the prevention and treatment of chronic gouty arthritis is the potential hazard of toxic side reactions. Drug sensitivity (rash) developed in approximately 10 per cent of our patients. There was no indication of bone marrow depression, hepatotoxicity or neurotoxicity in this series but the observations are too few and too brief to warrant conclusions.

REFERENCES

1. Brodie, B. B., Yü, T. F., Burns, J. J., Chenkin, T., Paton, B. C., Steele, J. M., and Gutman, A. B., Observations on G–25671, a phenylbutazone analogue (4-(phenylthioethyl)-1,2-diphenyl 3,5-pyrazolidinedione). Proc. Soc. Exper. Biol. & Med., 1954, 86, 884.
2. Yü, T. F., Chenkin, T., Paton, B. C., and Randolph, V., Effect of G–25671, a phenylbutazone analogue, on urate clearance, glomerular filtration rate and renal plasma flow. J. Pharmacol. & Exper. Therap., 1955, 113, 57.
3. Burns, J. J., Gutman, A. B., Yü, T. F., Paton, B., Perel, J., Steele, J. M., and Brodie, B. B., Isolation, identification and physiologic effects of phenylbutazone metabolites. Federation Proc., 1955, 14, 323.
4. Burns, J. J., Rose, R. K., Goodwin, S., Reichenthal, J., Horning, E. C., and Brodie, B. B., The metabolic fate of phenylbutazone (Butazolidin) in man. J. Pharmacol. & Exper. Therap., 1955, 113, 481.
5. Goldring, W., and Chasis, H., Hypertension and Hypertensive Disease. New York, The Commonwealth Fund, 1944.
6. Sirota, J. H., Yü, T. F., and Gutman, A. B., Effect of Benemid (p-[di-n-propylsulfamyl]-benzoic acid) on urate clearance and other discrete renal functions in gouty subjects. J. Clin. Invest., 1952, 31, 692.
7. Yü, T. F., Sirota, J. H., and Gutman, A. B., Effect of phenylbutazone (3,5 dioxo-1,2-diphenyl-4-n-butylpyrazolidine) on renal clearance of urate and other discrete renal functions in gouty subjects. J. Clin. Invest., 1953, 32, 1121.
8. Burns, J. J., Rose, R. K., Chenkin, T., Goldman, A., Schulert, A., and Brodie, B. B., The physiological disposition of phenylbutazone (Butazolidin) in man and a method for its estimation in biological material. J. Pharmacol. & Exper. Therapy., 1953, 109, 346.
9. Yü, T. F., and Gutman, A. B., Ultrafiltrability of plasma urate in man. Proc. Soc. Exper. Biol. & Med., 1953, 84, 21.
10. Huffman, E. R., Smyth, C. J., Wilson, G. M., Jr., and Hill, R., Uricosuric effect of phenylbutazone. Ann. Rheumat. Dis., 1955, 14, 97.
11. Wyngaarden, J. B., The effect of phenylbutazone on uric acid metabolism in two normal subjects. J. Clin. Invest., 1955, 34, 256.
12. Gutman, A. B., Yü, T. F., and Randolph, V., Further observations on the uricosuric effects of probenecid (Benemid) in tophaceous gout. Tr. A. Am. Physicians, 1954, 67, 250.
13. Yü, T. F., and Gutman, A. B., Paradoxical retention of uric acid by uricosuric drugs in low dosage. Proc. Soc. Exper. Biol. & Med., 1955, 90, 542.
14. Gutman, A. B., and Yü, T. F., Current principles of management in gout. Am. J. Med., 1952, 13, 744.
15. Kuzell, W. C., Schaffarzick, R. W., Naugler, W. E., Gaudin, G., Mankle, E. A., and Brown, B., Phenylbutazone (Butazolidin) in gout. Am. J. Med., 1954, 16, 212.