The Effectiveness of Allopurinol in the Treatment of Gout

By JAMES R. KLINENBERG, M.D.

The Johns Hopkins Hospital

I will review briefly our studies performed at the National Institutes of Health in collaboration with Drs. Stephen Goldfinger and J. E. Seegmiller in evaluating the effectiveness of allopurinol in the treatment of gout.[1] We studied 8 patients with gout, 3 normal volunteer subjects and one patient who had the rare metabolic defect, xanthinuria. The drug was tolerated well in dosages up to 800 mg. daily in 11 of the 12 subjects. One normal volunteer subject developed a rash, fever and leukopenia 11 days after allopurinol was given in the dosage of 400 mg. daily for 6 days and 800 mg. daily for 5 days. All of these manifestations disappeared when the drug was discontinued, recurred within 24 hours after reinstitution of drug therapy, and disappeared again when the drug was stopped. They did not occur when a placebo was administered, so we believe that this was probably a bona fide drug reaction.

All studies were performed on a metabolic ward. During all phases of the investigations, patients received a 2,600 calorie "purine-free" diet containing 70 Gm. protein. No salicylates or uricosuric agents were administered during the studies.

Figure 123 shows a representative balance study in one of our patients. This was a 72-year old lady with tophaceous gout who never really manifested a very striking hyperuricemia. However, when started on allopurinol her serum urate concentration decreased coincidentally with an increase in urinary oxypurines. The data are plotted as millimols per day to allow the addition of oxypurines and uric acid as total purine excretion.

Initially the excretion of uric acid in the urine did not decrease very dramatically. We noted in many patients that there was no real decrease in the urinary uric acid excretion. This is especially true in patients with tophi. We have attributed this to the mobilization of urate from tissue deposits as the serum concentration begins to decline.

The effect of allopurinol administration on the plasma urate concentrations in 11 of our 12 subjects is shown in Figure 124. The twelfth subject, who had xanthinuria, had exeremely low plasma urate concentrations. The three normal volunteers, all with normal control plasma urate concentrations, showed significant decreases while on allopurinol therapy. Each of the gouty subjects also showed a significant decrease in plasma urate. Each subject achieved urate concentrations below 7 mg./100 ml. while on therapy. This includes one patient (J. F.) who was found to be quite refractory to conventional uricosuric therapy, including maximal doses of probenecid and sulfinpyrazone.

Table 39 is a summary of our data showing balance studies over varying

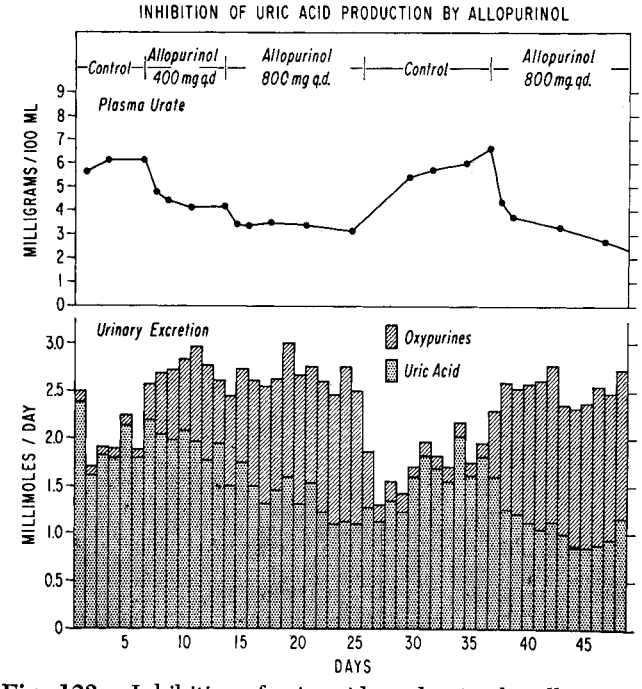

Fig. 123.—Inhibition of uric acid production by allopurinol.

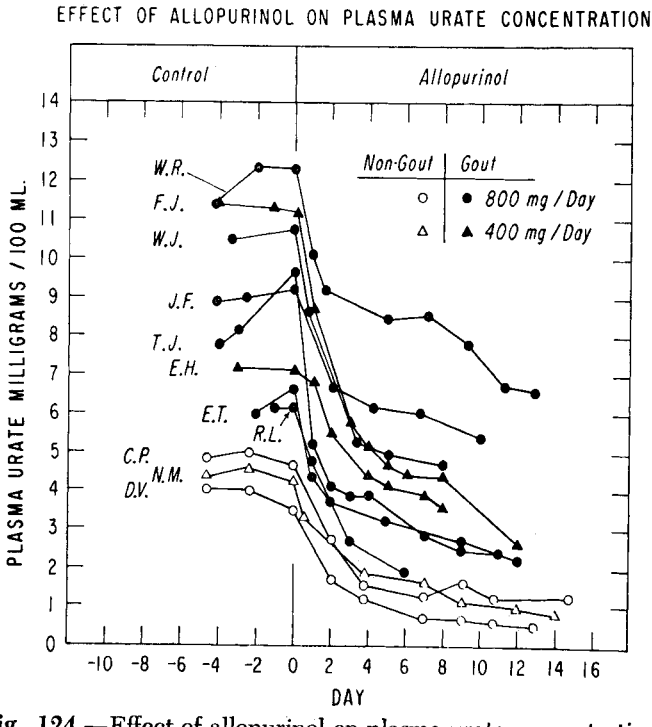

Fig. 124.—Effect of allopurinol on plasma urate concentration.

Table 39.—*Effect of Allopurinol Administration on the Purine Content of Urine*

Subject	Tophi	Uric Acid		Oxypurines		Total Purines						
		Control	Allopurinol	Control	Allopurinol	Control			Allopurinol			Change
		mM/24 hr.	mM/24 hr.	mM/24 hr.	mM/24 hr.	days	mM/24 hr.	mg./24 hr.	days	mM/24 hr.	mg./24 hr.	mg./24 hr.
						Gout:						
E. T.	Yes	1.6	1.0	0.1	1.2	24	1.7	285	37	2.2	370	+85
E. H.*	No	2.3	1.8	0.1	0.7	3	2.4	405	8	2.5	420	+15
T. J.	Yes	5.8	1.9	0.3	4.0	3	6.1	1025	10	5.9	990	−35
F. J.*	No	7.1	2.3	0.3	3.7	3	7.4	1245	13	6.0	1010	−235
R. L.	No	2.6	1.2	0.1	1.2	3	2.7	455	6	2.4	405	−50
W. R.	Yes	3.2	2.9	0.1	1.2	9	3.3	555	25	4.1	690	+135
W. J.	Yes	3.0	1.9	0.1	1.1	3	3.1	520	8	3.0	505	−15
J. F.	Yes	1.4	1.0	0.1	0.6	11	1.5	250	40	1.6	270	+20
						Xanthinuria:						
V. P.		<0.03	<0.03	1.5	1.5	6	1.5	250	20	1.5	250	0
						Normal volunteers:						
C. P.		3.0	1.2	0.1	1.1	8	3.1	520	18	2.3	385	−135
D. V.		2.6	0.7	0.2	1.5	4	2.8	470	14	2.2	370	−100
N. M.		1.7	0.5	<0.03	1.0	8	1.7	285	16	1.5	250	−35

The dosage of allopurinol was 200 mg. every 6 hours except for patients indicated by * who received 100 mg. every 6 hours. Oxypurines are expressed as equivalent mg. of uric acid to permit summation. Values shown represent the mean excretion over the number of days indicated.

periods of time. Again our data are expressed in millimols per 24 hours so that additions can be made to express total purine excretion. We have found, using slightly different analytical methods, that most of our patients while on allopurinol excreted in excess of 150 mg. of oxypurine (expressed as uric acid) in a 24-hour period. This is somewhat in excess of the quantities which Dr. Wyngaarden reported.

The two patients with the greatest total purine excretion (T. J. and F. J.) have both been shown to be overproducers of uric acid. Patient V. P. has the metabolic disorder xanthinuria, which accounts for a daily excretion of uric acid of less than 5 mg. Except for this patient, all subjects treated with allopurinol had a diminished uric acid excretion and an increased oxypurine excretion during the period of drug administration. The total purine excretion (uric acid plus oxypurines) was either increased or showed no significant change in the five patients with tophaceous gout and in one patient without demonstrable tophi.

In order to examine adequately whether there was an inhibition at some other stage of purine biosynthesis, or if this were just a direct effect on xanthine oxidase, similar studies were performed on normal volunteer subjects who did not have either demonstrable tophi or the possibility of micro tophi. Two patients with nontophaceous gout and three normal volunteers had a decrease in total purine excretion of from 11 to 26 per cent during allopurinol administration.

It is quite likely that if there is an effect of allopurinol on purine biosynthesis at some other stage, the xanthinuric subject would show a diminution in total purine production while on allopurinol. Such a study on patient V. P. (Table 39) showed that there was no change in total purine excretion during allopurinol administration.

In view of what Dr. Wyngaarden has previously mentioned, another point should be made. Our maximum duration of therapy in these studies was 40 days. I think it is possible that had we continued these studies for longer periods of time, a disparity may have become more apparent.

We have also studied the oxypurine clearance in four patients who were receiving allopurinol. The oxypurine/inulin clearance ratios ranged from 0.74 to 1.22 (Table 40). This represented a 6 to 16 fold increase over the urate/inulin urine clearance ratio. Thus it appears that oxypurines are cleared by the kidney much more readily than uric acid. We wondered whether this was due entirely to drug effect or was related to the way that the kidney handled oxypurines.

However, studies on the infusion of the oxypurines xanthine and hypoxanthine into normal volunteer subjects confirmed these ratios.[2] Thus these values represent the actual clearance of the oxypurines and are not the result of a direct effect of allopurinol on the kidney. This was further confirmed by the fact that our patient with xanthinuria had an oxypurine/creatinine clearance of 0.8. We did not find any change in the urate/inulin clearance ratios in patients who were treated with allopurinol as compared to the ratios before allopurinol therapy was begun.

Table 40.—*The Renal Clearance of Oxypurines and Uric Acid during Allopurinol Administration*

Patient	C Oxypurine ml./min.	C Uric Acid ml./min.	C Inulin ml./min.	$\frac{C\ Oxy}{C\ I}$	$\frac{C\ U}{C\ I}$	$\frac{C\ Oxy}{C\ U}$
E. T.	82.9	13.6	112.5	0.74	0.12	6.1
R. L.	43.7	4.3	55.0	0.79	0.08	10.2
T. J.	106.5	7.9	87.5	1.22	0.09	13.5
F. J.	93.7	5.6	81.0	1.16	0.07	16.7

C represents a mean of 3 clearance periods.
Corrected to a standard body surface of 1.73M².

Table 41.—*Solubility of Purine in Serum and Urine*

	(mg./100 ml.)		
	Uric Acid	Xanthine	Hypoxanthine
Serum—pH 7.4	7	10	115
Urine—pH 5	15	5	140
Urine—pH 7	200	13	150

Finally, we also studied the solubility of xanthine and hypoxanthine in biological fluids. These studies (Table 41) show that xanthine has a solubility very similar to that of uric acid, while hypoxanthine is much more soluble. Due to the very rapid renal clearance of the oxypurines, even in our greatest overproducers of uric acid when on allopurinol therapy, the highest oxypurine concentration in the plasma was 0.9 mg./100 ml. This was significantly below what we considered to be the critical solubility for xanthine in plasma. Therefore, we conclude that due to the very rapid clearance of oxypurines and due to the solubility factors, this conversion of a large portion of the uric acid to xanthine and hypoxanthine may well be very beneficial in the treatment of gout.

REFERENCES

1. Klinenberg, J. R., Goldfinger, S. E., and Seegmiller, J. E.: The Effectiveness of the Xanthine Oxidase Inhibitor Allopurinol in the Treatment of Gout. *Ann. Int. Med. 62*:639, 1965.
2. Goldfinger, S. E., Klinenberg, J. R., and Seegmiller, J. E.: The Renal Excretion of Oxypurines. *J. Clin. Invest. 44*: 623, 1965.