ALLOPURINOL IN THIAZIDE-INDUCED HYPERURICAEMIA

BY

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Thiazide diuretics have been used in the treatment of arterial hypertension either alone or to potentiate the action of hypotensive drugs (Aleksandrow, Wyszynacka, and Gajewski, 1959).

Thiazides have a hyperuricaemic action due to a specific inhibition of the tubular secretion of uric acid (Demartini, 1965). A paradoxical uricosuric effect is produced when the drug is administered intravenously (Nash and Kirkendall, 1962). This hyperuricaemic action appears not only with thiazide derivatives but also with other diuretics not chemically related to them (Melvin, Farrelly, and North, 1963; Humphreys, 1966). We have recently demonstrated this hyperuricaemic effect in two diuretics, *polythiazide* and *clopamide* (Table I). The data shown in this Table indicate that many thiazide derivatives have a similar hyperuricaemic effect. On the other hand several authors have observed a significantly higher serum uric acid (SUA) level in hypertensive patients with apparently normal glomerular filtration rate (GFR) before treatment in comparison with a normal group. This effect has been attributed to a tubular lesion, probably specific in these patients (Breckenridge, 1966). It is also known that different hypotensive drugs may produce hyperuricaemia, probably related to a decrease in GFR (Dollery, Duncan, and Schumer, 1962).

In gout the incidence of arterial hypertension with or without overt renal damage seems to be higher than in the general population (Hall, 1966; Talbott, 1964). In 94 of 203 gouty patients seen in the last 3 years we found a diastolic blood pressure higher than 95 mm. Hg. The hypertension was mild or moderate (less than 120 mm. Hg (diastolic) in 80 per cent. of our cases), and it is in this condition that diuretic treatment is specially indicated. The reports of Aronoff (1960) and Warshaw (1960) have shown, however, that prolonged administration of these drugs can induce acute attacks of gout or recurrences in known gouty patients. In 28 of our patients the articular symptoms were aggravated and in eight cases the gouty disease appeared for the first time; some of the latter group had a positive familial history of gout.

To control diuretic-induced hyperuricaemia salicylates (Scott, 1966), probenecid (Brest, Heider, Mehbood, and Onesti, 1966), sulphinyprazole (Sperber, Fisch, DeGraaff, and Freudenthal, 1965), or high doses of potassium and ammonium chloride (Zwaifler and Thompson, 1965) have been used.

This paper shows how diuretic-induced hyperuricaemia was prevented by the administration of allopurinol (HPP).

TABLE I
COMPARISON OF SERUM URIC ACID CHANGES WITH DIFFERENT THIAZIDE DERIVATIVES

Approved Name	Authors	Date	Daily Dose (mg.)	No. of Patients	Change in Serum Uric Acid (mg./100 ml.)
Chlorothiazide	Monroe, Grant, Sasahara, and Littmann	1959	500	9	+1.79 ±1.26
Hydrochlorothiazide	Healey, Magid, and Decker	1959	25	10 males	+1.33 ±0.76
Cyclothiazide	Swartz, Seller, Fuchs, Spitzer, Onesti, Brest, and Moyer	1963	8	19	+1.40 ±0.23
Polythiazide	Rapado, Jimenez Casado, and Rodicio	1963	1	3 males 16 females	+2.13 ±1.12 +1.66 ±1.13
Chlorthalidone	Bryant, Yü, Berger, Schwartz, Torosdag, Fletcher, Fertig, Schwartz, and Quan	1962	100	16 males 46 females	+1.78 ±1.51 +1.15 ±1.18
Clopamide	Rapado and others	1965b	20	11 males 16 females	+2.97 ±1.35 +1.68 ±0.95

* Mean ± standard deviation.

Material and Methods

In-patient Study (20)

Four normal individuals (1-4), six hypertensives with normal renal function (6-10), four hypertensives with chronic renal failure (11-14) (GFR less than 60 ml./min.), and six hypertensive gouty patients (two with normal renal function (15-16) and four with chronic renal failure (17-20)) were admitted to hospital. Urinary uric acid (UUA) and creatinine excretion were determined on a purine-free diet with periodic estimations of SUA, serum creatinine, and serum electrolytes. Blood pressure was measured twice daily.

In all patients SUA was first reduced to normal with allopurinol (300 to 600 mg./day, depending on the response) and after a week of stable results a known hyperuricaemic dose of either *Polythiazide* (1 mg./day) or *Clopamide* (40 mg./day) was given orally for one week.

Out-patient Study (18)

Eighteen patients regularly attending the out-patient clinic were instructed in the careful collection of 24-hr urine samples on a low-purine diet. In these patients SUA, serum creatinine and electrolytes, and UUA and creatinine excretion were determined biweekly. Five were hypertensive patients (21-25) (hyperuricaemic during the chronic administration of thiazides) and thirteen were hypertensive gouty patients (26-38) (all with normal GFR). In all of the gouty group except three the uricaemia had previously been reduced to normal with allopurinol; thiazides were later added for better control of blood pressure. In four cases (25, 29, 32, 35) guanethidine or reserpine was added at the same time.

The period of study ranged from 4 to 12 months (mean 6.2). Hepatic function and peripheral blood were studied at monthly intervals. The gouty patients were encouraged to drink a copious fluid intake and also received maintenance doses of colchicine.

Serum and urinary creatinine were determined by the

Folin-Wu method and SUA and UUA by the method of Caraway (1955); in some the differential spectrophotometric method with uricase was used (Praetorius, 1949).

Results

In-patient Study (Table II, overleaf)

Normal Controls (Cases 1-4).—Allopurinol, as in the other groups studied, reduced the SUA level and UUA elimination without any significant change in urate clearance (C_{urate}) or in the ratio of urate to creatinine clearance. When thiazide diuretics were given at the same time as allopurinol, the SUA rose and C_{urate} fell without any change in the 24-hour UUA output (Fig. 1, overleaf, p. 663).

Hypertensive Patients with Normal Kidney Function (Cases 5-10).—The effect of allopurinol alone was the same as in the healthy controls. The diuretic caused a rise in SUA and a sharp drop in C_{urate} and in the ratio of urate to creatinine clearance (Fig. 1).

Fig. 2 shows for comparison the results obtained in thirteen cases of essential hypertension treated with the same diuretic in a similar dose (Rapado, Jimenez Casado, and Diago, 1965b). Without the addition of allopurinol, the rise in SUA was distinctly and significantly larger while the other values were virtually unchanged.

Hypertensive Patients with Impaired Renal Function (Cases 11-14).—The administration of diuretics during allopurinol treatment did not alter either the SUA level or the UUA excretion. Thiazide, however, produced a fall in GFR and consequently reduced the ratio of C_{urate} to $C_{creatinine}$ (Fig. 1).

Gouty Hypertensive Patients with Normal Renal Function (Cases 15 and 16).—In these patients,

Fig. 2.—Changes (in percentage of control values) in SUA and different renal parameters after thiazide administration in thirteen hypertensives (abbreviations as in Fig. 1) (after Rapado and others, 1965b).

TABLE II
ALLOPURINOL ADMINISTRATION TO PREVENT THIAZIDE-INDUCED HYPERURICAEMIA

Patient No.	Diagnosis		Treatment (mg./day)	GFR (ml./min.)	SUA (mg./100 ml.)	Uric Acid		UA Clearance GFR × 100
						Clearance (ml./min.)	Excretion (mg./day)	
1	Normal		Control HPP (300) HPP + P(1)	104 107 116	5.2 3.7 5.8	9.0 8.9 4.9	670 442 378	8.5 8.2 4.3
2			Control HPP (300) HPP + P(1)	130 134 125	5.6 2.2 2.4	9.2 12.3 10.8	684 382 373	7.1 9.2 8.7
3			Control HPP (300) HPP + C (40)	130 134 105	5.6 2.2 3.1	9.2 12.3 10.6	684 382 365	7.1 9.2 10.1
4			Control HPP (400) HPP + C (40)	86 80 113	5.0 1.6 6.4	9.2 8.4 10.0	665 287 432	10.7 10.5 8.8
5	Arterial Hypertension with Normal Renal Function		Control HPP (400) HPP + C (40)	93 113 124	5.7 3.7 5.5	7.2 7.2 4.2	591 392 293	7.8 6.4 3.4
6			Control HPP (300) HPP + C (40)	98 109 57	4.6 2.9 6.5	8.8 9.4 3.1	587 393 296	9.0 8.6 5.5
7			Control HPP (300) HPP + P (1)	108 113 102	6.2 3.6 5.1	8.8 7.7 5.2	568 397 308	8.1 6.8 5.1
8			Control HPP (400) HPP + C (40)	158 160 155	5.8 3.7 4.8	8.7 8.6 7.6	732 460 415	5.5 5.4 4.9
9			Control HPP (300) HPP + P (1)	88 89 80	6.2 4.3 6.8	5.1 5.3 4.6	604 472 436	5.8 6.0 5.7
10			Control HPP (300) HPP + P (1)	87 84 79	5.9 2.7 3.7	9.4 11.9 6.5	800 480 344	10.8 14.2 8.2
11	Arterial Hypertension with Chronic Renal Failure		Control HPP (300) HPP + C (40)	47 54 40	4.2 3.5 4.5	6.8 5.5 4.1	417 279 267	14.5 10.2 10.3
12			Control HPP (400) HPP + C (40)	25 22 15	9.0 3.0 3.5	5.1 5.0 2.1	550 142 106	20.4 22.8 14.0
13			Control HPP (400) HPP + P (1)	62 68 52	8.8 4.3 3.8	4.2 4.1 3.9	510 253 230	6.8 6.1 7.5
14			Control HPP (400) HPP + C (40)	62 68 54	8.8 4.3 4.3	4.2 4.1 3.4	510 253 209	6.8 6.1 6.3
15	Arterial Hypertension with Gout	Normal Renal Function	Control HPP (600) HPP + C (40)	105 108 110	9.3 4.4 6.0	9.3 9.5 7.2	906 454 400	8.9 8.8 6.6
16			Control HPP (600) HPP + C (40)	115 116 110	7.9 3.6 4.0	7.1 6.5 5.2	706 350 350	6.2 5.6 4.7
17		Chronic Renal Failure	Control HPP (300) HPP + C (40)	26 20 6	9.8 5.9 6.7	1.8 1.6 0.9	262 134 92	6.9 8.0 15.0
18			Control HPP (300) HPP + P (1)	17 19 17	9.4 5.3 5.0	1.5 2.1 2.3	320 145 240	8.8 11.0 13.5
19			Control HPP (400) HPP + P (1)	42 45 42	10.0 4.5 5.1	2.4 3.3 3.1	294 215 173	5.7 7.3 7.4
20			Control HPP (600) HPP + C (40)	61 59 56	8.0 2.6 6.2	8.7 7.5 8.2	577 355 647	14.2 12.7 14.1

C = Clopamide. P = Polythiazide. HPP = Allopurinol.

ALLOPURINOL SYMPOSIUM, 1966

Fig. 1.—Prevention of thiazide-induced hyperuricaemia by allopurinol. GFR: Glomerular filtration rate (creatinine clearance); SUA: Serum uric acid; UA: Uric acid.

previously treated with allopurinol, thiazide administration neither increased SUA nor lowered C_{urate} significantly (Fig. 1).

Gouty Hypertensive Patients with Impaired Renal Function (Cases 17-20).—A decrease in GFR was observed without a hyperuricaemic response or variation in urate clearance. This caused a rise in ratio of urate to creatinine clearance (Fig. 1). An example of this group (Case 18) is shown in Fig. 3.

Fig. 3.—Case 18. After polythiazide administration the patient suffered an acute attack of gout in the big toe (AA) in spite of the normal SUA value (abbreviations as in Fig. 1).

Out-Patient Study (Table III, opposite)

Hypertensives with Thiazide-induced Hyperuricaemia (Cases 21-25).—In all the cases after allopurinol administration SUA returned to normal and the same occurred in UUA (Fig. 4).

Gouty Hypertensives (Cases 26-38).—In the group previously treated with thiazide, allopurinol administration caused a return of SUA to normal values and diminished 24-hour UUA excretion. In the group previously treated with allopurinol, diuretic administration produced no significant differences in either SUA or UUA (Fig. 4).

Fig. 4.—Changes in serum uric acid level and urinary uric acid elimination in patients treated with allopurinol and thiazide derivative for from 1 to 12 months. Each point represents the mean of at least six bi-weekly determinations per patient.

Other Effects

On Blood Pressure.—The hypotensive action observed with diuretic administration was not modified by allopurinol administration.

On Articular Symptoms.—In five of the nineteen gouty patients in whom the SUA had been previously restored to normal by allopurinol, thiazide precipitated an acute attack, mainly at the beginning of treatment (e.g. Fig. 3). These all showed a SUA level appreciably lower than before treatment. In one case diuretic administration had to be discontinued but in the others the acute attack was easily controlled by increasing the colchicine dosage. No acute articular symptoms were observed in the normal controls or in the hypertensive group.

Other Side-effects.—During this study no significant side-effects were seen; there were no alterations in the blood picture or hepatic function during allopurinol administration.

Discussion

In allopurinol-treated patients there was a decrease in SUA and UUA without significant changes in C_{urate} , GFR, and the ratio of urate to creatinine clearance. These changes were consistent

TABLE III
LONG-TERM STUDIES OF PREVENTION OF THIAZIDE-INDUCED HYPERURICAEMIA BY ALLOPURINOL IN EIGHTEEN HYPERTENSIVE PATIENTS

Patient No.	Additional Diagnosis	Treatment (mg./day)	Duration (mths)	Serum Uric Acid (mg./100 ml.)	Uric Acid Elimination (mg./day)
21		P (1)	3	7.4	535
		P + HPP (300)	5	4.5	306
22		C (40)	2	6.7	432
		C + HPP (300)	4	5.6	356
23		C (20)	1	6.3	532
		C + HPP (400)	3	4.3	350
24		P (1)	1	6.2	615
		P + HPP (300)	6	2.3	174
25		C (40)	2	6.0	697
		C + HPP (300)	7	4.3	415
26	+ Gout	Control	3	8.3	630
		HPP (300)		4.0	359
		HPP + C (20)	7	4.0	244
27	+ Gout	Control	1	8.9	523
		HPP (400)		6.1	313
		HPP + C (20)	6	7.0	290
28	+ Gout	Control	4	11.3	915
		HPP (400)		6.9	384
		HPP + P (1)	4	6.2	410
29	+ Gout + Urate lithiasis	Control	2	9.3	1175
		HPP (600)		5.7	490
		HPP + C (20)	6	4.3	160
30	+ Gout	Control	2	9.7	920
		HPP (400)		5.1	312
		HPP + C (40)	10	4.7	120
31	+ Gout	Control	1	9.2	716
		HPP (400)		6.0	370
		HPP + C (40)	4	6.1	325
32	+ Gout	Control	1	9.1	765
		HPP (400)		5.7	420
		HPP + C (20)	8	5.2	340
33	+ Gout	Control	3	7.5	562
		HPP (300)		4.3	190
		HPP + C (40)	6	3.5	140
34	+ Gout	Control	3	12.7	780
		HPP (400)		5.4	400
		HPP + P (1)	4	5.2	420
35	+ Gout	Control	2	11.6	535
		HPP (400)		5.3	245
		HPP + C (40)	5	5.1	228
36	+ Gout	Control	2	7.3	655
		C (40)		8.9	384
		C + HPP (400)	6	5.3	242
37	+ Gout + Recurrent urate lithiasis	Control	2	7.1	1145
		P (1)		7.5	520
		P + HPP (400)	12	4.3	297
38	+ Gout	Control	1	7.5	600
		P (1)		9.2	335
		P + HPP (400)	8	6.1	180

C = Clopamide. P = Polythiazide. HPP = Allopurinol.
Uric acid values are averages of bi-weekly determinations throughout the study.

and independent of renal function or of underlying disease, but were related to dosage and to pre-treatment values of SUA.

Thiazide diuretics raise the SUA level in normal individuals, in hypertensive patients, and in gouty

hypertensive patients with normal renal function, decreased C_{urate} , and slightly lowered UUA excretion. When renal function is considerably impaired, as observed by Dreyfus, Duarte, Kodama, and Moyer (1960), no significant changes occur,

either in SUA or in the tubular handling of uric acid, while GFR decreases.

When a patient has been previously treated with allopurinol, thiazide therapy causes significantly less hyperuricaemia both in controls and in hypertensives. In gouty patients no significant increase in SUA is observed.

The reason for these differences is still obscure, partly because of the small number of patients studied. It may be that renal response to oral diuretics is qualitatively different in gouty patients, or it may be that the higher doses of allopurinol used in this group prevent a significant rise in SUA compared with the other groups.

In relation to acute gouty attacks, allopurinol administration before diuretic therapy may prevent acute joint inflammation in most cases; the precipitation of acute attacks by thiazide in the presence of a normal or low SUA poses the question of the mechanism by which these drugs may precipitate such attacks.

Summary

Allopurinol will prevent a rise in the serum uric acid level in thiazide-treated patients and will restore to normal any rise in serum uric acid produced by them. This finding, along with the decrease in urinary uric acid elimination, suggests that the use of allopurinol is indicated in patients for whom thiazide treatment is essential, but who suffer from gout or renal urate lithiasis or who are predisposed by heredity to the development of gouty arthritis.

However, the liability to acute attacks of gout in spite of this treatment and in the presence of normal serum uric acid levels, suggests the additional need of specific therapy directed against the development of acute gout.

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