

EFFECT OF COMBINED THERAPY IN PATIENTS WITH UROLITHIASIS OF LOWER URINARY PH

Wei Xi-YUAN

Chienese research fellow of Department of Urology, Hyogo College of Medicine

(Director: Prof. F. Ikoma)

The effect of combining therapy with hydrochlorothiazide, allopurinol and systemic alkalization for urolithiasis with lower urinary pH was examined. A total of 90 patients were followed up for 1 to 3 years, the average follow up period being 18 months. The total stone disappearance rate was 60% (kidney stone), 74% (ureter stone) and 20% (bladder stone). Large amounts of thiazide diuretics, potassium and magnesium were intravenously administered to a patient with systemic alkalization at slow infusion speed, neither serious side effects nor complication occurred. This method is simple and an effective remedy. It is also very practical in the developing countries of the third world.

Key words: Urolithiasis, Lower urinary pH, Allopurinol, Thiazide, Systemic alkalization

INTRODUCTION

The morbidity of urolithiasis is continuously increasing in China. The most common type of calculi are uric acid stones, urate stones, calcium oxalate stones and mixed calculi. In some sea-side areas the proportion is as high as to 40% or more^{7,16)}. Many patients with calcium oxalate stone have been associated with hyperuricaciduria. The urinary pH of patients with hyperuric-aciduria were acidic. Low pH urine promotes formation of urinary calculi. Ninety patients with urolithiasis whose urine specimens showed a pH lower than 5.5 were treated with administration of large amounts of hydrochlorothiazide, allopurinol and systemic alkalization between January, 1983 and December, 1985. The results obtained suggest that this complex treatment could not only prevent stone formation but also dissolve and discharge urinary calculi.

MATERIALS AND METHODS

The patients (male 82, female 8) were between 22 and 79 years old. Their chief complaints were typical renal colic. Urinalysis showed a pH lower than 5.5 and either macro- or microscopic hematuria

was observed on their first visit. Blood chemistry revealed a normal range of serum calcium and phosphorus but serum level of uric acid elevated in 63 cases (70%) ranging from 7.5 to 14.5 mg/dl.

The diagnosis of urolithiasis was established by the detection of a positive or negative filling defect on radiograph, including plain film, excretory urography (IVP) or retrograde pyelography. Also computerized tomography (CT scans) and ultrasonography often were used to confirm the presence of the calculi. With the latter techniques urinary calculi and or hydronephrosis (due to ureteric obstruction) were differentiated from other diseases (Fig. 1).

Therapeutic regimens:

1. Hydrochlorothiazide 50 mg
Allopurinol 100 mg
Potassium chloride 1,000 mg
Sodium bicarbonate 1,000 mg
aa p.o. t.i.d. continued 3 to 12 months or more
2. Inj. Sodium lactate M/6—500 ml
Inj. Magnesium sulfate 10%—10 ml
aa mixt i.v.gtt. q.d. continued 7 to 10 days, rest 3 days re-injection
3. At the same time encourage patients a large fluid intake^{2,11)} to increase

Methods of diagnosis	Position of stones		
	Kidney	Ureter	Bladder
Radiograph			
Plain film	10/20	38/65	4/5
IVP			
Hydronephrosis	1/10	35/40	—
Negative filling defect	8/10	15/40	—
Retrograde pyelography			
Ureter obstruction	—	4/5	—
C.T. Scans	10/10	6/8	—
Ultrasonography			
Hydronephrosis	1/20	50/65	—
Stone shadow	18/20	45/65	—
Cystoscopy	—	—	5/5
Retrograde intubation	—	4/5	—
total	20	65	5

Fig. 1. Diagnosis of urinary calculi

Response of treatment	Position of stones		
	Kidney	Ureter	Bladder
Radiograph			
Plain film stone shadow			
Dissolution	2/10	28/38	0
Decrease	4/10	8/38	1/4
No response	4/10	2/38	0
Increase	0	0	0
I.V.P.			
Hydronephrosis			
Disappearance	1/1	33/35	—
Aggravation	0	0	—
C.T. Scans			
Decrease	6/10	1/8	—
No response	4/10	1/8	—
Increase	0	0	—
Ultrasonography			
Hydronephrosis			
Disappearance	1/1	45/50	—
Aggravation	0	0	—
Stone shadow			
Dissolution	10/18	40/45	1/5
Decrease	4/18	—	1/5
No response	4/18	5/45	3/5
Increase	0	—	0
Stone discharge	8/20 (40%)	35/65 (54%)	1/5 (20%)
Total stone disappearance	12/20 (60%)	48/65 (74%)	1/5 (20%)

Fig. 2. Result of treatment

urinary volume to at least 2,000 ml every day.

RESULTS:

The patients have been followed for 12 to 36 months (mean 18 months) (Fig. 2).

DISCUSSION

Thiazide diuretics could lower urinary

calcium excretion. During the last decade thiazides have been extensively used in the prevention of recurrent urolithiasis formation^{1,3}). Thiazides are particularly indicated in the presence of all types of hypercalciuria^{5,15,18}). Thiazide therapy has also been claimed to be equally effective in patients with normocalciuria¹⁷). Long-

term thiazide treatment might result in potassium and magnesium deficiency. Combined treatment with thiazide and magnesium appears to decrease urinary calcium and increase urinary magnesium resulting in a reduced Ca/Mg quotient and apparently a lower risk of forming urine supersaturated with calcium¹³. Both potassium and magnesium were, therefore, administered at the same time in our routine therapeutic regimens.

Three different processes: nucleation, crystal growth and aggregation are considered to be important in the formation of urinary stone. The nucleus of mixed urinary stones containing calcium frequently was urate and or uric acid or both¹³. Allopurinol, a xanthine oxidase inhibitor, reduces the serum uric acid level and reduces the urinary excretion of uric acid and urate, which decrease nucleation of urinary stones^{6,9}.

The administration of allopurinol has also been shown to inhibit the growth and aggregation of crystals of calcium oxalate and calcium phosphates in urine^{14,15,17}. This may be accomplished by a reduced excretion of urate secondarily followed by increased concentrations of inhibitors of growth and aggregation. The increased crystal growth inhibition during administration of allopurinol might be of fundamental importance since it suggests that allopurinol might be of value as a prophylactic method in patient with different types of abnormalities in their urine composition^{9,12,14}.

Since the type of uric acid stone formation is often associated with a persistently acidic urine⁴, the use of alkalinizing agents is an important aspect of therapy. Stone formation occurs because uric acid is in associated form in the presence of acidic urine and supersaturation and subsequent crystallization are likely. When urinary pH approaches 7.0 or more then half of the uric acid is in the dissociated form and not only is crystallization unlikely but dissolution often occurs^{2,10}. When a patient is administered oral sodium bicarbonate or sodium potassium citrate, urinary alkalization with this agent is inter-

mittent⁸. On the other hand, intravenous infusion with one-sixth molar sodium lactate resulted in sustained urinary alkalization, which may be effective in stone dissolution.

An infusion rate of 40~50 ml per hour seemed to be safe and often was sufficient to maintain adequate urinary alkalization. Urinary pH was monitored and usually was maintained at 7.0 to 7.5 within 4~6 hours. This could alkalinize the urine rapidly to effect dissolution of obstructing ureteral stones and uric acid stones within renal pelvis^{8,10}. Sodium lactate is a racemic salt in which the levo form is oxidized to bicarbonate and the dextro form is converted to glycogen. One-sixth molar sodium lactate solution is isotonic and when metabolized in the normal manner it has the potential for acid neutralization equivalent to 340 ml of a 5% sodium bicarbonate solution and an anti-ketogenic effect equivalent to 500 ml of a 6% dextrose solution. Sodium lactate is completely converted to bicarbonate in only 1 to 2 hours⁸. As with other alkalization regimens excess sodium loading is possible with this combined therapy. Serum electrolytes, blood pressure and cardiac status must be monitored carefully. Although our method is somewhat complex, neither serious side effects nor complications occurred in our series because the infusion speed was kept low.

The author thanks Dr. Hiroki Shima for editorial assistance in preparing this manuscript.

REFERENCES

- 1) Ahlstrand C and Tiselius HG: Biochemical effects in patients with calcium oxalate stone disease during combined treatment with bendroflumethiazide and magnesium oxide. *Br J Urol* 56: 125~130, 1984
- 2) Atsman A, DeVries A, Lazebnik J and Salinger H: Dissolution of renal uric acid stones by oral alkalization and large fluid intake in a patient suffering from gout. *Am J Med* 27: 167~169, 1959
- 3) Backman U, Danielson BG, Johansson G, Ljunghall S and Wikström B: Effect of therapy with bendroflumethiazide in patients with recurrent renal calcium stone. *Br J Urol* 51: 175~180, 1979

- 4) Barzel US, Sperling O, Frank M and De Vries A: Renal ammonium excretion and urinary PH in idiopathic uric acid lithiasis. *J Urol* 92: 1~4, 1964
- 5) Eiomaa I, Ala-Opas M and Porkka L: Five years of experience with selective therapy in recurrent calcium nephrolithiasis. *J Urol* 132: 656~661, 1984
- 6) Hedelin H, Eddeland A, Larsson L, Pettersson S and Öhman S: The composition of catheter encrustations including the effects of allopurinol treatment. *Br J Urol* 56: 250~254, 1984
- 7) Huang JG: Uric acid urolithiasis in China. *Chinese J of Physicians Advanced Study* 7: 12~14, 1984
- 8) Kursh ED and Resnick MI: Dissolution of uric acid calculi with systemic alkalization. *J Urol* 132: 286~287, 1984
- 9) Leading articles: Allopurinol treatment for calcium stone disease *Br Med J* 2: 1302~1303, 1977
- 10) Lewis RW, Roth JK, Polanco EJ and Roberts JA: Molar lactate in the management of uric acid renal obstruction. *J Urol* 125: 87~90, 1981
- 11) Pak cyc, Sakhaee K, Crowther C and Brinkley L: Evidence justifying a high fluid intake in treatment of nephrolithiasis. *Ann Intern Med* 93: 36~40, 1980
- 12) Robertson WG, Knowles F and Peacock M: Inhibitors of the crystal growth and aggregation of calcium oxalate crystals in vivo. *Clinical Chemical Acta* 43: 31~37, 1973
- 13) Shen SJ: Plain KUB films in urolithiasis. *Chinese J Urol* 5: 353~355, 1984
- 14) Tiselius HG: Inhibition of calcium oxalate crystal growth in urine during treatment with allopurinol. *Br J Urol* 52: 189~192, 1980
- 15) Woelfel A: Effect of hydrochlorothiazide therapy on the crystallization of calcium oxalate in urine. *Metabolism* 26: 201~205, 1977
- 16) Wu JP: Urolithiasis in China. *Chinese J Urol* 1: 1~5, 1980
- 17) Yendt ER and Cohonim M: Prevention of calcium stone with thiazides. *Kidney International* 13: 397~409, 1978
- 18) Yendt ER and Cohonim M: Experience with thiazide diuretics in calcium oxalate urolithiasis. *World J Urol* 1: 176~179, 1983

(Accepted for publication November 18, 1986)

和文抄録

酸性尿を示す尿路結石患者に対する多剤併用療法について

兵庫医科大学泌尿器科学教室（主任：生駒文彦教授）

魏 熹 元*

酸性尿を示す尿路結石患者を対象として、フロプリノール、サイアザイド、全身アルカリ化による多剤併用療法の効果について検討した。対象症例は90例、経過観察期間は1年から3年、平均18カ月であった。結

石消失率は腎結石、尿管結石、膀胱結石でそれぞれ60%、74%、20%であった。全身アルカリ化と点滴静注による大量のサイアザイド利尿剤、カリウム、マグネシウム投与による重篤な副作用や合併症は認められなかった。この方法は簡単でかつ効果的であり、発展途上国においても施行可能な治療であると思われる。

* 特別研究員