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

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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 40% or more7,10). 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 show a pH lower than 5.5 were treated with administration of large amounts of hydrochlorothiazid 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 pH than 5.5 and either macro-or microscopic hematuria was observed on their first visit. Blood chemistory 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
   a.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
   a.a 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
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\(^1,2\). Thiazides are particularly indicated in the presence of all types of hypercalciuria\(^3,15,18\). Thiazide therapy has also been claimed to be equally effective in patients with normocalciuria\(^17\). 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 calcium. 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 both. 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.

The administration of allopurinol has also been shown to inhibit the growth and aggregation of crystals of calcium oxalate and calcium phosphates in urine. 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 suggest that allopurinol might is of value as a prophylactic method in patient with different types of abnormalities in their urine composition.

Since the type of uric acid stone formation is often associated with a persistently acidic urine, the use of alkalizing 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. When a patient is administered oral sodium bicarbonate or sodium potassium citrate, urinary alkalization with this agent is intermittent. 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 and monitored and usually was maintained at 7.0 to 7.5 within 4~6 hours. This could alkalify the urine rapidly to effect dissolution of obstructing ureteral stones and uric acid stones within renal pelvis. Sodium lactate is a racemic salt in which the levo form is oxidized to bicarbonate and the dextre form is converted to glycogen. One-sixth molar sodium lactate solution is isotonous 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 hours. 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.

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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

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酸性尿を示す尿路結石患者を対象として、プロブリノール、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ヶ月であった。結

* 特別研究員

石消失率は腎結石、尿管結石、膀胱結石でそれぞれ40%、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悪性な副作用や合併症は認められなかった。この方法は簡便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。