The Turkish Journal of Pediatrics
Volume 26, Nos 1-4, 1984

THE MEDICAL PROPHYLAXIS OF RENAL CALCULI*

*John P. Blandy MCh, FRCS***

Key words: medical prophylaxis, renal calculi, renal tubular acidosis

After he has suffered the agony of renal colic, or an operation for a stone, the patient asks his surgeon — what can I do to prevent having another stone? The surgeon feels obliged to say something. Just to tell the patient to drink plenty of water seems such a weak and ineffectual thing to say. But my purpose today is to remind you, as doctors, that if you do not know what to reply to your patient's question, you should try very hard not to talk nonsense. If in doubt, only advise those things which do no harm, and do not make life miserable. Do not be ashamed to tell him to drink plenty of water.

Stones as Crystals

Stones are crystalline, and much of our confusion has arisen from a preoccupation with the physical laws of the solution of crystals in water.

Common salt is an example. If you continue to add salt to water then sooner or later no more can be dissolved. We know that sodium and chloride ions can move freely about in the water, and that when no more can be taken up into the solution we have what is called an oversaturated solution, that is the product of the concentration of each ion exceeds the solubility product or saturation concentration for that particular substance. When there is less than this concentration, the solution is said to be undersaturated.

In the laboratory, if we continue to add salt we reach a stage where the solubility product is so greatly in excess that there will be spontaneous nucleation and crystals will be precipitated. In human stone disease it is difficult to detect this stage, but we probably encounter it in conditions such as cystinuria where there is a huge excess of these substances in the urine.

In truth, things are not so tidy. For most salts in solution there is an intermediate stage where, although the saturation concentration is exceeded, crystals will only

* From the Department of Urology, London Hospital Medical School, University of London, United Kingdom.
** Professor of Urology, London Hospital Medical School, University of London.

begin to form if a nucleus is added on which they can start to build — you remember how at school we dissolved copper sulphate in water, and put a wisp of cotton into the solution and watched the crystals grow. This is the metastable state.

It is important to recognise that the metastable state is normal for most people for most of the day, for when we are passing — say — 1 to 1.5 litres of urine per 24 hours, the calcium salts in urine exceed the solubility product, and are well into the metastable range. It only needs a tiny foreign body, such as a bacterium, for calcium salts to be deposited in the urinary tract.

The reason why calcium salts do not form in all of us all the time, is the real question we should set out to answer. Much has been made of protective substances in the urine. Trace elements such as magnesium help keep tiny crystals in suspension — and many doctors give their patients magnesium oxide in the hope that this will prevent stone recurrence[1]. Other substances are thought to form a protective film of colloid around the tiny crystals and stop them sticking together[2]. Some of these can be measured in the urine as glycosaminoglycans, and 30 years ago there was a fashion for giving patients hyaluronidase — a precursor of these protective colloids — in the hope of preventing stone formation[1]. In life, this metastable state is not fixed, it is altered by a number of biological circumstances: perhaps the most important of these are stagnation and changes in pH.

Stagnation

Is the solution stagnant or agitated? If one constantly stirs the glass of salt solution, crystals may form, but have no chance to aggregate into lumps so large that they will cause trouble in the urinary tract. This concept is of crucial importance in the understanding and the management of human stone disease. It means that — whatever the biochemical content of the urine — if there is a rapid flow of urine through the system — stones have no chance to form. For this reason one of the most important investigations of a patient with a stone is an intravenous urogram to rule out all causes of stagnation of urine — obstruction, hydronephrosis, and diverticula — as well as any foreign body or necrotic tissue in the urinary tract.

Equally important is it to make sure that there is a good flow of urine through the system. If you measure the 24 hour urines of your patients with stone disease, as you will when you are checking their 24-hour output of calcium, you will be struck by one constant finding — these patients put out a very small volume of water every day. They swear to you that they drink liters and liters of water — but their 24 hour urine volume seldom exceeds 1 liter per day. With such a sluggish flow of urine even a normal urinary tract must be regarded as stagnant.

Urine pH

The metastable state is also dependent on the pH of the urine. This is especially important in uric acid stone disease, cystine stone disease and tubular acidosis, where it works in different ways.

Uric acid stone disease. In uric acid stone disease, if we keep the pH of the urine greater than pH 6.5 we can almost guarantee that the patient will never have another stone. Unlike his mammalian cousins, Man is born without the enzyme uricase in the liver. In most mammals, uricase converts the uric acid waste products of our protein metabolism into allantoin, which is very soluble in urine. In man, we have to get rid of uric acid itself. If the urine is kept alkaline, then the uric acid is largely converted to sodium urate which is 20 times more soluble than uric acid, and this is what happens in most of us: thanks to the variations in our urinary pH throughout the normal day, we get rid of our uric acid load without trouble, so long as we form enough urine.

But patients with uric acid stones usually form an acid urine with a fixed pH 5, at which all the uric acid remains in the insoluble form. There are some uric acid stone-formers whose occupations make them lose an unusual amount of sweat, and so they become dehydrated: some others who lose abnormally large quantities of alkaline small bowel fluid as a result of diarrhoea or an ileostomy. The remedy in all these cases is obvious: make them take more water by mouth and add enough sodium bicarbonate to keep the urine on the safe side of pH 6.5.

Cystinuria. In cystinuria there is a different enzymatic defect. These patients cannot reabsorb cystine from the renal tubule, and lose about 600 mgm of cystine a day in their urine. The solubility of cystine depends on the pH of the urine. At a pH of 7.0 the urine can only dissolve 400 mgm/liter: at a pH of 7.8 it can accept twice this quantity. Hence in treating cystinuria we should increase the total urine volume, and keep the pH as high as possible to prevent them from having another stone. In practice patients dislike this regime. One may be tempted to give D-penicillamine — but it is not without its toxic complications — and if a patient will only obey the simple instructions to drink sufficient, and keep his urine pH above 7.2 — he will usually escape any trouble.

Distal Renal Tubular Acidosis. Urinary pH affects stone formation in yet another way. In distal renal tubular acidosis there are 3 phases to the metabolic disorder. First, the distal tubule cannot get rid of hydrogen ions properly. Given an acid load, instead of secreting hydrogen ions, the tubule releases potassium, calcium and sodium, and the urine remains alkaline and rich in calcium.

In the second phase, loss of sodium in the urine lowers the plasma sodium concentration: this is interpreted by the anterior pituitary as if the body is getting dehydrated, so it stops secreting anti-diuretic hormone, and there is a diuresis.

In the third phase, as a result of the diuresis the patient does indeed lose too much water and there is a shrinkage of the extracellular volume, to which the adrenals react by releasing aldosterone, to force the kidneys to retain sodium and chloride. The result in the plasma is to increase the chloride, and decrease the potassium and

pCO_2, while calcium and phosphate are unchanged. The urine shows hypercalciuria, and remains alkaline even when the patient is given an acid load.

It will at once strike you that this syndrome is just what we see when there is serious renal tubular damage from other causes, e.g. obstruction and infective scarring. Since many stone patients have structural damages to their tubules it is in practice very difficult to be sure when renal tubular acidosis is the cause or the effect of stone disease. It is important to recognise the pure form of renal tubular acidosis because it is easy to correct it by giving the patient potassium and sodium citrate.

pH and infective struvite stones. The pH of urine is of even more importance in the formation of the common mixed infective struvite stone. Here, infection with a urea splitting organism such as Proteus mirabilis, causes ammonia to be formed from urea, which makes the urine more alkaline, so that ordinary normal calcium, magnesium, ammonium and phosphate ions exceed their solubility product and precipitate as the typical soft crumbly stone. It is important in managing this condition to remember that this material is deposited around and between the bacteria — so that inside every struvite calculus there reside millions of living Proteus organisms. In practice also, one needs to be aware of a diagnostic trap. The Proteus mirabilis organisms are not always detected in the urine. You may only find them in the stone when it is ground up and cultured after being removed at operation. There is no hope of preventing stone formation unless Proteus is eliminated, and on the other hand it is impossible to kill the Proteus unless all the stones are removed. One interesting new suggestion for dealing with these stones is to give the patient a substance that will stop the Proteus from turning urea into ammonia. Of these acetohydroxamic acid was the prototype[3], though it is too toxic for common use, and has been superceded by propionhydroxamic acid[4]. We are at present involved in a controlled trial of this drug in the Institute of Urology in London; it is still too early to report on our results, but so far I am unconvinced that it has done any good at all. Far more important, in my view, is to make sure that all the hiding places for the germs have been removed — i.e. all the stones are removed at the time of surgery — and to follow the patients with the utmost diligence with antimicrobial therapy.

Hypercalciuria

Although hypercalciuria is of unquestionable importance as a cause of stone disease it is important to get it in perspective.

Hyperparathyroidism

First, we must all take care not to miss hyperparathyroidism and every patient with a calcium-containing stone needs to be investigated with a view to ruling out this rare condition. How is it to be done in practice in a busy urological department? We can

forget the difficult metabolic tests which so preoccupied our predecessors 20 years ago. Only 2 measurements are of value: the measurement of serum calcium and of parathyroid hormone. The serum calcium measurement must be repeated more than once and the measurement must be made by a laboratory which uses a reliable method, monitors its normal range regularly, and can give repeatable results on a single specimen. Errors in the diagnosis of hyperparathyroidism are nearly always due to laboratory error. Equally, in the second test — the measurement of the plasma parathyroid hormone — the radioimmunoassay must be trustworthy and give repeatable results.

At the London Hospital although we have had an interest in parathyroid disease for more than 60 years, today it is rare to discover a parathyroid tumor when investigating a patient with a stone.

Let me warn you of one source of difficulty. Now that it is possible to measure parathyroid hormone levels, we may find them elevated in patients with normal plasma calcium estimations. Siminovitch et al[5] have shown that removing the parathyroid in such patients does not prevent further stone formation. The moral is clear: unless the calcium is elevated as well, there is no use removing the parathyroids. Indeed, now that we have available a specific inhibitor of bone resorption of calcium — in the form of clodronate disodium, we can afford to be even more cautious in offering parathyroidectomy to patients with stone disease[6].

Idiopathic hypercalciuria

Let us now consider the matter of so-called Idiopathic Hypercalciuria. Most stone patients have no abnormality in the anatomy of their urinary tract: they have no stagnant collections of urine, no foreign body, and no infection. They excrete no excess of uric acid or of cystine: their plasma calcium and parathyroid levels are normal as are their plasma electrolytes, and they can vary the pH of their urine according to their intake of acid and alkali. We were at a loss to advise such patients on how to prevent formation of another stone. Then came the concept of idiopathic hypercalciuria: i.e. the patient was passing more than a normal amount of calcium in his or her urine.

A new industry was born — the diagnosis and management of idiopathic hypercalciuria. Every month a new regime was introduced and claimed to do good, because a patient who gave a history of many stones in the previous few years would, after starting the wonder-treatment, form fewer stones.

Hypercalciuria has to be defined by what is regarded as the normal value for calcium in the urine. But over the last 30 years, what is accepted as the normal level of calcium in the urine has steadily increased: perhaps from an overall improvement in our diet. When we looked at this problem in our stone clinic at the London Hospital

10 years ago, we followed up some 400 patients with stone disease over a period of 5 years. There was no difference in the incidence of new stones in those who had a raised urine calcium and those who did not[7]. Moreoever, as you continue to follow patients who have once had a stone, the chance of their getting another stone steadily decreases as the years go by. This means, in effect, that any claims for success with any treatment regime must be prospectively compared with a control group, for in all groups there will be a tendency to show an improvement. More recently, Marshall's group have found no difference in the daily excretion of calcium, oxalate, glycosaminoglycans and uric acid, nor the 24 hour urinary pH and volume in normal controls and stone-formers attending a large stone clinic[8].

If this is so, then we can forget most of the folklore on the topic of idiopathic hypercalciuria. This is unpopular: I feel like the little boy who pointed out that the Emperor had no clothes on — nevertheless in my opinion it is high time we stopped looking in vain at the physical chemistry of urine in the search for a cure for calculous disease. This means that most of the dietary regimes now in fashion for the prevention of stone recurrence can be disregarded: if it makes no difference whether the urine is hypercalciuric or not, why prescribe diets that restrict calcium, or precipitate it with cellulose phosphate[9] or bran[10]. Why reduce the oxalate concentration[11] or forbid protein[12] or deny the patient sugar[13]?

If we believe these clever stone-doctors, our patients must avoid milk, cheese and cream because they contain calcium: they are not allowed protein, or refined sugar. They cannot have fresh tea, green vegetables, strawberries or chocolate because they contain oxalate. Let them eat bran and drink water. It may seem to them that they have a pretty miserable choice — to avoid getting another stone they must die of starvation.

Conclusion

We know one thing for certain about stone disease. If the patients drink enough fluid, they will dilute their urine, and lessen the chance of crystals forming. If they make enough urine, the urinary tract will be scoured out from top to bottom. In my opinion the single and most important piece of useful advice one can give a patient who has once passed a stone is to measure his urinary output and make sure it exceeds 3 litres per day. And then — I suggest — he can eat and drink whatever he likes.

REFERENCES

1. Butt AJ. Etiologic factors in Renal Lithiasis. Springfield, Thomas, 1956.
2. Gardner GL, Doremus RH. Crystal growth inhibitors in human urine. Effect on calcium oxalate kindetics. *Invest Urol* **15**:478, 1978.
3. Feldman S, Putcha L, Griffith DP. Pharmacokinetics of acetohydroxamic acid. Preliminary investigations. *Invest Urol* **15**:498, 1978.

4. Martelli A, Buli P, Brunocilla E. Propionohydroxamic acid in infected renal stones. A preliminary clinical report. *J Urol* **128**:1130, 1982.

5. Siminovitch JM, James RE, Esselstyn CB, et al. The effect of parathyroidectomy in patients with normocalcemic calcium stones. *J Urol* **123**:335, 1980.

6. Douglas DL, Kanis JA, Paterson AD, et al. Drug treatment of primary hyperparathyroidism: use of clodronate disodium. *Br Med J (Clin Res)* **286**:587, 1983.

7. Marshall V, White RH, De Saintonge MC, et al. The natural history of renal and ureteric calculi. *Br J Urol* **47**:117, 1975.

8. Ryall RL, Darroch JN, Marshall VR. The evaluation of risk factors in male stone-formers attending a general hospital outpatient clinic. *Br J Urol* **56**:116, 1984.

9. Backman U, Danielson BG, Johansson G, et al. Treatment of recurrent calcium stone formation with cellulose phosphate. *J Urol* **123**:9, 1980.

10. Shah PJR, Green NA, Williams G. Unprocessed bran and its effect on urinary calcium excretion in idiopathic hypercalciuria. *Br Med J* **281**:246, 1980.

11. Drach GW. Urinary Lithiasis. In Harrison JH, Gittes RF, Perlmutter AD, et al (eds). *Campbell's Urology* (4th ed). Vol. 1, 1978, pp 779-880.

12. Robertson WG, Peacock M, Heyburn PJ, et al. Should recurrent calcium oxalate stone formers become vegetarians? *Br J Urol* **51**:427, 1979.

13. Rao PN, Gordon C, Davies D, Blacklock NJ. Are stone formers maladapted to refined carbohydrates? *Br J Urol* **54**:575, 1982.