Clinical Case Discussion

Recurrent vesical calculi, hypercalciuria, and biochemical evidence of increased bone resorption in an adult male with paraplegia due to spinal cord injury: is there a role for intermittent oral disodium etidronate therapy for prevention of calcium phosphate bladder stones?

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Study design: Clinical case report with comments by colleagues from Sweden, Poland, Spain, Brazil, Japan, Belgium and Switzerland.

Objectives: To discuss the role of disodium etidronate therapy for prevention of calcium phosphate vesical calculi in persons with spinal cord injury, who have hypercalciuria and biochemical evidence of increased bone resorption.

Setting: Regional Spinal Injuries Centre, Southport, UK.

Methods: A 21-year-old male sustained paraplegia (T-10; ASIA scale: A) in a road traffic accident in June 2001. He had an indwelling urethral catheter until the end of August 2001, when he started self-catheterisation. He developed bladder stones and electrohydraulic lithotripsy (EHL) was performed in May 2002. All stone fragments were removed. Recurrence of vesical calculi was noted in October 2002. These stones were fragmented by lithoclast lithotripsy in two sessions, in December 2002 and February 2003; all stone fragments were removed at the end of the second session. This patient reverted to indwelling catheter drainage when vesical calculi recurred. In September 2003, X-ray of the abdomen showed recurrence of vesical calculi. By February 2004, the stones had increased in size and number. EHL of vesical calculi was again performed in April 2004. Complete clearance was achieved.

Results: A 24-h urinalysis detected hypercalciuria – 18.7 mmol/day (reference range: 2.5–7.5). Biochemical analysis of vesical calculus revealed calcium phosphate (85%) and magnesium ammonium phosphate (15%). Plasma C-terminal telopeptide (CTX) was increased – 1.06 ng/ml (reference range: 0.1–0.5 ng/ml). Free deoxypyridinoline/creatinine ratio (fDPD/Cr) in urine was also increased – 20.2 (reference range: 2.3–5.4). In April 2004, this patient was prescribed disodium etidronate 400 mg day. Nearly 3 months after commencing therapy with etidronate, plasma CTX decreased to 0.87 ng/ml. fDPD/Cr in urine also decreased to 12.4. After 4 months of etidronate therapy, 24-h urinary calcium excretion had decreased to 6.1 mmol/day.

Conclusion: Etidronate (400 mg daily) is a very effective inhibitor of calcium phosphate crystallisation. Etidronate decreased urinary excretion of calcium, an important factor in prevention of calcium phosphate bladder stones. Etidronate therapy is not a substitute for other well-established methods for prevention of vesical calculi in spinal cord injury patients, for example, large fluid intake, avoiding long-term catheter drainage. Intermittent therapy with

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etidronate may be considered in selected patients, in whom hypercalciuria persists after instituting nonpharmacological therapy for an adequate period, for example, early mobilisation, weight-bearing exercises, and functional electrical stimulation. However, possible side effects of etidronate, and the fact that etidronate is not licensed in United Kingdom for prevention of urolithiasis, should be borne in mind.

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Keywords: hypercalciuria; urinary bladder; calculi; etidronate

Introduction

Common predisposing factors for the occurrence of bladder stones in persons with spinal cord injury are: stasis of urine in the bladder, urinary infection, and long-term indwelling catheter drainage.¹ It is generally believed that metabolic abnormalities do not play a pivotal role in the causation of bladder stones in persons with spinal cord injury. Lamid *et al*² found no significant difference in the incidence of bladder stone formation in patients with hypercalciuria compared with those with normal urinary calcium excretion.

In regions endemic for urolithiasis, metabolic abnormalities have been described in patients with vesical calculi. Singh *et al*³ studied 59 stone formers with bladder stones in northwest India, where urolithiasis is endemic. A 24-h urinary excretion of calcium, oxalic acid, inorganic phosphorus, magnesium, and citric acid revealed presence of hypercalciuria and hyperoxaluria in 18.6 and 44.1%, respectively, while 11.9% of patients had both abnormalities. Hypomagnesuria and hypocitraturia were present in 67.8 and 69.5%, respectively, while 45.7% had both of these abnormalities. Normal urine chemistry in respect of parameters studied, was observed only in 1.7% of cases. Of the 59 patients, one risk factor was present in 15.2% of patients, while 83.1% had two or more risk factors.³

Bisphosphonates inhibit calcium oxalate crystal growth *in vitro*. Older- and newer-generation bisphosphonates inhibited calcium oxalate vesical lithiasis in male Sprague–Dawley rats, and the inhibitory effect of bisphosphonates was demonstrable at relatively infrequent dosing intervals *in vivo*.⁴ We present a spinal cord injury patient with recurrent bladder stones, hypercalciuria, and biochemical features of increased bone resorption, who was prescribed disodium etidronate.

Case report

A 21-year-old male sustained fracture dislocation of T-7 and T-8 and developed paraplegia at T-10 level (ASIA scale - A) in a road traffic accident in June 2001. Spinal fixation was performed with USS system from T-5 to L-1. He was managing his bladder by indwelling catheter until the end of August 2001, when he started self-catheterisations along with oxybutynin by mouth. X-ray of abdomen, taken in September 2001, showed a very faint radio opaque shadow in the region of the urinary bladder (Figure 1).

The USS system was removed in November 2001. He was discharged from the spinal unit in January 2002. In March 2002, he developed urine infection and started leaking urine between catheterisations. X-ray of abdomen showed two large radio opaque shadows in the region of urinary bladder (Figure 2). There were no calculi in the kidneys or ureters. Flexible cystoscopy confirmed the presence of vesical calculi. Electrohydraulic lithotripsy was performed in May 2002. All stone fragments were removed. Intravenous urography, performed in October 2002, showed calculi in the urinary bladder. There was prompt excretion of contrast by both kidneys; there was no hydronephrosis. X-ray of urinary bladder, taken in December 2002, showed several calculi in the bladder (Figure 3). These stones were fragmented by lithoclast lithotripsy in two sessions, in December 2002 and February 2003. All stone fragments were removed at the end of the second session of lithotripsy. Although he started self-catheterisations along with oxybutynin by mouth, he reverted to indwelling catheter drainage when vesical calculi re-

Figure 1 X-ray of abdomen, taken on 28 September 2001, shows a faintly radio opaque calculus projected over the bladder

Figure 2 X-ray of abdomen, taken on 15 March 2002, shows two larger radio opaque calculi in the bladder

Figure 3 X-ray of pelvis, taken on 12 December 2002, shows several calculi in urinary bladder located around the Foley catheter balloon

curred. In September 2003, he attended the spinal unit with a history of repeated blocking of his indwelling urethral catheter. X-ray of abdomen showed recurrence of vesical calculi (Figure 4). By February 2004, the stones had increased in size and number (Figure 5). Electrohydraulic lithotripsy of vesical calculi was performed in April 2004. Complete clearance was achieved.

Bacteriuria was noticed in this patient on many occasions. In August 2001, urine microbiology showed *Pseudomonas aeruginosa*. In September 2001, urine culture yielded *P. aeruginosa* and *Enterococcus faecalis*. In February 2003, urine microbiology showed *Staphylo-*

Figure 4 X-ray of pelvis, taken on 29 September 2003, shows recurrence of bladder stones

Figure 5 X-ray of pelvis, taken on 26 February 2004, shows the stones have grown in size and are located around the balloon of Foley catheter

coccus aureus and *Escherichia coli*. In March 2004, *E. coli* was grown in urine, and this organism was resistant to gentamicin, ciprofloxacin, ceftazidime, and tazocin.

A 24-h urine biochemistry analysis, performed on 3 October 2003, detected hypercalciuria of 18.7 mmol/day (reference range: 2.5–7.5). Repeat measurement of 24-h urinary calcium, performed after dietary restriction of calcium, showed a value of 14.1 mmol/day. Biochemical analysis of a vesical calculus demonstrated calcium phosphate (85%) and magnesium ammonium phosphate (15%).

The 24-h urinary excretion of urate was 2.0 mmol/day (reference range: 1.2–3.0), that of oxalate was 265 μ mol/

Table 1 Results of blood tests

Test	Reference range	3 July 2001	5 July 2001	28 September 2001	9 October 2002	12 December 2002	28 September 2003	15 March 2004	15 July 2004
Sodium	133–146 mmol/l	135	136	139	141	140	140	141	142
Potassium	3.5–5.2 mmol/l	4.2	4.0	4.1	3.8	3.9	3.7	4.2	3.9
Urea	2.3–7.5 mmol/l	4.4	4.1	4.5	3.2	4.2	3.8	3.4	2.4
Creatinine	0–135 μ mol/l	64	77	77	66	85	73	81	64
Albumin	31–47 g/l	36	36	42	42	48	43	45	39
Calcium	2.20–2.60 mmol/l	2.28	2.23	2.40	2.39	2.32	2.19	2.42	2.33
Alkaline phosphatase	40–120 U/l	114	115	72	72	67	66	74	74
Adjusted calcium	2.20–2.60 mmol/l	2.36	2.31	2.36	2.31	2.16	2.13	2.32	2.35
Phosphate	0.80–1.50 mmol/l	1.40	1.36	1.41	1.08	1.04	1.07	0.99	1.09

day (reference range: 189–477 μ mol/day) and that of phosphate was 21.8 mmol/day (reference range: 12.9–42.0 mmol/day).

Serum sodium, potassium, urea, creatinine, alkaline phosphatase, calcium, and phosphate were within normal range (Table 1). Thyroid profile showed euthyroid status. TSH: 0.6 mU/l (reference range: 0.3–5.0 mU/l); Free T-4: 19.9 pmol/l (reference range: 9.0–24.0 pmol/l).

Plasma C-terminal telopeptides (CTX) was increased – 1.06 ng/ml (reference range: 0.10–0.50 ng/ml). Free deoxypyridinoline/creatinine ratio (fDPD/Cr) in urine was also increased – 20.2, reference range: 2.3–5.4.

Parathyroid hormone was 1.6 pmol/l (reference range: 1.1–6.9 pmol/l); this value was appropriate for the adjusted calcium at that time. 1,25 Vitamin D was within normal limits (74 pmol/l; reference range: 43–144 pmol/l). In April 2004, this patient was prescribed disodium etidronate 400 mg/day.

Nearly 3 months after commencing therapy with oral disodium etidronate, plasma CTX level had decreased to 0.87 ng/ml (reference range: 0.1–0.5 ng/ml). fDPD/Cr in urine also decreased to 12.4 (reference range: 2.3–5.4). But both plasma CTX and free fDPD/Cr in urine were still high when compared to the reference range in healthy adults. After 4 months of etidronate therapy, 24-h urinary calcium excretion decreased to 6.1 mmol/day, which was within the normal range.

Bone mineral densitometry of lumbar spine (L-1–L-4) performed in July 2004, showed T score of –1.53, which denoted osteopaenia. T score of left hip was –3.70, which indicated osteoporosis. In September 2004, patient was advised to take etidronate intermittently (2 weeks on and 12 weeks off). The 24-h urine calcium, plasma CTX and urine fDPD/Cr will be checked every 12 weeks.

Discussion

In the past, etidronate therapy for urolithiasis led to side effects^{5,6} probably because etidronate was administered continuously or, phosphate was also prescribed. Hope-

fully, side effects such as osteomalacia may not occur with intermittent etidronate therapy, which is represented by 3–4 months of continuous therapy, followed by 2 weeks of etidronate and 12 weeks without. This case raises some important issues in management of spinal cord injury patients, who develop recurrent vesical calculi.

- *What is the role of bisphosphonates in prevention of calcium phosphate vesical calculi in spinal cord injury patients?* Diphosphonate had no inhibitory effect on struvite bladder calculi, which were induced in rats with an intrarenal injection of urease-producing human T mycoplasma strain T960.⁷ Ebisuno *et al*⁸ examined the effect of etidronate on the crystallisation of calcium oxalate, calcium phosphate, and magnesium ammonium phosphate using *synthetic urine* and measured by an aggregometer. Etidronate affected the crystallisation of not only calcium phosphate and calcium oxalate, but also magnesium ammonium phosphate in *synthetic urine*. The inhibitory activities on these crystallisations were detected at extremely low drug concentrations. Are these observations, made on *synthetic urine*, applicable to *in vivo* situation in spinal cord injury patients, who develop stones in urinary bladder?
- *Does therapy with bisphosphonate represent first-line therapy of hypercalciuria in spinal cord injury patients?* Or, should spinal cord clinicians focus on nonpharmacological therapy, for example, early mobilisation, optimal nutrition (with care to avoid exacerbating hypercalciuria), weight-bearing exercises, functional electrical stimulation, cycle ergometry, etc.,⁹ and prescribe bisphosphonates to selected patients, in whom hypercalciuria persists after instituting non-pharmacological therapy for an adequate period. Several reports in the 1970s suggested that etidronate disodium might be clinically useful to prevent calcium stones, but the use of etidronate in the urolithiasis field was discontinued due to adverse effects of this drug on skeletal turnover and mineralisation.⁸

- Which bisphosphonate should we prescribe and what should be the duration of treatment with bisphosphonate for prevention of urinary calculi in spinal cord injury patients, who show biochemical features of increased bone resorption? Etidronate, if administered continuously, may lead to abnormal mineralisation of osteoid and microfractures, which might potentially result in increased susceptibility to fractures, especially non-vertebral fractures. Although etidronate prevents decreases in the bone mineral density in hemiplegic stroke patients by decreasing the serum calcium through inhibition of bone resorption and causing a subsequent increase in the serum 1,25-dihydroxyvitamin D concentration,¹⁰ etidronate has not been licensed in the United Kingdom to treat persons with spinal cord injury, who show increased bone resorption.
- What are the limitations and possible complications of disodium etidronate treatment in spinal cord injury patients? Oral amino derivatives of bisphosphonates may induce dose-related serious gastrointestinal lesions, especially erosive oesophagitis. Amino-bisphosphonate administration has been also associated with the sporadic occurrence of uveitis, scleritis and phlebitis and, in single cases, with irritative reactions at the skin, peritoneum and pericardium.¹¹ After some months/years of therapy with etidronic acid for osteoporosis, some patients developed mood, concentration and memory problems. The complaints diminished within several weeks after withdrawal of the drugs, and reappeared after rechallenge.¹²

Comments by Olof Jonsson (MD, PhD, Professor of Urology, Department of Urology, Sahlgrenska University Hospital, S-413 45 Göteborg, Sweden)

At the Spinal Cord Injury Centre at Sahlgrenska University Hospital, Göteborg, Sweden, we have about 100 spinal cord injuries per year. The patients arrive at the Spinal Cord Injury Ward as soon as possible after the injury. During the stay at the Intensive Care Unit, they usually have an indwelling catheter but as soon as possible, clean intermittent catheterisation (CIC) is instituted. At time of discharge from the Spinal Injury Ward, 70% of the patients perform CIC and 20% have normal micturition. Only about 5% of the patients do have a catheter *à demeure* or a suprapubic catheter. At first follow-up, 70% of the patients still perform clean intermittent catheterisation. The number of patients with catheter *à demeure* or suprapubic catheter is about 10%. The results of the neurourological follow-up 1 year after injury are discussed at a urological conference and based on this discussion, 30% of the patients are advised to consider some kind of alteration in their bladder regimen. The commonest recommendations are alterations in the mode of performing clean intermittent catheterisation and addition of anticholinergic treatment. Also 2 years after injury, about 70% of the patients still are on clean intermittent catheterisation. Most patients use the LoFric catheter (AstraTech).

Antibiotics are only given when the patient has clinical signs of urinary tract infection. The bladder is regularly rinsed with sodium chloride or sodium chloride plus chlorhexidine in connection with catheterisation.

We very seldom see bladder stones in our patients. This is probably due to the fact that most patients are on clean intermittent self-catheterisation. I cannot remember in our practice any single patient, who had a similar bladder stone problem, as the patient presented in the Clinical case of the month. Thus, we do not regularly measure the calcium content of the urine.

In summary, I do not consider bladder stones as a major problem in our patients. I strongly support the use of clean intermittent self-catheterisation in these patients. When an indwelling catheter is used, it should be changed regularly before encrustations on the surface of the balloon occur.

Comments by Dr AZ Buczynski (MD, PhD, Department of Neuro-Urology, Metropolitan Rehabilitation Centre, Konstancin, Poland)

Thank you for invitation for my comments concerning this very interesting case. I have not had any experience with the use of disodium etidronate in patients with paralysis. As far as I know, this drug is mainly used for postmenopausal osteoporosis in female patients.

According to my experience with cystolithiasis of paraplegic and tetraplegic patients, a very high percentage of bladder stones in such patients (except those who have had stones before accident) are struvite stones. These stones contain ammonium, magnesium, calcium, and phosphates with increased content of calcium especially in young men. Prolonged immobilisation, infections, especially by urea splitting, mainly nosocomial microorganisms, residual urine, and indwelling catheter are the most important factors for stone formation in such cases.

Precise removal of bladder stones fragments after lithotripsy, subsequent exact eradication of infection, liquidation of residual urine, and keeping urine in low pH usually prevent recurrent bladder stone formation.

In this particular case presented here, a very abnormal level of urine calcium and biochemical markers of bone resorption suggest an explanation for nontypical frequent recurrence of bladder stones. The necessity for removal of bladder stones in one patient more than twice in a period of just a couple of years is extremely rare in my personal experience of hundreds of such patients (paraplegic and tetraplegic patients with bladder stones) during the last 30 years.

Comments by Dr F Grases (PhD, Professor and Director of the Laboratory of Renal Lithiasis Research, Institute of Health Sciences Research (IUNICS), University of Balearic Islands, Palma de Mallorca, Spain)

Urine is always supersaturated (contains higher amounts of solute than the maximum total amount that

can remain indefinitely solved) with respect to calcium oxalate and depending on its pH value, is also supersaturated with respect to uric acid (urinary pH inferior to 5.5) or calcium phosphates (urinary pH superior to 6.0). In spite of this, crystallisation processes (stone formation) only take place in uncontrolled pathological situations. The question is, why does crystallisation not take place indiscriminately in all human urines and yet only appears in pathological situations? The answer is now clear. There are four main aspects that must be considered to explain pathological crystallisation: supersaturation higher than usual of the crystallising substance, and/or the presence of heterogeneous nucleants (crystallisation inducers) as any preformed solid particles (cellular residues, bacterial debris, etc), and/or deficit of crystallisation inhibitors (substances that disturb crystal formation and development), and/or urinary stasis (the increase of the urinary residence time in the urinary track obviously increases the possibility of crystallisation of supersaturated substances). Thus, in healthy conditions, the presence of crystallisation inhibitors at adequate concentrations prevents the development of solid concretions during the urine permanence in the urinary track. In fact, the crystallisation inhibitors act delaying the crystallisation of supersaturated substances, avoiding that crystallisation takes place before the renovation of the corresponding urine.

If all these aspects are applied to the very interesting case presented in your paper, the following facts must be considered:

- The analysis of the calculus revealed calcium phosphate (hydroxyapatite) + magnesium ammonium phosphate (struvite). The aetiology of these calculi implies a urinary pH superior to 6.0 (to reach calcium phosphate supersaturation). The existence of a persistently elevated urinary pH also favoured bacterial colonisation. In fact, in this patient bacteriuria was noticed on several occasions (urealitic and nonurealitic bacteria). Urealitic bacteria, due to their metabolic activity, still increase the pre-existent urinary pH and also generate ammonium (as a consequence magnesium ammonium phosphate is also formed). Owing to all these mentioned aspects, it is very important in these patients to avoid urinary pH values superior to 6.0. For this reason, a strict control of all dietetic components that increase urinary pH must be recommended. Thus, these patients must avoid carbonic beverages (or bicarbonate ingestion), foods that contain citrate (lemon, orange, kiwi, etc) and strict vegetarian diets. It would also be important to perform a regular precise control of urinary pH.
- According to the literature and our experience, *etidronate and other related polyphosphates act as very effective inhibitors of calcium phosphate crystallisation at appropriate urinary concentrations*. Considering the low urinary excretion of these products (around 1–2% of the ingested amounts) and oral etidronate dose of

400 mg/day would imply urinary concentrations around 1–4 mg/l. These amounts are high enough to produce significant inhibitory effects, and as a consequence, etidronate can exert a notable role on preventing calcium phosphate stone.

- Hypercalciuria constitutes an important risk factor of calcium oxalate and calcium phosphate stone development since it increases supersaturation of these compounds. The decrease of calciuria by the oral etidronate therapy constitutes another clear factor for prevention of calcium phosphate bladder stones.
- Finally, to avoid development of solid particles that could act as heterogeneous nucleants, when an indwelling catheter is used, it would be very important to change the catheter regularly before encrustations on the surface occur. Of course, a high water intake (2–3 l/day) is also fundamental to dilute the urine, to avoid urinary stasis and to carry away all incipient solid particles formed.

Comments by Ita Pfeferman Heilberg (MD, PhD, Professor of Nephrology, Nephrology Division, Federal University of São Paulo, São Paulo, Brazil)

The present case illustrates that spinal cord injury patients may develop bladder stones, but this is unlikely to occur among patients with normal urinary tract. Therefore, stone formation must have been consequent to urine stasis, bacterial colonisation and catheter use, leading to a condition worsened by the presence of bone resorption-induced hypercalciuria. However, it is clear that hypercalciuria itself would have induced renal and not bladder stones if the former factors were not to be present. In addition, the size of the calculi and recurrence rate over such a short period of time suggests that probably these stones have not migrated from the upper urinary tract but were rather formed within the bladder. Considering the highly recurrent bladder stone formation in this patient and given the need for very frequent urological procedures to remove calculi, I think that it was wise and cost-effective to search for metabolic abnormalities in this context, in order to provide not only treatment but also a preventive approach.

Early attempts to treat calcium urolithiasis, retarding the crystal growth of urinary brushite with bisphosphonates have been reported in the literature,^{5,13} but it seems that the potential bone hazards have overcome their efficacy on stone formation. Surprisingly, there were no significant changes in urinary calcium in the latter cited study.

In the present case, etidronate induced a decrease on bone resorption as expected, and this was evidenced by the values of specific biochemical markers; urinary calcium excretion also decreased. Albeit the treatment of immobilisation hypercalcaemia with bisphosphonates is very well established in the literature, and that alendronate is able to prevent bone loss and avert hypercalciuria when given in anticipation of a 3 weeks of

strict bedrest,¹⁴ the potential effect of such drugs in spinal cord injury patients concerning control of hypercalciuria remains unknown.

Considering the antiresorptive potency of the distinct bisphosphonates and their side effects, I think that either clodronate or the second generation (alendronate) or even one of the third-generation bisphosphonates would be a better choice without the need of cyclic therapy. However, I still cannot say if therapy with bisphosphonates represent first-line therapy of hypercalciuria in spinal cord injury patients. It is possible that, as suggested by the authors of the present case, early mobilisation, weight-bearing exercises, functional electrical stimulation, etc. if applicable, would be most useful, and that bisphosphonates could be relegated to a secondary role in controlling hypercalciuria. Not only bone densitometry or bone markers but also urinary calcium must often be determined in order to answer some of these unsolved questions. Most of the studies employing this drug do not report the results on urinary calcium. Another important point to mention is that the classic prescribed therapy for hypercalciuria (thiazides) would probably be very difficult to be managed by these patients due to the enhancement of urinary flow.

In the present case, bisphosphonate would be indicated even if the bladder stones were not present, if one considers the profound bone loss (T-score of left hip of -3.70), leading to osteoporosis. I think that the clinical course of the present case, namely the evolution of urinary calcium levels, as well as the rate of new stone formation, will tell and teach us more than we can find in the literature to date.

Comments by Takahiro Yasui, Keiichi Tozawa, and Kenjiro Kohri (Department of Nephro-Urology, Nagoya City University Graduates School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan)

We consider that clear intermittent self-catheterisation is best for the management of urine in spinal cord injury. In this particular case, both a high level of hypercalciuria and infection explained the frequent recurrence of bladder stone. Bisphosphonate is effective in decreasing urinary calcium excretion and bone metabolism by the domination of osteoclasts. In this case, especially, bisphosphonate was adequate in the beginning term of spinal cord injury and for long-term bed rest and hypercalciuria. Etidronate and other related bisphosphonates act as very effective inhibitors of calcium phosphate crystallisation at an appropriate urinary concentration *in vitro*.

Bisphosphonates, which decrease bone resorption, may possibly be considered in patients with hypercalciuria due to increased bone resorption. Indeed, alendronate, a new generation bisphosphonate, has been reported to decrease urinary calcium and saturation with urinary calcium phosphate, so that the values after immobilisation through bed rest never reach

previously attained levels. The hypocalciuric effect of bisphosphonates may possibly be of use in certain patients with increased bone resorption.

Bisphosphonates are classified by generation according to their structural differences. Etidronate is an old generation bisphosphonate compound, which has been used for osteoporosis. It decreases calcium oxalate and calcium phosphate crystallisation *in vitro*. However, etidronate cannot be used to treat urinary stones because the dosages required preventing stone formation causes disorders in skeletal turnover and bone mineralisation, generally. In some studies showing an effect in chronic stone-formers, the dose necessary to obtain inhibition of crystal growth in urine was so high that it could also induce inhibition of skeletal mineralisation. Therefore, generally, etidronate should not be recommended for use in urolithiasis.

Consequently, novel bisphosphonates classified as a new generation have been synthesised. They are pharmacologically 100–1000-fold more potent than etidronate in terms of bone antiresorptive activity, and can be clinically applied to tumour-induced hypercalcaemia and osteoporosis. The P-C-P structure of bisphosphonates allows considerable variation, either by changing the two lateral chains on the carbon atom or by esterifying the phosphate groups. Thus, each bisphosphonate has unique physicochemical and biological characteristics. New generation bisphosphonates are considered useful for this or similar cases, although we have no experience with recurrent bladder stone after spinal injury with hypercalciuria.

Comments by Professor Jean-Jacques Wyndaele (Centrum Urologische Revalidatie, Universitair Ziekenhuis Antwerpen, 10 Wilrijkstraat, B 2650 Edgem, Belgium)

Stone formation in patients with spinal cord injury has a high prevalence. Approximately 6% of spinal cord damaged patients will develop upper tract calculi compared with 2% in the general population. There is no clear relationship between incidence of upper tract calculi and neurological level. Calculi are rare in patients with lesion below L1.¹⁵ Bladder calculi are much more prevalent and related to infection and foreign material, for example, catheters.¹⁶

The metabolic changes after spinal cord injury are important. Calcaemia does not seem to change though individual cases of dangerous hypercalcaemia have been described early after injury.¹⁷ The other changes in blood chemistry are known: an increase in phosphate, alkaline phosphatase, and calcitonin. In the urine, hypercalciuria is observed from day 2–3 after spinal cord injury, which reaches normal levels again at month 5–8.

Chronically, the danger for hypercalciuria remains probably because of the lack of weight bearing on the bones.¹⁷ It is long ago that Issekutz *et al*¹⁸ showed that long-term standing alone could lower the hypercalciuria. Moreover, calciuria can be increased by intake of drugs

such as ammonium chloride, ascorbic acid, hexamine methionine mandelamine acid.

A high fluid intake is accepted as a prevention measure, but its limitations have been shown before.¹⁹ Infection has a very negative role especially the feared *Proteus* infection. The presence of catheters offers another substrate to stone formation. This case study shows a positive effect of the use of oral disodium etidronate in this patient; plasma CTX level has been decreased. However, it remains to be seen whether lowering of plasma CTX will be enough to prevent further stones from developing. We will need an update after 6 and 12 months.

Comments by Professor B Schurch, (MD, Department of Neuro-Urology, Spinal Cord Injury Centre, University Hospital Balgrist, Zurich, Switzerland)

First of all, we have to admit that we have no experience with the use of bisphosphonates for para- or tetraplegic patients. Even though we see about 1000 patients with neurogenic bladder per year (most of them are spinal cord injury patients) in our outpatient clinic, the occurrence of bladder stones seems to be quite rare (approximately 3–4/year). In these cases, we do not routinely perform 24-h urine analyses and therefore, we cannot comment on the occurrence of metabolic disorders such as hypercalciuria. We agree to the common sense that bladder stone-formation results from repeated infections in combination of indwelling catheter and neurogenic bladder dysfunction. Our treatment in such cases is removal of the bladder calculi and long-term follow-up by ultrasound and/or cystoscopy. We try to prevent repeated urine infections by informing patients the need for regular intermittent catheterisation. Our protocol comprises of good patient education, high fluid intake, and lowering the pH of urine by use of L-methionine. As we have not used bisphosphonates, we cannot comment on your questions concerning the use of bisphosphonates. We need well-designed, randomised, double-blinded studies to evaluate use of bisphosphonates to prevent bladder stone-formation in paralytic patients. The question remains if such a study will be worth the effort, considering the low incidence of bladder stones in spinal cord injury patients.

Concluding remarks by United Kingdom team

Although 24-h urinary excretion of calcium decreased after etidronate therapy, X-ray of abdomen, taken on 16 September 2004, showed a small opacity in pelvis, indicative of recurrent vesical calculus. This is not surprising, as this patient continues to have long-term indwelling urethral catheter drainage of bladder and has been suffering from recurrent urine infection. We failed miserably in persuading this patient, as well as many others, to consider intermittent catheterisation as the preferred option for management of neuropathic bladder. We wish we could emulate Dr Olof Jonsson in

Salhgreńska University Hospital, Göteborg, Sweden, where 70% of spinal cord injured patients perform intermittent catheterisation, only about 5% of the patients do have a catheter *à demeure* or a suprapubic catheter, and consequently, bladder stones are seldom seen in spinal cord injured patients.

This patient was prescribed etidronate, but we wish to emphasise that etidronate has *not* been licensed in the United Kingdom either for treatment of increased bone resorption in persons with spinal cord injury, or for prevention of urolithiasis. This case illustrates that many factors contribute to the pathogenesis of vesical calculi in persons with spinal cord injury. Treatment of hypercalciuria by etidronate is not sufficient by itself to prevent recurrence of vesical calculi, especially when other causes, such as, long-term catheter drainage and recurrent urine infection, have not been dealt with.

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This work is dedicated to the memory of Mr KR Krishnan, who was Consultant in Spinal Injuries, Southport from 1971 to 1996 and a member of International Medical Society of Paraplegia (presently, International Spinal Cord Society).

References

- 1 Ord J, Lunn D, Reynard J. Bladder management and risk of bladder stone formation in spinal cord injured patients. *J Urol* 2003; **170**: 1734–1737.
- 2 Lamid S, El Ghatit AZ, Melvin JL. Relationship of hypercalciuria to diet and bladder stone formation in spinal cord injury patients. *Am J Phys Med* 1984; **63**: 182–187.
- 3 Singh PP, Pendse AK, Rathore V, Kiran R, Dashora PK. Interdependence of urinary factors in calcareous bladder stone patients. *Int Urol Nephrol* 1989; **21**: 145–151.
- 4 Gupta M, Tuncay OL, Valderrama E, Smith AD. Inhibition of calcium oxalate urolithiasis in a rat model of lithogenesis using bisphosphonates. *J Endourol* 1997; **11**: 1–4.
- 5 Bone III HG, Zerwekh JE, Britton F, Pak CY. Treatment of calcium urolithiasis with diphosphonate: efficacy and hazards. *J Urol* 1979; **121**: 568–571.
- 6 Heilberg IP *et al.* Effect of etidronate treatment on bone mass of male nephrolithiasis patients with idiopathic hypercalciuria and osteopenia. *Nephron* 1998; **79**: 430–437.
- 7 Lamm DL, Johnson SA, Friedlander AM, Gittes RF. Medical therapy of experimental infection stones. *Urology* 1977; **10**: 418–421.
- 8 Ebisuno S *et al.* Effects of etidronate disodium on crystallizations in synthetic urine and calcium oxalate crystal adhesion to Madin-Darby canine kidney (MDCK) cells. *Int J Urol* 1998; **5**: 582–587.
- 9 Ott SM. Osteoporosis in women with spinal cord injuries. *Phys Med Rehabil Clin N Am* 2001; **12**: 111–131.
- 10 Sato Y, Asoh T, Kaji M, Oizumi K. Beneficial effect of intermittent cyclical etidronate therapy in hemiplegic patients following an acute stroke. *J Bone Miner Res* 2000; **15**: 2487–2494.
- 11 Adami S, Zamberlan N. Adverse effects of bisphosphonates. A comparative review. *Drug Saf* 1996; **14**: 158–170.

- 12 Wolffenbuttel BH, van der Klauw MM. Psychiatric side effects associated with diphosphonate treatment. *Ned Tijdschr Geneesk* 2003; **147**: 35–37.
- 13 Pak CY, Ohata M, Holt K. Effect of diphosphonate on crystallization of calcium oxalate *in vitro*. *Kidney Int* 1975; **7**: 154–160.
- 14 Ruml LA, Dubois SK, Roberts ML, Pak CY. Prevention of hypercalciuria and stone-forming propensity during prolonged bed rest by alendronate. *J Bone Miner Res* 1995; **10**: 655–662.
- 15 Gardner BP, Parsons KF. Upper tract dilatation and stones. In: KF Parsons, JM Fitzpatrick (eds). *Practical Urology in Spinal Cord Injury*. Springer Verlag: London 1991, pp 43–56, Chapter 5.
- 16 Wyndaele JJ, De Sy W, Claessens H. Evaluation of different methods of bladder drainage used in the early care of spinal cord injury patients. *Paraplegia* 1985; **23**: 18–26.
- 17 Conley SB, Shackelford GD, Robson AM. Severe immobilization hypercalcemia, renal insufficiency and calcification. *Pediatrics* 1979; **63**: 142–145.
- 18 Issekutz Jr B, Blizzard JJ, Birkhead NC, Rodahl K. Effect of prolonged bed rest on urinary calcium output. *J Appl Physiol* 1966; **21**: 1013–1020.
- 19 Burr RG, Nuseibeh I. Diuresis and urinary saturation in patients with neurogenic bladder. *Invest Urol* 1981; **18**: 331–333.