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Effects of oral pyridoxine upon plasma and 24-hour urinary oxalate levels in normal subjects and stone formers with idiopathic hypercalciuria

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Summary. The effect of pyridoxine hydrochloride, 200 mg/day (0.97 mmol/day) for 3 weeks, upon plasma and urinary oxalate has been determined in ten normal subjects and seven patients with idiopathic hypercalciuria while both groups were on low-oxalate diets. Patients had higher basal urinary oxalate levels than normal subjects. In normal subjects pyridoxine administration decreased plasma oxalate levels and raised urinary oxalate. The patients showed no change in either plasma or urinary oxalate.

Key words: Plasma oxalate – Urine oxalate – Pyridoxine

Calcium oxalate urolithiasis is common in developed countries. The probability that urinary oxalate is of more importance than urinary calcium in calculus formation [19] led to more attention being given to oxalate metabolism.

In recent years, the assaying of oxalate in urine and plasma has revealed more and more cases of hyperoxaluria, and reducing urinary oxalate in oxalate stone formers has become a rational therapy. There is a relationship between vitamin B6 deficiency and an increase in urinary oxalate in both animals [6] and man [5]. Therefore, there has been considerable interest in the metabolism of vitamin B6 and oxalate in stone patients. Large reductions in urinary oxalate excretion were observed when high doses of pyridoxine hydrochloride were given daily to patients with primary hyperoxaluria [20]. Since then, many investigators have tried pyridoxine in the treatment of primary hyperoxaluria, and it is clear that not all patients respond. In patients with idiopathic stone formation the situation is even more confusing. This highlights the need for further studies on pyridoxine metabolism in normal subjects and patients with idiopathic stone formation.

This paper reports the effect of pyridoxine supplements on normal subjects and patients with idiopathic hypercalciuria and high levels of oxalate excretion.

Subjects and methods

Ten normal volunteers (four women, six men) and seven calcium oxalate stone formers (six men, one woman) were on a diet low in oxalate and ascorbate and with a daily fluid intake or 2,000 ml for 25 days. The patients all had mild hyperoxaluria (of above 0.45 mmol/24 h) and idiopathic hypercalciuria (IHC), which was controlled by means of a restricted-calcium diet and in some cases also a thiazide diuretic.

Within the first 4 days of starting the diet, two 24-h collectins of urine and one blood sample were taken as basal levels. During the remaining 3 weeks, 200 mg (0.97 mmol) of vitamin B6 (pyridoxine hydrochloride) per day was given as two 50-mg tablets every morning and evening. One blood sample (4-h after taking tablets) and two 24-h urine collections were taken each week. Urine was collected in a plastic container with thymol as preservative. After measurement of pH the 24-h urine was acidified to pH 2.5 by adding concentrated HCl, and 20 ,ml of each collection was stored at −25 ° C until assay. Heparinised plasma was separated by centrifugation and was also stored at −25 °C.

Oxalate in plasma and urine was measured by auto-analyser using immobilised oxalate oxidase [12, 13]. Glycollate in urine was determined by an oxidase method [11]. For measuring the various B6 compounds we used the HPLC method [4]. The creatinine level in plasma and urine was measured by centrifugal analyser system (Jaffe reaction). The results were analysed statistically with Student's *t*-test. *P*-Values Smaller than 0.05 were regarded as significant.

Results

The results of the 24-h urinary excretion of measured substances in normal subjects and idiopathic hypercalciuria stone formers are shown in Table 1.

The IHC patients had a higher 24-h mean urine volume than the normal subjects. This difference was statistically significant ($P < 0.01$).

The urinary oxalate excretion was significantly higher among the group of patients than among the normal subjects. This difference remained significant after correction of the results for creatinine (24-h urinary oxalate ÷ 24-h urinary creatinine × mean creatinine for each subject). Supplements of pyridoxine hydrochloride to IHC stone formers failed to produce a fall in urinary

Table 1. The effect of 200 mg (0.97 mmol) pyridoxine hydrochloride on 24-h urinary excretions of various chemicals in normal subjects ($n = 10$) and in idiopathic hypercalciuria stone formers ($n = 7$)

		Basal value (± SEM)	During B6 supplement (total mean ± SEM)		
			1 Week	2 Weeks	3 Weeks
Urinary volume (ml)	Normal subjects	1,781 (± 149)	1,949 (± 154)	2,110 (± 200)	1,977 (± 152)
	IHC stone formers	3,202 (± 501)	3,248 (± 452)	3,318 (± 438)	3,151 (± 310)
Urinary oxalate (mmol/24-h)	Normal subjects	0.19 (± 0.02)	0,21 (± 0.01)	0,21 (± 0.02)	0.23 (± 0.02)
	IHC stone formers	0.35 (± 0.06)	0.31 (± 0.04)	0.32 (± 0.05)	0.36 (± 0.06)
Urinary glycollate (mmol/24-h)	Normal subjects	0.20 (± 0.04)	0.20 (± 0.02)	0.19 (± 0.02)	0.19 (± 0.01)
	IHC stone formers	0.23 (± 0.05)	0.26 (± 0.06)	0.22 (± 0.04)	0.26 (± 0.03)
Urinary creatinine (mmol/24-h)	Normal subjects	14.1 (± 1.27)	13.3 (± 0.83)	13.3 (± 1.09)	12.84 (± 1.03)
	IHC stone formers	18.3 (± 1.60)	15.5 (± 1.81)	15.8 (± 1.62)	17.5 (± 1.03)
Urinary 4-pyridoxic acid (mmol/24 h)	Normal subjects	0.02 (± 8.73 E-03)	0.56 (± 0.03)	0.48 (± 0.05)	0.5 (± 0.05)
	IHC stone formers	3.78 E-03 (± 1.23 E-03)	0.48 (± 0.08)	0.42 (± 0.07)	0.48 (± 0.07)

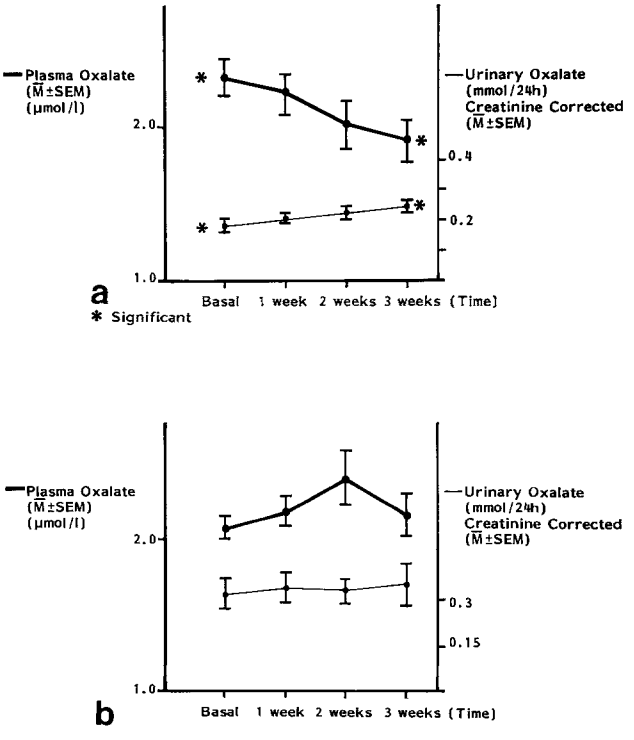

Fig. 1a, b. The effect of 20 mg pyridoxine per day on the mean (± SEM) plasma (*thick lines*) and urinary (*thin lines*) oxalate levels of 10 normal subjects (**a**) and 7 stone formers wiht IHC (**b**)

oxalate excretion. However, normal subjects showed a significant elevation ($P = 0.027$) of oxalate excretion after taking pyridoxine hydrochloride for 3 weeks when results were corrected for creatinine (Fig. 1).

There was no marked difference between patients and normal subjects in urinary 4-pyridoxic acid excretion either before or after 3 weeks of taking pyridoxine hydrochloride (Fig. 2). No significant change occurred in urinary glycollate excretion in either patients or normal subjects (Fig. 3).

The effects of the pyridoxine hydrochloride supplement on plasma oxalate in both normal subjects and stone formers are shown in Fig. 1. There was a reduction in mean plasma oxalate levels of normal subjects after 3 weeks' supplement of pyridoxine hydrochloride (200 mg/day), from 2.3 ± 0.37 to 1.91 ± 0.49 µmol/l ($P = 0.008$ in the paired t-test).

The study showed no diffeence in plasma pyridoxal 5-phosphate levels between the stone formers and the normal subjects either before or after administration of pyridoxine hydrochloride (Fig. 4).

Discussion

Since the first step in the treatment of stones is to dilute the urine and lower the concentration of lithogenic substances, most patients are recommended to have a high fluid intake across the day. The fact that our patient group

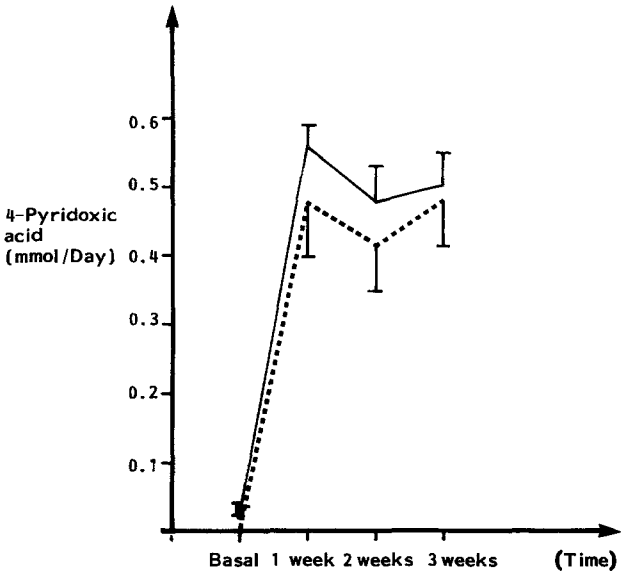

Fig. 2. Mean (±SEM) urinary 4-pyridoxic acid excretions as mmol/24 h in 10 normal subjects (*thick line*) and 7 stone formers with IHC (*broken line*) before and during intake of 200 mg pyridoxine per day

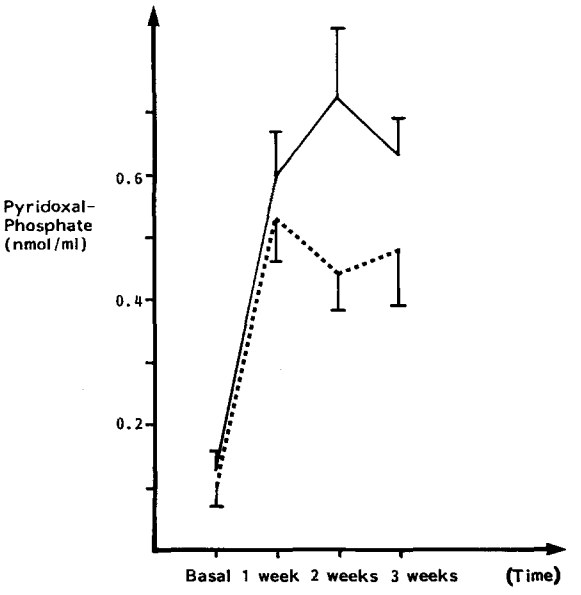

Fig. 4. Mean (±SEM) plasma 5-pyridoxal phosphate levels before and during 200 mg pyridoxine per day in 10 normal subjects (*thick line*) and 7 stone formers with IHC (*broken line*)

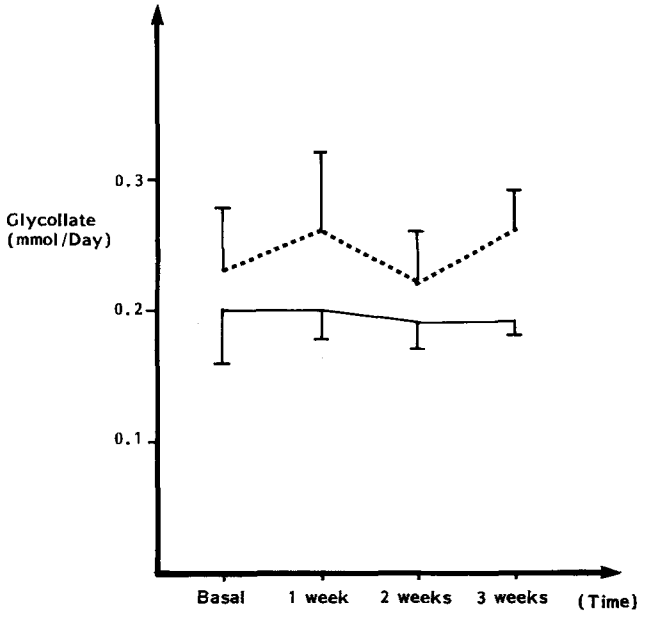

Fig. 3. Mean (±SEM) urinary glycollate excretions before and during 200 mg pyridoxine per day in 10 normal subjects (*thick line*) and 7 stone formers with IHC (*broken line*)

shows a higher urinary mean volume than the normal subjects group indicates good general compliance with this recommendation. A second factor could also have been operative, since some publications report a reduced ability to concentrate urine in idiopathic hypercalciuria patients [1, 15, 16]. The IHC stone formers in our studies proved to have higher urinary oxalate values under low oxalate diet conditions than normal subjects. The reason for this is not clear in view of the controlled diet and normal urinary glycollate values, but there are a number of possible explanations. First, it has been thought that raised urinary volume can increase urinary oxalate [9, 21, 24], and perhaps this was the cause. Second, the patients were on low calcium intake, whereas the normal subjects were not, and it is known that low calcium intake increases absorption of dietary oxalate [10]. Third, it has been said by some [7, 8], although others have disagreed [3], that thiazides slightly raise urinary oxalate, and four out of seven of our patients were taking thiazides.

The rise in urinary oxalate in normal subjects after pyridoxine surprised us, although it has been seen by others. Tiselius and Almgard [22] reported an increased oxalate excretion in 9 out of 12 subjects (7 stone formers and 5 normal subjects) on administering a dose of 200 mg pyridoxine per day for 3 weeks. All normal subjects responded with an increased oxalate excretion, and 3 patients who had high oxalate excretion values prior to therapy responded with a fall in urinary oxalate levels. Nakada et al. [18] have shown a significant reduction of urinary oxalate excretion in IHC patients given 60 mg pyridoxal phosphate per day for 3 months.

We could not see any changes in urinary oxalate levels in patients with IHC during the 3 weeks of pyridoxine supplementation.

The tendency of plasma oxalate levels to fall in our norml subjects also surprised us. Since the blood samples were all collected at the same time of day (12 noon) the explanation could not have been circadian variations in plasma oxalate, which are known to occur [14]. We can find no other reports in the literature of the effect of pyridoxine upon plasma oxalate levels in normal subjects or in stone formers. However, the effect of vitamin B6 administration on plasma oxalate levels in haemodialysed patients has been investigated by several groups. Two

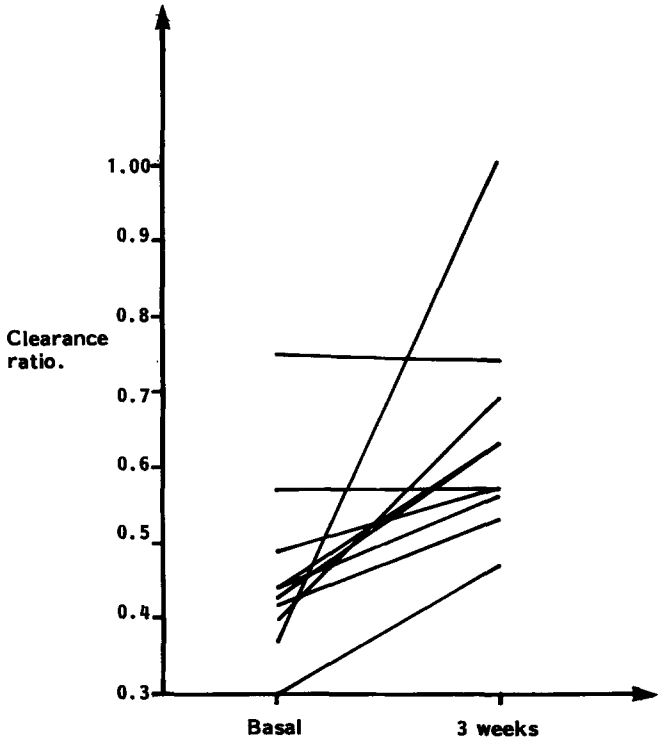

Fig. 5. Oxalate-to-creatinine clearance ratios before during 200 mg pyridoxine per day in 10 normal subjects

groups showed a significant reduction in plasma oxalate concentrations on giving 600 mg and 800 mg pyridoxine per day, respectively [2, 17], whereas a third group demonstrated that administration of 100 mg pyridoxine per day did not alter plasma oxalate levels [23] although it normalised the activity of erythrocyte aspartate aminotransferase (EAST), an indicator of nutritional status with respect to pyridoxine.

Since the normal subjects showed significant falls in plasma oxalate values together with increase urinary oxalate, the oxalate-to-creatinine renal clearance ratios (mean $\pm$ SEM) showed a significant ($P = < 0.01$) elevation, from 0.45 ± 0.14 to 0.64 ± 0.15 (Fig. 5). In the case of the patients the oxalate-to-creatinine clearance ratio rose from 0.86 (± 0.13) to 0.97 (± 0.17), but this difference was not statistically significant ($P + 0.427$).

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