Urol Res (2009) 37:353–357
DOI 10.1007/s00240-009-0222-4

SYMPOSIUM PAPER

Drug dosage protocol for calcium oxalate stone

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Received: 16 September 2009 / Accepted: 23 September 2009 / Published online: 14 October 2009

Abstract In earlier studies, we have confirmed that in most patients with calcium oxalate stone formation, a combination of allopurinol and pyridoxine is best suited for treatment and prevention of the stone forming process. The objective of this study is to identify the most effective directed medical treatment of urinary stones. The drug dose adjustment was based on clinical, radiological, biochemical, and microscopic parameters. 444 patients with proved calcium oxalate stone disease who were getting a combination of allopurinol and pyridoxine for a minimum period of 36 months were enrolled in this prospective study. The dosage schedule of these patients was recorded. Dosage adjustment was made depending upon the various clinical, biochemical, microscopic, and radiological changes during the study period. The dosage schedules were in six categories, namely very high dose chemotherapy (VHDC), i.e. allopurinol 600 mg/day and pyridoxine 240 mg/day, high-dose chemotherapy (HDC), i.e. allopurinol 300 mg/day and pyridoxine 120 mg/day, moderate dose prophylaxis (MDP), i.e. allopurinol 200 mg/day and pyridoxine 80 mg/day, low-dose prophylaxis (LDP), i.e. allopurinol 100 mg/day and pyridoxine 40 mg/day, and very low-dose prophylaxis (VLDP), i.e. allopurinol 50 mg/day and pyridoxine 20 mg/day and intermittent VLDP, wherein the VLDP was given on alternate months and still later at longer intervals. The temporary risk was assessed at each visit and dosage adjustment was made. The effect of the intervention was assessed during the next visit. All the patients involved in the study needed dose adjustment. The following schedules were initiated: VHDC (12) 3.5%, HDC (103) 23.2%, MDP (78) 17.57%, or LDP (251) 56.53%. Patients who defaulted for more than a month were excluded from the study. During each visit for follow up, all patients were advised change over of dose depending upon the clinical situation at the time of review. Patients on VHDC were advised reduction to lower doses systematically. On passage of stones, the dose was immediately reduced to LDP in all situations unless prevented by the presence of significant crystalluria or severe pain. All patients on MDP had reduction of dose to LDP subsequently. Patients started on LDP needed elevation in dose in 63 (16.8%) to HDC and 23 patients (12.87%) to MDP. Dose of 247 patients could be reduced to VLDP (55.63%) and later on to intermittent VLDP 85 (19.14%). 74 (16.7%) patients continued to be on LDP throughout the period of study. It is concluded that in managing the stone patient, the clinical, radiological, microscopic and biochemical parameters should be taken into consideration in deciding the reduction/increase in the dose of drugs. The principle of giving chemotherapy/chemoprophylaxis should be to administer the least number of drugs in the least dosage depending upon the requirement of the disease.

Keywords Urolithiasis · Chemotherapy · Chemoprophylaxis · Allopurinol · Pyridoxine · Symptom score

11th international symposium on urolithiasis, Nice, France, 2–5 September 2008 Urological Research (2008) 36:157–232. doi: 10.1007/s00240-008-0145-5. http://www.springerlink.com/content/x263655772684210/fulltext.pdf.

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Introduction

Several drugs are now available in the market for medical management of idiopathic calcium oxalate urinary stone disease [1]. However, most of the drugs do not stand the test of time. Patient compliance and therapeutic efficacy are the hallmarks of effective medical management. Most of the reports available in literature on medical management of stone disease are empirical and not modulated. Most of the drug trials are not randomised and blinded. Every patient is different in the way the stone is formed and grows. The extent of crystalluria does not vary uniformly with type of stone formed. The biochemical abnormalities are widely variable in the same patient at different times. In India, primary idiopathic calcium oxalate stones form the vast majority. In earlier studies, we have confirmed that in most of these patients with calcium oxalate stone formation, a combination of allopurinol and pyridoxine is best suited for treatment and prevention of the stone forming process. The objective of this study is to identify the most effective patient friendly and least toxic dosage schedule for medical management of urinary stones. The process of initiating and sustaining dosage schedules for short term chemotherapy and long-term prophylaxis in patients with urolithiasis was based on clinical, radiological, biochemical and microscopic parameters.

Methods

444 patients with proved calcium oxalate stone disease, who were getting a combination of allopurinol and pyridoxine for a minimum period of 3 years were enrolled in this prospective study. The dosage schedule of these patients was recorded for 3 years. Dosage adjustment was made depending upon the various clinical, biochemical, microscopic and radiological changes during the study period. The dosage schedules (Table 1) were in six categories, namely very high dose chemotherapy (VHDC), high-dose chemotherapy (HDC), moderate-dose prophylaxis (MDP), i.e. low-dose prophylaxis (LDP), very low-dose prophylaxis (VLDP) and intermittent VLDP, wherein the VLDP was given on alternate months and still later at longer intervals. A typical history of a patient with very bad stone history who was administered directed drug dosage protocol for 12 years and continuing a stone free follow-up period is presented as an example of the experience in successful stone prophylaxis using drug dosage modifications, based on clinical, biochemical, microscopical and radiological evidences.

The temporary risk was assessed at each visit and dosage adjustment made. The effect of the intervention was assessed during the next visit based on details given in Table 2.

Results

All the patients involved in the study needed dose adjustment. The following schedules were initiated: VHDC (12) 3.5%, HDC (103) 23.2%, MDP (78) 17.57% or LDP (251) 56.53%. Patients who defaulted for more than a month were excluded from the study. During each visit for follow up, all patients were advised changeover of dose depending upon the clinical situation at the time of review as detailed in Table 2. Patients on VHDC were advised reduction to lower doses systematically. On passage of stones, the dose was immediately reduced to LDP in all situations unless prevented by the presence of significant crystalluria or severe pain. All patients on MDP had reduction of dose to LDP subsequently. Patients started on LDP needed elevation in dose in 63 (16.8%) to HDC and 23 patients (12.87%) to MDP. Dose of 247 patients could be reduced to VLDP (55.63%) and later on to intermittent VLDP 85 (19.14%). 74 (16.7%) patients continued to be on LDP though out the period of study. None of the patients required addition of other medications to control stone disease other than symptomatic treatment for pain. The

Table 1 Different dosage schedules of drugs initially administered to patients based on clinical, biochemical, microscopic, radiological and ultrasound status

No	Name	Allopurinol (mg/day)	Pyridoxine (mg/day)	Number	%	Indication
1	VHDC	600	240	12	3.5	Uncontrolled
2	HDC	300	120	103	23.2	Stone/severe symptoms
3	MDP	200	80	78	17.57	LDP insufficient
4	LDP	100	40	251	56.53	Basic prophylaxis
5	VLDP	50	20	–	–	Maintenance
6	IVLDP	VLDP on alternate months		–	–	Low risk group

VHDC very high dose chemotherapy, *HDC* high dose chemotherapy, *MDP* moderate dose prophylaxis, *LDP* low dose prophylaxis, *VLDP* very low dose prophylaxis, *IVLDP* intermittent VLDP, given on alternate months

Table 2 Follow-up protocol for deciding drug dosage

Unique No: Date:
Name: Age: Sex:
Diagnosis:

Date	On Tt.	Symptom	Score	Treatment	Duration	Post	Decision
	IVLDP	Pain Stone		IVLDP			IVLDP
	VLDP	Pain Colic		VLDP			VLDP
	LDP	Pain Cystalluria		LDP			LDP
	MDP	Haematuria		MDP			MDP
	HDC	Crystalluria		HDC			HDC
	VHDC	Stone – x-ray / USS		VHDC			VHDC
		Total					
	IVLDP	Pain Stone		IVLDP			IVLDP
	VLDP	Pain Colic		VLDP			VLDP
	LDP	Pain Crystalluria		LDP			LDP
	MDP	Haematuria		MDP			MDP
	HDC	Crystalluria		HDC			HDC
	VHDC	Stone – x-ray / USS		VHDC			VHDC
		Total					
	IVLDP	Pain Stone		IVLDP			IVLDP
	VLDP	Pain Colic		VLDP			VLDP
	LDP	Pain Crystalluria		LDP			LDP
	MDP	Haematuria		MDP			MDP
	HDC	Crystalluria		HDC			HDC
	VHDC	Stone – x-ray / USS		VHDC			VHDC
		Total					

details of follow-up were charted in individual graphs for each patient to depict the changes in disease process in relation to adjustment of dose of drugs (Fig. 1). It was noted from the graphs that the severity of symptoms reduced substantially with higher doses of drugs and the low doses could sustain symptom-free periods. In patients who discontinued the drugs, symptoms appeared after varying period of time. The symptoms reduced significantly on increasing the dose of drugs. The pattern of advice given to the patients during the follow up (Table 3) indicates that the dosage schedule was significantly more centred on very low-dose prophylaxis in the later part of the follow-up period. Many patients needed increase in the dosage schedule due to occurrence of symptoms or appearance of blood cells or significant crystals on routine urine examination.

A typical history of a patient who had a very bad stone history and obtained the benefit of long-term directed medical treatment for prophylaxis is presented. A male patient (dob: 1953) presented at age 34 years to the stone clinic in 1987 with a history of having had a pyelolithotomy right side 1 year ago for a partial stag horn stone, which was predominantly calcium oxalate monohydrate (COM). He had a large pelvic stone on the left side, for which pyelolithotomy was done in 1988. Even though medically directed treatment was advised, patient did not consume the drugs as advised and returned with recurrent large stones. He had repeat pyelolithotomy on right side in

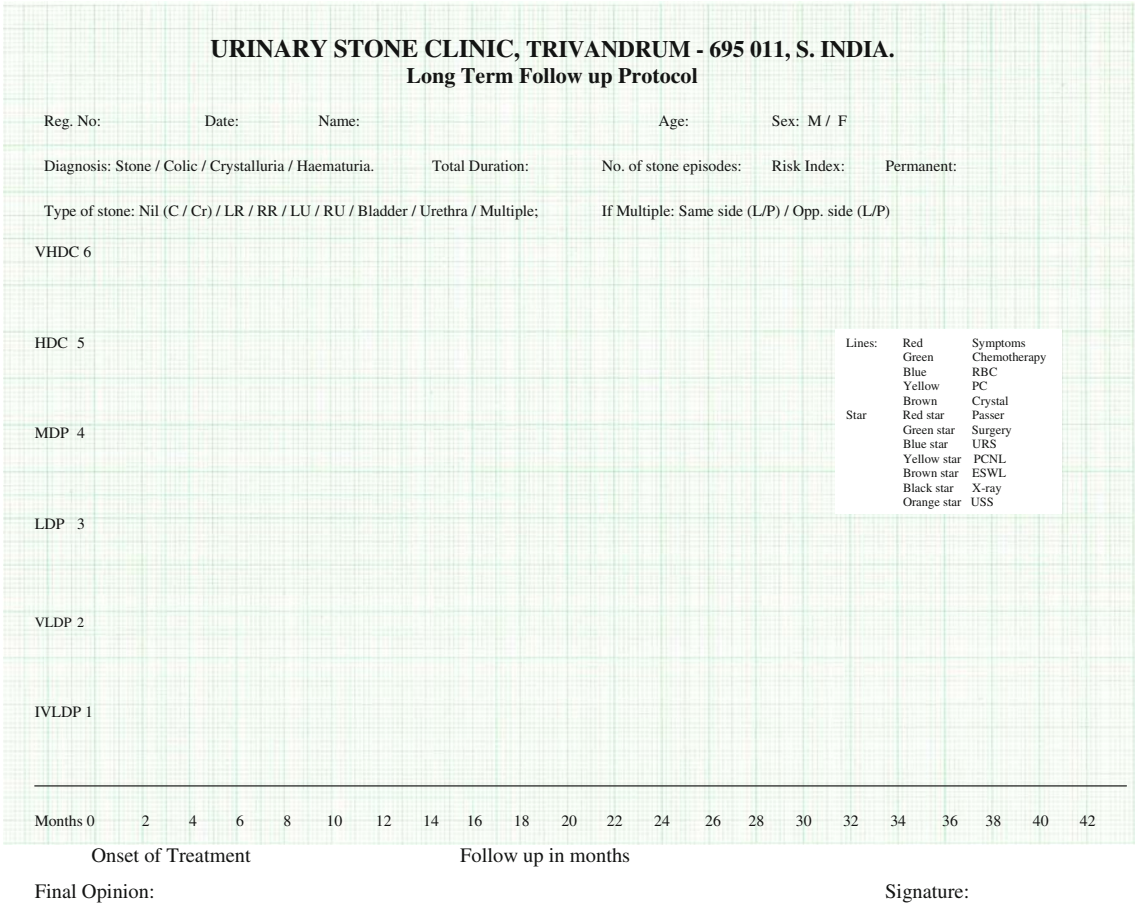

Fig. 1 Graph to record modulated medical therapy and follow-up of stone problem

Table 3 Pattern of dosage of drugs during follow up

No.	Drugs dose	Onset	6	12	18	24	30	36	40
1	VHDC	12	7	3	6	4	6	3	4
2	HDC	103	78	67	45	34	29	31	27
3	MDP	78	34	47	42	36	30	26	36
4	LDP	251	313	291	160	205	307	74	97
5	VLDP	–	12	36	179	123	167	178	163
6	IVLDP	–	–	–	12	35	67	124	117
7.	Nil	–	–	–	–	7	5	8	8
	Total	444	444	444	444	444	444	444	444

1991 and 1996 and pyelolithotomy left side in 1993. All stones were predominantly COM stones. After five surgical retrievals, he settled to "compliant prophylaxis". He was started on HDC in 1996 for clearing residual fragments following the last surgery and later switched on to LDP 3 months and further to VLDP after a year with total symptomatic and microscopic clearance. However, in 2001, he developed symptoms of crystalluria and showed COD crystals and had the dose increased to LDP for 5 months and then reverted to VLDP. In 2003, he developed right ankle pain while on VLDP and showed hyperuricaemia and uric acid crystals in urine. Gout was identified and he was put on HDC. His ankle pain subsided in 6 months, but recurred on reducing the dose to MDP. The patient was maintained on HDC with absolute freedom from joint pain and crystal clearance. After 12 years of unbroken chemoprophylaxis under medical direction, he has been stone free and symptom free. He has had no side effects and is having uninterrupted professional work in the Gulf countries.

Discussion

Various drugs have been advocated for the management of renal and ureteric calculi [1] including sodium citrate, sodium bicarbonate, mixture of sodium and potassium salts, ammonium chloride, ammonium nitrate, sodium biphosphate, sodium phytate, salicylates, salicylamide, *N*Acetyl- *p*-Aminophenol, basic aluminium carbonate gel, aluminium hydroxide gel, alone or in combination with a low phosphorus diet (Shorr regimen), magnesium oxide, magnesium trisilicate, monosodium phosphate, disodium

phosphate, hyaluronidase, vitamin A, pyridoxine, renacidin and D-Pencillamine. Medical expulsive therapy is part of the established therapeutic armamentarium for ureteric calculi alongside observation, shock wave lithotripsy, ureteroscopy, and ureterolithotomy [2].

Many of the medical managements have been centred on smooth muscle relation of the ureteric muscles [3–6]. However, directed medical management has been centred on prevention of stone formation. Some of the recognised therapeutic regimes include thiazides [7] which prevent calcium stones through an effect independent of their diuretic properties by reducing urinary calcium excretion in renal leak hypercalciuria and absorptive hypercalciuria. Allopurinol has proven benefits in reducing calcium stone formation [8]. Dosage is adjusted to maintain a reduced urinary excretion of uric acid and serum uric acid level at or below 6 mg%. Prevention of uric acid stones can also depend on alkalinization of the urine with citrate (in the form of Sholh's solution, sodium bicarbonate, or acetazolamide, a carbonic anhydrase inhibitor).

Various problems are encountered in assessing the role of modulated chemotherapy in stone disease. Every patient is different in the pathophysiology of calculogenesis and in spite of rigid research designs like double-blinded placebo-controlled studies, severe limitations are noted. Several stones would have passed out without treatment. Randomised controlled trials with the patients acting as their own controls will be fool-proof methods for identifying the role of drugs and dosage schedules in urolithiasis. In most of the studies found in literature, the effect of directed medical treatment has been centred on biochemical profiles and need for repeated stone retrieval procedures [9]. Little stress has been placed on the symptoms of the patients and the presence of significant urinary deposits in the patients during follow-up. The present study has attempted to identify the changes produced by appropriate chemotherapy/chemoprophylaxis to help the patient in relieving symptoms and in attaining a crystal free urinary milieu, so that stones do not deposit in their urinary tracts.

Conclusion

It is concluded that in managing the stone patient, the clinical, radiological, microscopic and biochemical parameters should be taken into consideration in deciding the reduction/increase in the dose of drugs. The principle of giving chemotherapy/chemoprophylaxis should be to administer the least number of drugs in the least dosage depending upon the requirement of the disease.

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