A possible role of essential oil terpenes in the management of childhood urolithiasis

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Background: Most treatments for childhood urolithiasis are preventive, and conservative management such as chemical dissolution has its limitations. As a result, open surgery is still required in childhood lithiasis. With lithotripsy, repeated sessions are often required, a uretral stent may be required and the shock wave may damage the renal parenchyma, particularly when nephrocalcinosis is present. Some authors have reported the disappearance of radiological-proven calculi in adult patients in association with the use of nontoxic terpenes, the essential oils contained in the roots, seeds and leaves of various plants. **Patients & methods:** From January 2001 to November 2004, 6 patients (5 males and 1 female) with ultrasonographically proven renal or uretral stones were enrolled in a clinical study investigating the possibility of using terpene oily capsules in the management of childhood urolithiasis. A total of 4 children had hypercalciuria and 2 had hyperoxaluria and distal renal tubular acidosis. Their ages ranged from 10 months to 5 years. They received traditional treatments for the underlying metabolic abnormalities, such as hypocalciuric diuretics for hypercalciuria. **Aim:** To provide children with sonographically proven urolithiasis, a stone-free state by the addition of essential oil capsules of the terpenic type to traditional preventive therapies. They received these therapies for a period ranging from 10 days to 12 weeks. Results: All patients achieved a stone-free state without the occurrence of any adverse effects. **Conclusion:** Terpenes may be of benefit in the management of childhood urolithiasis. A study enrolling a larger number of patients investigating the efficacy of these terpenes in the management of childhood urolithiasis is recommended as the small number of patients in this study preclude a definite conclusion.

Keywords: childhood urolithiasis, essential oil, stone-free state, terpenes

Most therapies for the treatment of childhood urolithiasis are preventive. Chemical dissolution of urinary stones has its limits. Cystine and uric acid stones can be dissolved chemically, while calcium stones, the most common type cannot. Surgery and lithotripsy are still required in childhood urolithiasis [1]. The development of percutaneous endoscopic surgery in 1976 [2], and extracorporeal shock wave lithotripsy (ESWL) in 1980 [3] has revolutionized the surgical management of urinary stones in adults. The lower incidence of urinary stones in children compared with adults, the fear of injury to the developing kidney and the size of instrument designed for adults, have all contributed to a delay in adapting these techniques for children. Furthermore, childhood urolithiasis is generally attributed to metabolic disorders such as hypercalciuria and hyperoxaluria that are associated with recurrence and/or the progression to nephrocalcinosis [4,5]. Surgery and lithotripsy have no effect on these underlying metabolic disorders – neither prevents the recurrence of stone disease nor the progression to nephrocalcinosis. Physicians managing children with stones must be conservative with these new techniques and be able to use a variety of methods to provide the most appropriate therapy for a particular situation [6].

Traditional treatments for children with urolithiasis and underlying metabolic abnormalities include a low sodium diet and anticalciuric diuretics such as thiaziades and amiloride in the case of hypercalciuria [7–9], pyridoxine and medications known to inhibit calcium oxalate aggregation or increase urinary crystallization inhibitors such as magnesium, citrate and phosphate in cases of hyperoxaluria [10–15], and correction of acidosis with alkali in distal renal tubular acidosis (RTA) [16]. Analgesics and antispasmodics are also used when needed [1]. Essential oil preparations of terpenic type, consisting of pinene (31%), camphene (15%), borneol (10%), anethol (4%), fenchone (4%) and cineol (3%), have been reported to have a useful effect in the management of adult urolihiasis [17,18]. Urinex (Pharco Co.) and Rowatinex® (Rowa® Pharmaceuticals Ltd.) are the two essential oil preparations available here, and have the same composition.

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Patients & methods

From January 2001 to November 2004, 6 patients (5 males and 1 female) with ultrasonographically proven renal or uretral stones were enrolled in a clinical study investigating the possibility of using terpene oily capsules in the management of childhood urolithiasis. None of the patients had an immediate indication for surgery such as intractable pain, severe obstruction or persistent urinary infection. Signed consent was obtained from parents/guardians prior to enrollment and the study was approved by the Scientific Committee of the University Hospital in Al-Kadhimiyia (Baghdad, Iraq).

In total, five patients had hypercalciuria, defined as a urinary calcium excretion of greater than 4 mg/kg/day [19,20], and two had hyperoxaluria, defined as urinary oxalate excretion over 3 mg/kg/day and 50 mg/1.73/m^2/day [4,21,22], and distal RTA. The diagnosis of distal RTA was based on the association of nephrocalcinosis, acidosis and hypokalemia. The remaining four patients underwent 24 h urinary examination of calcium, urica and oxalate excretion, cyanide niroprusside and monospot test for cystinuria and serum calcium. Patient age ranged from 10 months to 5 years. All patients received traditional treatments for the underlying metabolic abnormalities.

Aim of the study

The aim of the study was to provide children with sonographically proven urolithiasis, a stone-free state by the addition of essential oil capsules of the terpenic type to traditional preventive therapies. Patients received these therapies for a period ranging from 10 days to 12 weeks.

Patient 1

A male boy with heavy hypercalciuria (24 h urinary calcium excretion: 245 mg, 27 mg/kg/24 h) developed two episodes of renal stones; at the age of 10 months (5 mm right pelvic stone), and again at 15 months of age (3 mm right pelvic stone) as he didn't comply with hypocalciuric diuretics hydrochlorthiaziade and amiloride administered as moduretic (hydrochrothiazide 25 mg, amiloride HCl 2.5 mg) a quarter tablet daily. Both episodes presented with colic, excessive irritability and hematuria. During both episodes, the patient received terpene capsules for 10 days (gelatin oily capsules were divided and their content expressed and administered with sugar). During the first week, antispasmodics were required to control pain.

Patient 2

Patient 2 developed nine episodes of renal stone disease. The first episode, at the age of 18 months (8 mm stone in the left pole of the right kidney), was treated surgically 6 months later without determining the underlying metabolic abnormality as the stone persisted with significant symptoms of colic and hematuria. The only prophylactic measure undertaken after operation was increased fluid intake. The second episode occurred at the age of 3 years and oxalate excretion was above normal in 24 h urinary

excretion test. During the next 3 years, another seven episodes of renal stone disease occurred, with stones ranging from 4–10 mm in diameter. The patient received pyridoxine 100 mg daily in an attempt to reduce oxalate excretion. Citrate prophylaxis was not possible as its administration was refused after only 1 week. Therefore magnesium citrate in alternation with phosphate was administered in replacement. During the sixth episode, 24 h urinary examination revealed both hyperoxaluria (60 mg/24 h, 3 mg/kg/day) and hypercalciuria (189 mg/24 h, 9.45 mg/kg/day). Moduretic half tablet daily was instituted instead pyridoxine which didn't reduce oxalate excretion. During all the stone episodes, the patient received terpene capsules twice daily. Treatment was monitored by renal ultrasound every 2 weeks.

Patient 3

Patient 3, a 6-year old male, presented with renal colic and hematuria. Renal ultrasound showed 1cm stone at the lower third of the left ureter associated with moderate hydroureteronephrosis of the left kidney and normal right kidney. Intravenous urography showed the confirmed these ultrasound findings. A 24 h urinary examination of calcium, uric acid and oxalate revealed hypercalciuria (168 mg/24 h, 6.5 mg/kg/day). He was treated with a moduretic half tablet daily and terpene capsules three times daily.

Patient 4

Patient 4, a 3-year old female, presented with colic of 1 week duration. Renal ultrasound showed an 11mm stone within the left renal pelvis causing fullness of the pelvicalyceal system and was confirmed by x-ray. Results of 24 h urinary calcium excretion were 13.2 mg/kg/day. Serum calcium and urinary excretion of oxalate and uric acid were within normal, establishing the diagnosis of idiopathic hypercalciuria. The patient was treated with hypocalciuric diuretic and terpene capsules three times a day.

Patient 5

A male patient aged 39 months was diagnosed as having hereditary distal RTA at the age of 1 year due to the association of nephrocalcinosis, acidosis hypokalemia and polyuria. Prior to the start of treatment, laboratory investigations showed blood pH 7.26, plasma bicarbonate of 10.6 mmol/l, PCO_2 24.5 mmHg, serum potassium 2.3 mmol/l, serum chloride 110 mmol/l, serum creatinine 0.6 mg/dl, blood urea 20 mg/dl, urine pH 6, urine-specific gravity 1012, urinalysis was otherwise normal. Renal ultrasound showed bilateral nephrocalcinosis (tiny densities, calcifications throughout both kidneys). The patient was treated with alkali and potassium supplementation. Acidosis was corrected and the bicarbonate level was maintained at 18 mmol/l aswell as hypokalemia. The patient presented with colic and haematuria. Renal ultrasound showed a 5 mm stone in the right renal pelvis that was not present in previous ultrasound examinations, while the degree of nephrocalcinosis remained unchanged. The patient received 1 terpene capsule in the morning in addition to the traditional treatment of distal RTA.

Patient 6

A 26-month old boy presented with colic and hematuria of 1 week duration. Renal ultrasound showed an 8mm stone in the right lower pole calyx associated with mild pelvicalyceal dilatation. A 24 h urine examination showed hypercalciuria 124 mg/24 h (12.4 mg/kg/day), normal serum calcium established the diagnosis of idiopathic hypercalciuria. In addition to moduretic half tablet daily, the patient also received essential oil capsules twice daily.

Results

Patient 1

Relief of colic occurred within the first week of therapy during both episodes. Renal ultrasound demonstrated the disappearance of stone in both episodes at 2 weeks after the start of therapy. During the two treatment periods, no undue symptoms were observed apart from mild loosening of stools.

Patient 2

It was possible to achieve a stone-free state in nine stones without the occurrence of any adverse effect (**Table 1**).

Patient 3

After 4 weeks of treatment, patient 3 developed an attack of hematuria followed by a relief of symptoms and renal ultrasound showed no stone. The patient received terpene capsules for an additional 4 weeks which revealed only mild dilatation of the pelvicalyceal system with no stone.

Patient 4

Colic relieved within 2 weeks and the disappearance of the stone was demonstrated after 8 weeks.

Patient 5

Colic disappeared during the first 10 days of treatment and renal ultrasound demonstrated disappearance of the stone after 4 weeks.

Patient 6

Colic relieved within 2 weeks and renal ultrasound demonstrated the emergence of a stone-free state after 12 weeks of therapy.

Discussion

Childhood urolithiasis is generally attributed to metabolic disorders such as hypercalciuria, distal RTA, hyperoxaluria, cystinuria and disorders of purine metabolism [4]. Therefore, the medical treatment of childhood urolithiasis is largely preventive and representing treatments of the underlying metabolic disorders [1,7,8,10–12,16]. Traditional therapies are not always satisfactory and patients with urolithiasis, in particular when associated with hyperoxaluria, progress to nephrocalcinosis and end-stage renal failure despite these preventive therapies [12]. Alkali therapy in distal RTA is associated with less stone formation, whereas nephrolithisis and nephrocalcinosis tend to persist [16]. In the 1930s, the essential oil preparation Enatin was first introduced for the treatment of nephrolithiasis as it was thought that these terpenes increased urine stability by increasing urine glucouronides as they are excreted by the kidneys in conjunction with glucuronic acid [17]. Currently two essential oil preparations are available, urinex and rowatinex, and have been registered for use in approximately 50 countries including UK and other developed countries such as Italy and Japan. The use of these preparations has not been reported in patients under the age of 6 years. Childhood urolithiasis differs from adult urolithiasis by the frequent association with underlying metabolic disorders and the tendency for recurrence and progression to nephrocalcinosis. In addition, medical authorities still consider the use of these preparations in adult urolithasis as being of an unproven value [24]. This author has found that

Table 1. Summary of the results of this paper.

	Size & site of stone	Associated features	Duration of terpenes therapy – achieved stone-free state
Patient 1			
	1–5mm, right pelvic stone	Colic & hematuria	2 weeks
	2–3mm, right pelvic stone	Colic hematuria	2 weeks
Patient 2			
	1–6.9mm, Right pelvic stone	Colic and hematuria	10 weeks
	2–6 mm, right middle calyx	Colic & microscopic hematuria	8 weeks
	3–8mm, middle portion of right kidney	Asymptomatic, microscopic hematuria	6 weeks
	4–10 mm, middle calyx of right kidney	Painless hematuria	3 weeks
	5–4 mm, lower pole of right kidney	Asymptomatic	2 weeks
	6–5 mm, lower calyx of right kidney	Asymptomatic	3 weeks
	7–Right kidney: 9 mm middle pole calyx	Asymptomatic	6 weeks
	Left kidney: 4 mm Lower calyx	Asymptomatic	2 weeks
Patient 3			
	10 mm left lower urethral stone	Colic & hematuria	4 weeks
Patient 4			
	11 mm left pelvic stone	Colic	8 weeks
Patient 5			
	5 mm stone in the right renal pelvis	Colic & hematuria	4 weeks
Patient 6			
	8 mm in the right lower pole calyx	Colic & hematuria	8 weeks

the earlier reputable animal studies investigating the efficacy and toxicity of these terpenes provide a better scientific background to this study. The most important animal experiments are the investigations of Geintiz and Stern & Vukcevic [25]. These experiments demonstrated that stone formation regularly brought on by feeding rats a massively dosed stone-forming diet is inhibited by the simultaneous administration of terpene preparations. While nephrocalcinosis developed in most control animals, it was much less frequent and pronounced than in the terpene group. This inhibitory effect was attributed to terpene-induced renal hyperemia as the protected animals presented a distinctly better renal blood flow than the controls, which had very pale kidneys.

A toxicologic study has been carried out by Bauer who, in tests on 15 cats, found that even after 8 weeks feeding with terpenes at 100 to 400 times the therapeutic dosages there were no clinical, hematological, or nephrologic toxicity [25,26]. In fact, since it was first introduced into clinical practice in the 1930s, there has been no single report of the occurrence of any adverse effect in association with their use in humans. The latest randomized double blind study [18] evaluated the usefulness of essential oil terpenes in the treatment of adult patients with urolithiasis did not address the underlying scientific basis behind the use of terpenes. In addition, this study showed that terpenes improved the rate of stone expulsion and or disappearance of dilatation.

The management of adult urolithiasis has been fundamentally changed by the introduction of ESWL. This method is associated with residual stone fragments and in 50% of cases, ESWL has to be repeated within a year due to the same stone. Residual stone fragments may reaggregate, or act as the nuclei of new stones. Reformation of stones is favored by the fact that lithotripsy does not eliminate the metabolic disorder that's responsible for calculus formation in the first instance [27–30].

Expert opinion

In this study, it was possible to achieve a stone-free state in 14 stones occurring in 6 children with an underlying metabolic abnormality by the use of a novel therapeutic strategy combining the traditional preventive therapy and essential oils of the terpenic type without the occurrence of any adverse effect. The stones ranged in size from 3–11 mm in size. Spontaneous passage of urinary stones up to 6mm in diameter can be expected in 8–50% of children [31]. However, the sizes of six stones were 8 mm or larger in diameter in our study.

Out look

This study may provide preliminary evidence that essential oils could have a beneficial role in the treatment of childhood urolithiasis. However, the complexity of childhood urolithiasis, the small number of patients available and the fact that the mechanism of action of these terpenes is far from clear, precluded the formulation of a definitive conclusion.

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