Volume 9 Issue 12 December 2010 ISSN 1569-9056

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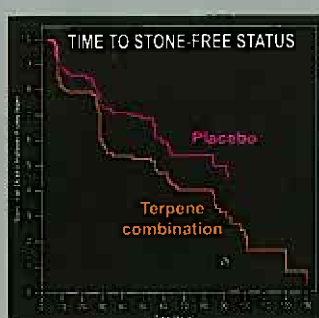

Terpenes in Urolithiasis

Proceedings of the ROWA Symposium
Düsseldorf, Germany, September 2010

Guest Editor:
Thomas Knoll, Sindelfingen, Germany

Cover images, from left to right:

Survival distribution functions of the intent-to-treat population; time to stone-free status. Magenta line: placebo; orange line: the terpene combination group (log-rank-test; $p = 0.0061$).
See article *Improving Stone Clearance After Extracorporeal Shock Wave Lithotripsy in Urolithiasis Patients by a Special Terpene Combination (Rowatinex®): Results of a Placebo-Controlled, Randomized Trial* in this supplement.

Kidney stone crystals, coloured scanning electron micrograph.

Microcalcifications on renal papilla that are thought to be precursors of calcium oxalate stones (Randall plaques).
See article *Epidemiology, Pathogenesis and Pathophysiology of Urolithiasis* in this supplement.

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Official Journal of the
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Abstracted/indexed in: ADONIS, BIOBASE, Current Awareness in Biological Sciences, EMBASE, Medical Documentation Service, Research Alert, Science Citation Index, Scisearch, SCOPUS, SIIC Data Bases, Uroline

Printed by Henry Ling Ltd, Dorchester, Dorset, UK

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The papers in this supplement were peer reviewed by two independent reviewers.
Provided with an unrestricted educational grant from ROWA Germany and Ireland.

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Editorial

Introduction: Symposium on "Terpenes in Urolithiasis," Düsseldorf, Germany, September 2010

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Urolithiasis shows a worldwide increasing prevalence and incidence [1]. Consequently, urinary stone disease has a significant medical and economic impact. Extracorporeal shock wave lithotripsy (ESWL) remains the recommended first-line treatment for most stones [2]. However, after disintegration is achieved, the fragments have to pass the upper urinary tract for complete clearance. Such fragments may cause renal colic or remain within the renal collecting system as residual stones, limiting the overall success of ESWL [3].

Several medical attempts have been evaluated in recent years to improve spontaneous stone passage, with the most promising data for α-adrenoreceptor antagonists such as tamsulosin (medical expulsive therapy [MET]). The American Urological Association/European Association of Urology working group for ureteral calculi recommends the use of MET for uncomplicated, well-controlled calculi of <10 mm in size [4]. Rowatinex, a terpene mixture, is well known for treatment of urinary stone-related symptoms all over the world. Recently, a randomized controlled trial (RCT) demonstrated a beneficial effect of Rowatinex application on stone passage after ESWL. This approach could offer patients the interesting therapeutic option of an herbal, well-tolerated treatment.

This supplement summarizes the contributions made at a symposium held in Düsseldorf, Germany, on September 21, 2010, by European urologists with particular experience and expertise in the field of urolithiasis, including Professor Romics, who performed the RCT on Rowatinex. The objective of the meeting was to achieve a state-of-the-art overview of urinary stone disease and noninterventional treatment modalities.

After an overview on epidemiology and pathophysiology of urinary stone disease by Professor Knoll (Sindelfingen, Germany), in his capacity as a meeting chairman, Dr. Bach (Hamburg, Germany) reported the available data for Rowatinex and the supposed principles of action. Dr. Seitz (Vienna, Austria) presented the current evidence supporting the application of medical expulsive therapies including data from recent meta-analyses. Professor Romics (Budapest, Hungary) presented the clinical data from his RCT on Rowatinex treatment after ESWL.

Conflicts of interest: In recent years, the authors have received consultancy or lecturer honoraria from Rowa Pharmaceuticals.

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1569-9056/$ – see front matter doi:10.1016/j.eursup.2010.11.005

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Epidemiology, Pathogenesis, and Pathophysiology of Urolithiasis

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Article info

Keywords:
Epidemiology
Pathogenesis
Urolithiasis
Calcium oxalate stones

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Abstract

Context: Urolithiasis (UL) is one of the most common diseases, with worldwide increasing incidence and prevalence. The pathogenesis of calcium oxalate (CaOx) UL, which accounts for >80% of all urinary stones, is only incompletely understood.
Objective: Our aim was to review trends in epidemiology and current concepts for the pathogenesis and pathophysiology of urinary stone disease.
Evidence acquisition: We reviewed data from the literature and our own series.
Evidence synthesis: Urinary stone formation is a result of different mechanisms. Completely different pathomechanisms lead to CaOx stone formation, with Randall plaques playing a key role in the pathogenesis.
Conclusions: The lithogenesis of key stones is multifactorial. Lifestyle and dietary choices are important contributing factors. The pathogenesis and pathophysiology of CaOx stones is still incompletely understood. Recent evidence suggests a primary interstitial apatite crystal formation that secondarily leads to CaOx stone formation.

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1. Introduction

Urolithiasis (UL) is one of the most common diseases, with approximately 750 000 cases per year in Germany [1]. Although most patients have only one stone episode, 25% of patients experience recurrent stone formation [2]. UL therefore has a significant impact on quality of life and socioeconomic factors [3]. The pathogenesis of calcium oxalate (CaOx) UL, which accounts for >80% of all stones, is only incompletely understood. This paper reviews trends in epidemiology and current concepts regarding the pathogenesis and pathophysiology of urinary stone disease.

2. Evidence acquisition

Urinary stone formation is a common disease with an increasing incidence and prevalence worldwide that appears even more pronounced in industrialized countries [2,4–10]. Such observations seem to underscore the impact of lifestyle and dietary choices as well as access to better medical care for urinary stone formation.

Renal stone formation and the predominant chemical stone composition are age and gender dependent [11]. Most stones are formed in older patients. However, clinical observations have indicated not only a changing frequency and composition of urinary calculi but also a shift in gender- and age-related incidences [11–13]. Urinary stone disease remains rare in children with a stable overall incidence in most series [14]. As in adults, factors implicated in the metabolic syndrome complex such as obesity pose risks for urinary stone formation in children [15].

Although some authors have suggested the impact of climate change [16,17], changing lifestyle and dietary choices are the more probable cause of the increasing incidence and prevalence of UL. Taylor and Curhan demonstrated a correlation of body weight and urinary calcium excretion [18]. In two large epidemiologic series, they also reported

diabetes as an independent risk factor for the development of kidney stones [4,19,20]. Siener confirmed such findings in studies on recurrent stone formers [21]. Changing chemical stone compositions have been reported, possibly as results of the described changes of lifestyle [22,23].

Calcium-containing calculi are predominant in males and females [11,24,25]. However, UL remains a disease with a clear predominance in males for all stone compositions except for infection stones. In our own series, including >200 000 stone analyses, this difference increased over the observation period with a 2.7:1 male-to-female ratio for the most common calcium-containing calculi [26]. Daudon et al showed a male predominance for CaOx and uric acid, and a female predominance for calcium phosphate (CaPh) and struvite stones [11]. Approximately 15% of all stone formers produce CaPh stones [27]. Up to a quarter of those CaPh stones contain calcium monohydrogen phosphate (brushite), which is difficult both to treat and to prevent [28]. Our own series demonstrated an increased prevalence of brushite [26] (Fig. 1).

Currently, uric acid composition seems to be the second most common stone in both genders. Daudon et al reported a significant increase in uric acid stone frequency, whereas in our own series the rate remained stable [11,26].

Stones due to infection have clearly declined over the years, attributable to improved medical care. Trinchieri et al reported a 15-yr series from Italy of stone analyses with a low number of infection stones [29]. Marickar and Vijay reported a decrease of infection stones in females despite an overall increase of urinary stone formation [7]. The decreasing number of staghorn stones in Europe supports this observation because urinary tract infections are the most common cause of such large renal calculi [30].

Cystine stones, formed by patients with cystinuria, account for only a small percentage of all urinary stones [26]. The higher peak in younger ages is in accordance with the first stone event, which typically occurs in the 2nd decade of life, whereas the lower frequency at older ages may be a result of preventive measures [31].

Interestingly, our German series demonstrated significant regional differences [26]. Although calculi containing uric acid were more prevalent in southern Germany, we observed a significantly higher frequency of stones due to infection in eastern Germany. We can only hypothesize an explanation for these findings. A diet based more heavily on red meat may explain the higher rate of uric acid calculi in southern Germany. The higher frequency of infection stones in the eastern part of the country (formerly the socialist German Democratic Republic) is surprising and cannot be adequately explained. However, this finding suggests that differences in medical care do exist.

3. Evidence synthesis

3.1. Pathogenesis and pathophysiology

Urinary stone formation is a result of different mechanisms. Whereas exceeding supersaturation (ie, free stone formation) is the cause of uric acid or cystine calculi, infection stones result from bacterial metabolism [32]. The formation of the most common fraction, the calcium-containing calculi, is more complex and, surprisingly, is not yet completely understood. Recent evidence suggests that both free and fixed stone formation is possible [33]. The long accepted simple explanation of exceeding the solubility product of lithogenic substances in the urine cannot describe these

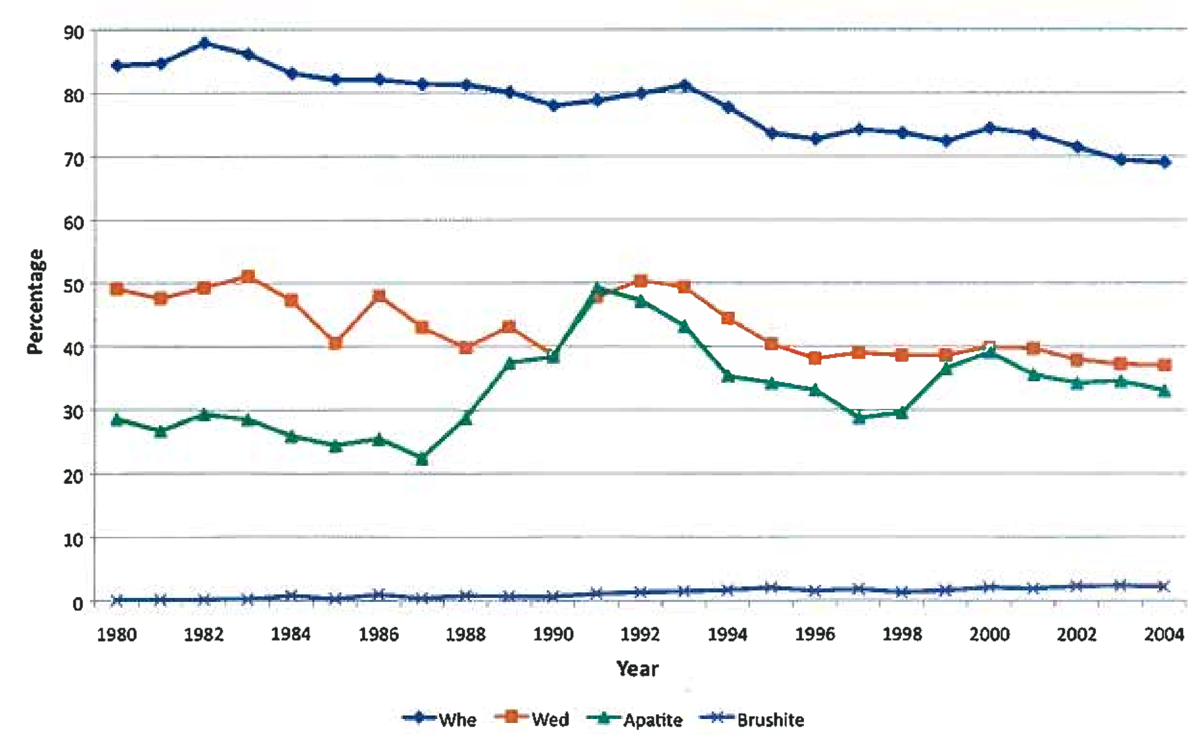

Fig. 1 – Frequency of hydroxyapatite, brushite, and calcium oxalate components in urinary stones, 1980–2004 (*n* = 111 196).

Fig. 2 – Microcalcifications on renal papilla are thought to be precursors of calcium oxalate stones (Randall plaques).

complex processes sufficiently [33]. Deviating from the hypothesis that claims the initial crystal deposition takes place in the lumens of renal tubules [34–36], new insights suggest a primary plaque formation in the interstitial space of the renal papilla [37,38]. CaPh crystals and organic matrix initially are deposited along the basement membranes of the thin loops of Henle and extend further into the interstitial space to the urothelium, constituting the so-called Randall plaques, which are regularly found during endoscopy of patients who form CaOx stones (Fig. 2). These CaPh crystals seem to be the origin for the development of future CaOx stones, which form by the attachment of further matrix molecules and CaOx from the urine to the plaque [39]. The driving forces, the exact pathogenetic mechanisms, and the involved matrix molecules are still largely unknown. Completely different pathomechanisms obviously lead to the common clinical diagnosis of "CaOx stone former."

Stoller et al raised another interesting hypothesis. They suggested an even closer participation of the vasa recta in the lithogenesis of kidney stones [40]. The descending and ascending vasa recta are vulnerable because of the hypoxic and hyperosmolar environment in the papillary tip and because the blood flow in the papillary tip changes from a laminar to a turbulent flow as the ascending vasa recta repeatedly bifurcates [41]. They proposed this could lead to atherosclerotic-like lesions and calcifications in the wall of the vasa recta. These calcifications could then erode to papillary interstitium and grow there, supported by cellular promotors [42]. The close participation of the vasa recta has led to a new hypothesis regarding the role of vascular phenomena in the lithogenesis of kidney stones.

3.2. Key role of Randall plaques

Randall plaques are thought to be involved in idiopathic CaOx stone formation. Seventy years ago, Randall described calcifications within the renal papilla that he found in 20% of autopsies [43]. These calcifications were made of CaPh (apatite). Randall proposed that the plaques are precursors of urinary stones. His idea was lost for decades until Evan et al were able to show that such plaques are present in all idiopathic CaOx stone formers but not in healthy controls [38,44,45]. When attached stones were removed from the renal papilla, they had the impression that the plaques were the connection of the stones to the papilla. Microscopic computed tomography examinations of CaOx stones confirmed this hypothesis by demonstrating the presence of apatite at the former attachment side [46]. Matlaga et al demonstrated a positive correlation of the frequency of stone recurrences and the total papillary surface covered by plaques [45]. Scanning microscopy of these plaques confirmed that the initial site of crystal deposit is within the base membrane of the thin loop of Henle, as hypothesized by Evan et al [38,47]. Intratubular crystallization was not found within the renal tubules or collecting ducts in idiopathic CaOx stone formers.

Although the site of stone formation has become clear, the initial trigger for crystallization remains under discussion. A multifactorial process seems to be the most probable. An increased urinary calcium excretion appears to play an important role because the measured papillary coverage correlates with urinary calcium and urine pH [48]. Earlier examinations showed higher calcium and oxalate concentrations within the renal papilla than within the renal cortex, medulla, or urine [49]. An acidic urinary pH leads to an increased bicarbonate resorption into the renal medulla and a consecutive increasing interstitial pH that may promote apatite depletion [45].

Recent findings have helped us understand the mechanism of CaOx stone formation on the Randall plaques (which are separated from the urine by the urothelial layer) [47,50]. Stones derived from biopsies of renal papillae were evaluated by immunohistochemistry, scanning microscopy, and infrared spectroscopy. These examinations demonstrated that the urothelium was lost at the attachment side. Organic matrix (mainly Tamm-Horsfall protein and osteopontin) and crystals formed belts that are obviously required to allow further crystal depletion and consequently CaOx stone formation.

4. Conclusions

UL is a common disease with an increasing incidence and prevalence worldwide. Lifestyle and dietary choices implicated in the complex of the metabolic syndrome are important factors contributing to such developments. The pathogenesis and pathophysiology of CaOx stones, the most common urinary stones, is still incompletely understood. Recent evidence suggests a primary interstitial apatite crystal formation (Randall plaque) that secondarily leads to CaOx stone formation.

Conflicts of interest

In recent years, the author has received consultancy or lecturer honoraria from Rowa Pharmaceuticals.

Funding support

None.

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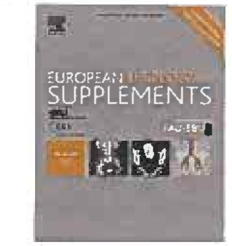

Medical Expulsive Therapy of Ureteral Calculi and Supportive Therapy After Extracorporeal Shock Wave Lithotripsy

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Article info

Keywords:
Expulsive therapy
Medical treatment
Shock wave lithotripsy
Urolithiasis

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Abstract

Context: Medical expulsive therapy (MET) augments expulsion rates and reduces colic events. Therefore, MET is an appropriate procedure to facilitate stone passage during the observation period in patients who have a newly diagnosed ureteral stone and whose symptoms are controlled. Increasing evidence indicates that supportive therapy following shock wave lithotripsy (SWL) for urolithiasis is also effective.
Objective: Our aim was to summarize the literature on MET in the treatment of urolithiasis.
Evidence acquisition: This paper is based on a presentation given at the symposium "Terpenes in Urolithiasis" that was held in Düsseldorf, Germany, in 2010.
Evidence synthesis: MET with α-blockade and calcium channel blockade resulted in accelerated and higher expulsion rates compared with a control group. Higher expulsion rates were demonstrated for the entire ureter, although the vast majority of studies only included distally located stones. MET showed favorable results for renal stones after extracorporeal SWL. The number of necessary analgesic rescue medications, colic episodes, and hospital admissions during treatment periods was reduced.
Conclusions: MET facilitates ureteral stone passage during the observation period in patients who have a newly diagnosed ureteral stone <10 mm and whose symptoms are controlled. In patients harboring renal stones undergoing SWL, stone expulsion is augmented as well. Large-scale placebo-controlled randomized trials and the investigation of promising new substances are still needed to better define the future role of MET.

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1. Introduction

Stone size, location, and symptom duration are the most important parameters to predict spontaneous stone expulsion in addition to patient-dependent factors such as pain tolerance and the development of infection that determine the need for active stone removal or decompression of the renal collecting system [1–3]. Miller and Kane reported the time to spontaneous stone passage of stones ≤2 mm, 2–4 mm, and 4–6 mm was an average of 8.2, 12.2, and 22.1 d, respectively, and 95% of those that passed did so by 31, 40, and 39 d, respectively [2]. A meta-analysis of studies in which spontaneous ureteral stone passage was assessed reported a median probability of stone passage of 68% for stones <5 mm ($n = 224$) and 47% for those >5 mm and <10 mm ($n = 104$) [4]. These studies had certain

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limitations including nonstandardization of the stone size measurement methods and lack of analysis of stone position, stone-passage history, and time to stone passage. According to the European Association of Urology guidelines, observation as initial treatment is an option for patients with controlled symptoms harboring ureteral stones <10 mm.

2. Evidence acquisition

2.1. Ureteral pathophysiology

An increase of cytoplasmatic free calcium concentration is one principal mechanism initiating ureteral contraction. It was demonstrated that calcium channel inhibitors counteract the phasic-rhythmic activity in isolated human caliceal segments [5] and in the ureter [6]. Endogenous prostaglandin synthesis and calcium influx induce spontaneous rhythmic contractions of the human ureter, which are inhibited by the calcium channel blockers nifedipine and verapamil [7]. This negative effect on ureteral contractility has evoked interest in using calcium channel blockers to facilitate medical-induced stone passage.

Three different subtypes of adrenergic receptors (ARs) have been pharmacologically identified: α_{1A}, α_{1B}, and α_{1D} [8]. A heterogeneous distribution of α_1 AR binding sites was detected, with the highest density in the distal ureter [9]. The distribution of ARs throughout the inner and outer smooth muscle of the ureter was highest for α_{1D}, especially in the distal ureter, followed by α_{1A} and α_{1B} ARs [10]. Of interest, heterodimers α_{1B}/α_{1A} and α_{1B}/α_{1D} do occur, whereas α_{1A}/α_{1D} ARs do not heterodimerize, suggesting a possible regulatory role of α_{1B} [11]. This ability to oligodimerize could influence future drug development.

The exact pathophysiology of ureteral colic and stone passage is not completely understood. A ureteral stone tends to induce a ureteral inflammatory response by ureteral stone obstruction and ureteral wall tension stimulating prostaglandin synthesis. Prostaglandins have a dilating effect on afferent arterioles resulting in an increased renal blood flow, further increasing ureteropelvic pressure, inflammation, and edema [12]. A subsequent increase of smooth muscle contraction impairs propulsive antegrade peristalsis aggravating ureteral obstruction, impaction, and pain [13,14]. Therefore the ideal agent to facilitate stone expulsion would reduce ureteral inflammation, edema, ureteral spasm, and uncoordinated ureteral contractions without altering propulsive peristalsis.

2.2. Medical expulsive therapy

A rational approach to expulsion therapy would be to increase peristaltic activity with high fluid intake increasing the volume transported through the ureter and thereby augmenting the hydrostatic pressure above the stone. In cases of obstruction, a high diuresis is likely to counteract the passage of the stone and to cause more pain. A systematic review evaluating the effect of fluids and diuretics found no credible evidence supporting a diuretic approach in terms of pain relief and stone expulsion [15]. A recent randomized comparison between high and normal diuresis during the primary session of shock wave lithotripsy (SWL) for removal of ureteral stones did not demonstrate a beneficial effect [16].

An improved understanding of ureteral physiology has led to an anti-inflammatory and antiedematous treatment by nonsteroidal anti-inflammatory drugs (NSAIDs), decreasing agonist-induced contractions in pig ureters [17]. Cyclooxygenase (COX)-2 inhibitors were able to inhibit prostanoid release and ureteral contractility [18]. NSAIDs have proved effective by inhibiting prostanoid synthesis and reducing vasodilatation with subsequent reduction of inflammation, glomerular filtration rate, and intrarenal pressure [12]. However, stone expulsion rates were not affected in double-blind placebo-controlled trials [19,20].

Terpenes were reported to have diuretic anti-inflammatory analgesic and spasmolytic properties. Among the reported properties the anti-inflammatory effect is achieved by the suppression of arachidonic acid metabolism and cytokine production [21]. In a prospective randomized placebo-controlled single-blind trial for prostatitis/chronic pelvic pain syndrome, Rowatinex demonstrated more improvement in the numerical value for pain score than ibuprofen [21]. Rowatinex was reported in recent randomized controlled trials (RCTs) to accelerate stone-free rates and reduce symptoms during stone passage in patients undergoing SWL for renal stones. No significant adverse events leading to discontinuation of the drug were reported [22]. Rowatinex will continue to be evaluated in the medical treatment of upper urinary stone disease.

Another potent analgesic and antipyretic drug that has been proposed to inhibit COX enzyme activity is dipyrone. Studies in animal and human ureters demonstrated a significant reduction of renal pelvic pressure with dipyrone and the NSAID indomethacin that alleviated colic pain [23]. Holmlund and Sjödin had already shown the effect of indomethacin in 1978 [24]. However, so far no study has reported an accelerated stone expulsion.

Antimuscarinics might relax genitourinary smooth muscle and thus reduce colic pain [25]. However, a randomized placebo-controlled trial determining whether N-butylscopolamine (Buscopan) reduces the amount of opioid analgesia required in renal colic showed no favorable effect [26]. N-butylscopolamine failed to reduce renal pelvic pressure significantly [23] and was less effective than dipyrone. The addition of spasmolytic agents (eg, hyoscine) to dipyrone did not improve its analgesic efficacy [27]. Those regimens have failed so far to demonstrate an increase in stone expulsion rates, but it might be interesting to explore the effects further in randomized studies.

Phosphodiesterases (PDEs) regulate intracellular cyclic nucleotide turnover influencing smooth muscle tension. Kühn et al found relaxing effects on potassium chloride–induced tension of ureteral smooth muscle by PDE4 and PDE5 inhibitors in vitro [28]. Gratzke et al demonstrated the ureteral smooth muscle relaxing effects of different PDE5 inhibitors in vitro. Results were similar to those reported for tamsulosin, suggesting the potential of using PDE inhibitors in the treatment of ureteral colic [29]. Another drug that

interferes with the PDE enzyme is papaverine, which results in an increase of adenosine monophosphate that causes ureteral smooth muscle relaxation. Its analgesic potential is similar to that of pethidine and diclofenac, and its superiority to hyoscine butylbromide was demonstrated in recent randomized trials [30,31]. Further studies are necessary to assess their potential role in expulsion therapy.

Corticosteroids have been reported to facilitate stone expulsion [32,33]. However, publications in peer-reviewed journals are necessary. So far no further evidence has confirmed whether corticosteroids alone are capable of facilitating stone expulsion.

α-Adrenoreceptor antagonists (α-blockers) inhibit contractions of ureteral musculature, reduce the basal tone, and decrease peristaltic frequency and colic pain facilitating ureteral stone expulsion. Davenport et al found a beneficial effect of both nifedipine and 5-methylurapidil on human ureteric activity with a median reduction in proximal versus distal ureteral tone of 47% versus 57% and 33% versus 65%, respectively [34]. These data suggest a beneficial effect for MET further supported by a pilot study investigating the in vivo effect of nifedipine and tamsulosin on ureteral contraction frequency, pressure, and velocity using a ureteric pressure transducer in humans. Both drugs allowed peristalsis to continue, which is important for successful stone expulsion [35].

3. Evidence synthesis

A recent meta-analysis offered evidence for an overall increased stone expulsion rate and reduced time to stone expulsion using an α-blocker or calcium channel blocker compared with a standard therapy or placebo control group (Fig. 1) [36]. A class effect for α-blockers was suggested after similar expulsion rates for tamsulosin, terazosin, and doxazosin were observed [37]. Similar results were obtained using terazosin, doxazosin, and the α_1-blocker naftopidil, further confirming the concept of a class effect [38–43]. Only one alfuzosin trial reported an inferior numerical outcome for the treatment group [44]. However, the time to stone

	Favours: Alpha-Blockade		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Autorino 2005	28	32	19	32	3.6%	1.47 [1.08, 2.02]
Avdoshin 2005	31	42	11	45	1.7%	3.02 [1.75, 5.20]
Ayubov 2007*	28	30	19	31	3.9%	1.52 [1.13, 2.05]
Cervenakov 2002	41	51	32	53	4.6%	1.33 [1.03, 1.72]
De Sio 2006	45	50	27	46	4.5%	1.53 [1.18, 1.99]
Dellabella 2003	30	30	21	30	4.9%	1.42 [1.12, 1.80]
Dellabella 2005	68	70	45	70	6.2%	1.51 [1.26, 1.81]
Erturhan 2007	43	60	26	60	3.4%	1.65 [1.19, 2.30]
Han 2006	29	35	17	32	3.1%	1.56 [1.09, 2.23]
Hong 2008*	119	138	27	42	5.0%	1.34 [1.06, 1.70]
Keshvary 2006	18	20	11	24	2.2%	1.96 [1.24, 3.11]
Kim 2006*	29	35	17	32	3.1%	1.56 [1.09, 2.23]
Kupeli 2004	8	15	3	15	0.5%	2.67 [0.87, 8.15]
Liatsikos 2007	33	42	16	31	2.9%	1.52 [1.05, 2.22]
Lojanapiwat 2008	27	50	1	25	0.2%	13.50 [1.95, 93.69]
Mohseni 2006	29	32	20	32	4.0%	1.45 [1.08, 1.94]
Mukhtarov 2007*	24	27	18	25	4.2%	1.23 [0.93, 1.63]
Pedro 2007	25	34	27	35	4.3%	0.95 [0.73, 1.25]
Perron 2008 $	27	38	24	39	3.6%	1.15 [0.84, 1.59]
Porpiglia 2004	24	28	12	28	2.2%	2.00 [1.27, 3.15]
Porpiglia 2006	46	66	23	48	3.4%	1.45 [1.04, 2.03]
Porpiglia 2008*	37	46	22	45	3.4%	1.65 [1.18, 2.29]
Resim 2005	26	30	22	30	4.6%	1.18 [0.91, 1.53]
Sayed 2008	40	45	23	45	3.8%	1.74 [1.28, 2.36]
Tekin 2004*	28	36	18	39	2.9%	1.69 [1.15, 2.47]
Ukhal 1999*	26	35	14	30	2.4%	1.59 [1.04, 2.45]
Vincendeau 2008*	47	66	43	63	5.1%	1.04 [0.83, 1.31]
Wang CJ 2008	51	64	17	31	3.3%	1.45 [1.03, 2.05]
Yilmaz 2005	67	86	15	28	3.1%	1.45 [1.01, 2.09]
Total (95% CI)		**1333**		**1086**	**100.0%**	**1.45 [1.34, 1.57]**
Total events	1074		590			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 46.99$, df = 28 (P = 0.01); $I^2 = 40\%$

Test for overall effect: Z = 9.40 (P < 0.00001)

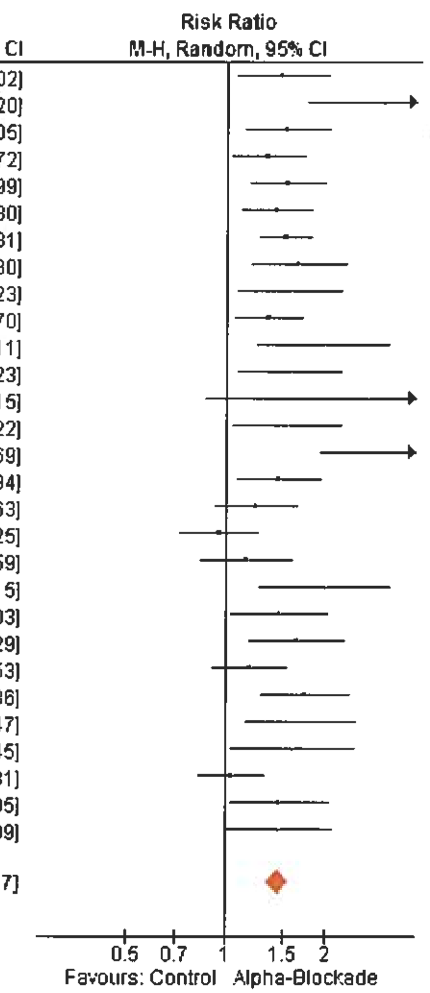

Fig. 1 – Forest plot of comparison: α-blockade versus control; outcome: stone free. Risk ratios (RRs) in each square with area proportional to the number of events comparing outcome in patients allocated to an α-blocker group with outcome in patients allocated to a control group, along with 95% confidence intervals (CIs) as the horizontal line. Overall RRs and CIs are plotted as a diamond. A square or diamond to the right of the vertical line of no effect indicates a benefit with α-blockers. This benefit is significant ($p < 0.05$) only if the horizontal line or diamond does not overlap the vertical line. Adapted from Seitz et al. [36].
M-H = Mantel-Haenszel test.

expulsions and pain scores were significantly in favor of the treatment group.

3.1. *Stone size and medical expulsion therapy*

Due to the high likelihood of spontaneous passage for stones up to about 4 mm, one would expect that the efficacy for medical expulsion therapy (MET) would decrease because of the high spontaneous expulsion rate.

Of interest, three high-quality double-blinded RCTs failed to demonstrate a significant higher expulsion rate for MET using alfuzosin or tamsulosin [44–46]. In addition to a possible lower effectiveness of alfuzosin, a small mean stone size of 3.8 mm could have accounted for high spontaneous stone passage rates leading to an underestimation of alfuzosin in promoting stone passage [44]. The same applies for the study of Vincendeau et al including distal ureteral stones with a mean stone size of 2.9 mm and 3.2 mm for the treatment and control groups, respectively [45]. In the study from Hermanns et al. [46], 76% and 84% of the patients in the tamsulosin and control groups harbored distal ureteral stones <5 mm. Tamsulosin did not improve expulsion rates in stones >5 mm (Table 1). However, as the authors stated, the study was not powered for this subgroup analysis [46]. Although the limited numbers of patients might account for the undetectable significant differences in the treatment of smaller stones, results might as well indicate that with decreasing stone size an additional benefit for MET is less likely owing to the high spontaneous expulsion rate. Nevertheless, a numerically accelerated expulsion rate and significant analgesic effect within the treatment group was observed [46]. Similarly, Ferre et al failed to demonstrate a significant higher expulsion rate in the tamsulosin group. Again, mean stone size was 3.6 mm [47]. However, the "ideal" stone size for MET is not known. It is reasonable to assume that the stone expulsion rate of MET will be greatest somewhere between 4 and 10 mm.

3.2. *Tamsulosin versus nifedipine in medical expulsion therapy*

Three studies compared the efficacy of tamsulosin compared with nifedipine for distal ureteral stones [48–50]. Keshvary et al found no statistical difference in expulsion rates between tamsulosin and nifedipine [48]. Porpiglia et al evaluated the effectiveness of tamsulosin versus nifedipine in combination with deflazacort for stones <10 mm. Expulsion rates and expulsion time were in favor of the tamsulosin group, although differences were not significant [49]. Dellabella et al compared the efficacy of tamsulosin and nifedipine in combination with deflazacort for stones >4 mm and found a significantly higher expulsion rate ($p = 0.001$) and shorter expulsion time ($p < 0.0001$) in the tamsulosin group, although stones in the tamsulosin group were significantly larger (7.2 vs 6.2 mm). Notably, stone size and expulsion time did not correlate, a finding that might be attributable to the concomitant administration of a corticosteroid [50]. Hospitalizations, loss of workdays, auxiliary measures, and the amount of rescue medication were significantly in favor of the tamsulosin group.

Table 1 – Efficacy and safety data from recent randomized controlled trials at different formulations for medical expulsive therapy

Reference	Blinded	Power calculated	Analgesic therapy	Treatment vs control	Expulsion rate/Sample size (%)	*p* value	Size range/ location	Size mean[¥] median	*p* value	Expulsion time, d (%)	*p* value	Analgesic dosage	*p* value	Adverse events leading to cessation	Study duration, d
Al-Ansari et al, 2010	Double	Yes	Diclofenac 75 mg	Tamsulosin 0.4 mg Placebo	41/50 (82) 28/46 (61)	0.02	<10 mm Distal ureter	5.9 6.0	NS	6.4 9.9	<0.05	68 mg 127 mg	0.001	None	28
Ferre et al, 2009 [47]	No	Yes	Ibuprofen plus oxycodone	Tamsulosin 0.4 mg Control[Ω]	27/35 (77.1) 24/37 (64.9)	NS	<10 mm Distal ureter	3.6[¥]	NS	–	NS	X	NS	None	14
Griwan et al, 2010	No	No	Diclofenac 50 mg	Tamsulosin 0.4 mg Control	27/30 (90) 21/30 (70)	0.04	4–10 mm Distal ureter	6.3[¥] 6.7*	NS	7 (50) 7 (27)	0.001	30 mg 63 mg	0.007	None	28
Hermanns et al, 2009 [46]	Double	Yes	–	Tamsulosin 0.4 mg Placebo	39/45 (86.7) 40/45 (88.9)	NS	≤7 mm Distal ureter	4.1 3.8	NS	7 10	NS	3 7 units	0.011	1	21
Kanekoet et al, 2010	No	⁻No	Diclofenac 50 mg	Tamsulosin 0.2 mg Control	24/31 (77) 17/34 (50)	0.002	X Proximal plus distal ureter	4.6 4.8	NS	14 17	NS	0.50 0.47 units	NS	None	28
Sun et al, 2009 [43]	No	Yes	Indomethacin supplement	Naftopidil 50 mg Control	27/30 (90) 8/30 (27)	0.001	4–15 mm Distal ureter	5.7 5.5	NS	7 6	NS	–	–	None	14
Zehri et al, 2010	No	Yes	Diclofenac 50 mg	Doxazosin 2 mg Control	23/33 (70) 12/32 (38)	0.009	4–7 mm Distal ureter	5.3 *5.5*	NS	7 12.5	0.005	7 16 units	0.005	None	28

NS = not significant.

3.3. *Shock wave lithotripsy and medical expulsion therapy*

It would be reasonable to assume that MET is effective after SWL for renal stones because the fragments have to pass the ureter. Pooled data for α-blocker after SWL suggested a treatment benefit for ureteral stones [36]. All tamsulosin 0.4 mg, doxazosin, and terazosin trials demonstrated a treatment benefit, suggesting a class effect. Colic episodes or analgesic doses in the α-blocker groups were significantly lower in six [42,51–55] of seven trials. Only one tamsulosin 0.2 mg trial after extracorporeal shock wave lithotripsy (ESWL) reported unfavorable outcomes for the treatment group, although differences were not significant. Nevertheless, the mean time to stone expulsion was significantly in favor of the treatment group (15.7 ± 6.1 vs 35.5 ± 53.7; $p = 0.04$) [56].

Four studies available for renal stones treated with ESWL showed a beneficial effect for α-blockade [52,57–59]. Additionally, the double-blind RCT from Romics et al also demonstrated a significant higher expulsion rate and decreased expulsion time with a special combination of terpenes (Rowatinex) after ESWL [60]. This is discussed in detail elsewhere in this supplement. α-Blockers also could prove beneficial for proximal ureteral stone locations because they mediate a reduction in proximal ureteral tone of 33% [34]. All fragments have to pass the distal ureter; therefore, stone passage might be facilitated with decreased expulsion time and fewer colicky episodes. Indeed, findings suggest a beneficial effect. Han et al administered tamsulosin for upper ureteral stones after ESWL and found a significant increased expulsion rate and significant decreased analgesic requirements versus a control group [61]. Porpiglia et al demonstrated a relatively higher expulsion rate for upper ureteral stones compared with a control group using nifedipine in conjunction with a corticosteroid. The expulsion rate in the treatment group was equal for upper and distal ureteral stones [62]. However, one single-centre nonblinded RCT including <15 mm proximal ureteral stones failed to demonstrate a significant treatment effect after SWL [63].

Similar to patients undergoing MET, stone size could also influence the efficacy of MET after SWL. Observations from SWL studies suggested an adjunct role of α-blocker to ESWL. Gravina et al and Bhagat et al found no significant difference in stone-free rates in 6- to 10-mm ureteral stones but with increasing stone size of ≥11 mm the difference became significant [52,57]. Similar findings were reported by Küpeli et al. [64]. The difference in expulsion rates between treatment and control groups for stones <5 mm was not significant. In contrast, stone-free rates in patients treated for stones >5 mm were significantly in favor of the treatment group. In patients receiving nifedipine after ESWL, Porpiglia et al demonstrated that the average stone size of the stone-free versus non–stone-free patients was not significantly different (11.8 vs 11.4 mm). In contrast, average stone size in stone-free versus non–stone-free patients in the control group was significantly different (8.8 vs 11.5 mm; $p = 0.002$), suggesting facilitated stone passage for larger stones in the nifedipine group [62].

3.4. *Adverse events in medical expulsion therapy*

Adverse events (AEs) rarely led to dropouts of patients and were reversible after discontinuation of the drug. Dropout rates might have been low in trials with previous exclusion of patients prone to side effects of the drugs used (eg, hypotensive patients) [6,49,65]. Inclusion of various drugs for standard treatment or steroids added to the treatment group possibly accounted for additional AEs, although a 10-d course of corticosteroids seems to be only associated with a low AE profile.

3.5. *Cost effectiveness of medical expulsion therapy*

Bensalah et al conducted an elaborate evaluation of the cost effectiveness of MET compared with conservative therapy for distal ureteral stones in five countries [66]. Calculations were based on the pooled risk ratio (RR) for treatment with an α-blocker (RR: 1.54; 95% confidence interval, 1.29–1.85) reported by Hollingsworth et al. [67]. It was assumed that failures underwent ureterorenoscopy, which was shown to be more cost effective than ESWL for ureteral stone treatment of any location in most of the countries investigated including the United States [68]. However, obvious but inevitable limitations of any cost analysis are intra- and international variations in the degree of reimbursement and subsidization of services and pharmaceutical costs.

4. Conclusions

In a patient who has a newly diagnosed ureteral stone <10 mm and whose symptoms are controlled, observation with periodic evaluation is an option. Patients may be offered an appropriate MET to facilitate stone passage. There is evidence that MET reduces additional analgesic requirements and accelerates the spontaneous passage of ureteral stones <10 mm as well as renal stone fragments generated with SWL. With decreasing stone size, an increased stone-free rate after MET is less likely because of the high spontaneous expulsion rate. Evidence suggests that MET can be suggested as an effective treatment option. However, large-scale placebo-controlled RCTs and the investigation of promising new substances is still needed to better define the future and optimized role of MET.

Conflicts of interest

In recent years, the author has received consultancy or lecturer honoraria from Rowa Pharmaceuticals.

Funding support

None.

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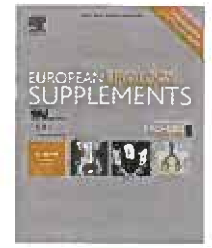

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Preclinical and Clinical Overview of Terpenes in the Treatment of Urolithiasis

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Article info

Keywords:
Urolithiasis
Terpenes
Rowatinex
Medical treatment
Expulsive therapy
Shock wave lithotripsy

Abstract

Context: Pharmaceutical support for spontaneous stone expulsion therapy or fragment clearance after shock wave lithotripsy (SWL) is standard of care in the daily urologic routine. Besides tamsulosin and calcium-channel antagonists, biological products such as terpen combinations are suggested as promoters of stone expulsion.
Objective: To summarize the literature on terpen combinations in the pharmaceutical treatment of urolithiasis.
Evidence acquisition: The manuscript is based on a presentation given at a symposium on "Terpenes in urolithiasis" that was held in Düsseldorf, Germany, in 2010. Data were retrieved from critically selected publications.
Evidence synthesis: Rowatinex is a combination of seven naturally available terpenes. The pharmaceutical effects of the included terpenes are diuretic, spasmolytic, antibacterial, and hyperemic. Consequently, Rowatinex is considered a valuable medication in the treatment of urolithiasis. Despite a long history of clinical availability for Rowatinex, with >50 yr since product placement, the number of available publications is straightforward; however, four open controlled and five prospective randomized trials are published. The majority of these publications show favorable results for Rowatinex compared with placebo in terms of stone expulsion rate and fragment expulsion after SWL. Rowatinex seems to have a good safety profile, with a low incidence of adverse events, which are mainly of gastroenterologic nature.
Conclusions: As a combination of seven naturally available terpenes, Rowatinex seems to have the potential to promote and accelerate stone expulsion in primary management of urolithiasis as well as fragment discharge after SWL. In doing so, Rowatinex shows superior results over placebo in the majority of the published studies. Large-scale randomized trials comparing the effect of Rowatinex versus tamsulosin and calcium-channel antagonists are pending.

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1. Introduction

Watchful waiting therapy to obtain spontaneous stone passage, either following shock wave lithotripsy (SWL) or as primary treatment, is an accepted treatment option for patients with controlled symptoms and nonimpaired renal function and without signs of infection. Accompanying this treatment strategy with pharmacologic medical expulsive therapy may improve stone-free rates and symptoms during stone passage. In particular, α-adrenergic blocking

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agents and calcium-channel antagonists have proven efficacy in randomized controlled studies [1–7]. Additional combination with nonsteroidal anti-inflammatory drugs, steroids, and spasmolytics may further improve stone passage [1,3,8]. Terpen combinations derived from naturally occurring essential oils have been suggested to improve stone-free rates and symptoms during stone passage in patients with urolithiasis [9–13]. This paper summarizes the published literature on terpen combinations in the treatment of urolithiasis.

2. Evidence acquisition

This paper was based on a presentation given at a symposium on "Terpenes in urolithiasis" that was held September 21, 2010, in Düsseldorf, Germany. Data were retrieved from critically selected publications.

3. Evidence synthesis

3.1. *Terpenes*

Terpenes are constituents of essential oils and are prevalent in many plants. In general, terpenes represent a heterogeneous group of chemical substances constructed from hydrocarbons. Variation in additional chemical compounds, such as alcohols, aldehydes, or ketones (terpenoids), define the variations of the different terpen composites.

The building block of all terpenes is the hydrocarbon isoprene (C_5H_8), and classification is achieved according to the number of isoprene units (eg, monoterpenes, carrying two isoprene units). Despite other effects, terpenes are known to have diuretic and antibacterial effects as well as spasmolytic and hyperemic effects. Consequently, terpenes may have the potential for use in the medical treatment of urinary tract pathologies, such as stone disease.

3.2. *Pharmacologic background of terpen combinations in the treatment of urolithiasis*

Rowatinex (ROWA Pharmaceuticals Ltd., Bantry, Co. Cork, Ireland) is a medical product containing a combination of seven naturally occurring terpenes (31% pinene, 15% camphene, 10% borneol, 4% anethole, 4% fenchone, and 3% cineole). Due to the pharmacologic effects of these terpenes, Rowatinex is thought to have beneficial effects on conservative stone management and to support medical expulsive therapy.

The pharmacologic effects of Rowatinex are defined through the single terpenes used in this formulation (Table 1). Antibacterial effects of Rowatinex were described by Cipriani and co-workers [14], with pinenes being the most potent antibacterial substance, followed by borneol and fenchone.

Various groups showed spasmolytic activity of terpenes in multiple animal model studies. Spasmolytic activity (intestinal segments) was proven in guinea pigs, rabbits (also with aortic segments), and cats [15–17]. In addition, hyperemic action could be demonstrated by Geinitz [18] and by Stern and Vukcevic [17] as early as 1956 and 1960, respectively.

Table 1 – Pharmacologic effects of terpenes

Terpenes	Pharmacologic effect
Pinene	Diuretic, antibacterial
Camphene	Hyperemic, choleretic, antibacterial, spasmolytic
Borneol	Choleretic, vasodilatory, antibacterial, analgesic, spasmolytic
Anethol	Diuretic, anti-inflammatory, antibacterial, choleretic, hyperemic
Cineole	Antibacterial, spasmolytic
Fenchone	Antibacterial.

Because terpenes are lipid-soluble substances, the components of Rowatinex are rapidly absorbed after oral intake and are metabolized and excreted mainly with the urine and only to a minor extent with the feces. Rodent studies for pinenes have indicated that hydrocarbons in this chemical category participate in similar pathways of absorption, metabolism to polar oxygenated metabolites, and excretion [19]. Terpen absorption and excretion was also investigated by Kohlert et al. [20]. The authors were able to demonstrate rapid increase of terpen plasma levels in pinenes, camphor, and limonene after dermal application in human subjects, whereas the majority of metabolites were excreted with the urine.

Due to the described pharmacologic effects, terpenes were considered to have potential use in urinary tract pathology, especially in urolithiasis. Rowatinex was introduced in Europe in 1954, and since then, it has been launched in >60 countries worldwide. According to the sales volume given by the manufacturer, an average of 1.5 Mio capsules of Rowatinex are administered per year, showing the broad distribution of the substance.

3.3. *Rowatinex in the treatment of urolithiasis*

Despite the long history of Rowatinex being introduced in the conservative treatment of urolithiasis, the number of published studies is manageable. In addition, a fair number of case reports have been published, including data from 1095 patients. However, due to the nature of these case reports (varying dosage and formulations as well as indications) and the limited possibility of comparing these results, case reports are omitted from further analysis in this overview. In the following sections, open controlled ($n = 4$) and prospective randomized ($n = 5$) trials are summarized to characterize the effects of Rowatinex in the treatment of urinary stone disease.

3.4. *Open controlled studies*

In 1959, Asai et al. [21] published an early report summing up their results of 24 patients treated with Rowatinex for urolithiasis. The authors report spontaneous stone passage in 14 of 24 patients (58.3%) and improvement in patients' symptoms in 21 of 24 subjects (87.5%). Within 2 wk of treatment initiation, 9 of 14 patients with stone passage

Table 2 – Overview of prospective randomized trials

	Primary end point	Group of randomization	No. of patients (male: female)	Age, yr	Stone diameter, mm	Treatment duration, days, n (range)	Success rate, n (%)		Side effects
Mukamel et al. [10]	Stone expulsion rate in ureteric calculi	Rowatinex	23 (20:3)	45 (26–74)	5.2 (1–12)	10.8 (1–21)	18/23 (78)		n = 6 (mild nausea)
		Placebo	17 (12:5)	40 (20–53)	2.5 (1–7)	11.7 (2–21)	9/17 (52)		None
Engelstein et al. [9]	Stone expulsion rate in ureteric calculi	Rowatinex	43 (38:5)	44 (26–74)	4.0 (1–12)	Approximately 14 (NR)	35/43 (81)		n = 7 (mild nausea)
		Placebo	44 (34:10)	48 (26–75)	2.6 (0.5–7)	Approximately 14 (NR)	26/44 (59)		None
Aldemir et al. [24]	Stone expulsion rate in distal ureteric calculi <10 mm	Rowatinex	30 (17:13)	46.5 (22–76)	6.8 (3–10)	6 (NR)	13/30 (43.3)		None
		Tamsulosin	31 (22:9)	42.2 (22–75)	6.7 (4–10)	3.5 (NR)	25/31 (80.6)		None
		Diclofenac	29 (19:10)	43.5 (18–71)	6.6 (4–10)	7 (NR)	11/29 (37.9)		None
Djaladat et al. [25]	Fragment expulsion rate after SWL	Rowatinex	50 (30:20)	38.3 ± 16.4	NR (10–20)	28 (NR)	Day 14 9/50 (18)	Day 28 12/50 (24)	None
		Placebo	50 (29:21)	40.9 ± 14	NR (10–20)	28 (NR)	2/50 (4)	9/50 (18)	None
Romics et al. [26]	Fragment expulsion rate after SWL	Rowatinex	106 (62:44)	51 (18–82)	6.5–7.0 (2–19)	98 (NR)	53/66 (80.3)*		n = 7 (diarrhea [3x], headache, vertigo, nausea, vomiting)
		Placebo	98 (53:45)	48 (18–78)	6.5–8.0 (3–20)	98 (NR)	41/74 (55.4)*		n = 2 (diarrhea)

NR = not reported; SWL = shock wave lithotripsy.
* Patients with complete 98-d follow-up.

expelled their stone and an additional 12 patients were reported to have significant stone migration. All discharged calculi were <0.9 cm. The authors conclude that Rowatinex may be an effective support of medical expulse therapy. In 1961, Hammer and Rothe [22] published a report on 50 patients treated with Rowatinex for radiologically proven calculi in the distal ureter or renal pelvis. Treatment duration in all patients exceeded 6 mo and led to spontaneous stone passage in 37 of 50 patients (74%). Furthermore, 43 patients (86%) reported improvement of their symptoms.

Siller et al. [23] were the first to evaluate the effect of Rowatinex on stone-free rates in patients who received SWL. In their study, 50 patients (28 men and 22 women) were treated with Rowatinex capsules after uncomplicated SWL of renal and ureteral calculi. Treatment was accompanied by increased fluid intake to ensure a daily urine volume of >2.5 l. Inclusion criteria in this study were stone size <20 mm without obstruction of the urinary tract and without the history of deobstructing interventions such as DJ-Stent placement or nephrostomy tube. All patients received Rowatinex capsules (three times per day) for 28 d following SWL and were followed up at days 1, 14, and 28 post-treatment. Pretreatment stone location was renal pelvis and calices in 89.2% of the cases and upper and middle section of the ureter in 10.8%. The stones were <10 mm in 86%, and the remainder were between 10 and 20 mm in size. All patients received one single session of SWL, with an average of 1841 shocks (range: 1000–3000). According to the authors, 84% of the patients started to pass stone fragments on day 1 post-treatment. Overall, 60% of the patients were stone free on day 14 and 82% of the patients were considered stone free at day 28. Of the remaining patients with residual stones, eight patients showed stone fragments <5 mm, mainly located in the lower and middle calyx, and one patient had a residual stone >5 mm in the middle calyx. In addition, the authors looked at symptoms, particularly pain reduction as measured by visual analog scale, and could show symptom reduction, with a total of 94% of patients pain free at day 28 postintervention.

3.5. *Prospective-randomized trials: Rowatinex in ureteric stone expulsion*

Five randomized controlled trials have been carried out to investigate the efficacy of Rowatinex in supporting spontaneous stone passage as the primary treatment option or following SWL (Table 2).

Mukamel et al. [10] were the first, in 1987, to investigate the effects of Rowatinex on spontaneous stone passage in a prospective randomized double-blind study. Forty patients who were referred to the authors' center with acute renal colic and definite evidence of ureteric stones were included in the study. After randomization, the patients were followed for stone expulsion. The authors could demonstrate significantly higher rates of treatment success within 3 wk of treatment in the Rowatinex group compared to placebo (78% vs 52%), despite a larger stone diameter in the Rowatinex group (5.2 vs 2.5 mm). Comparing patients with stones ≥3 mm, the expulsion rates were 61% versus 28% in favor of the Rowatinex group.

In 1992, Engelstein and co-workers presented a confirmative study on the above-mentioned investigation [9]. They included 87 patients in this observation and randomized them into a placebo group and a Rowatinex group. Again, the mean stone diameter was larger in the Rowatinex group (4 mm vs 2.6 mm). Supporting the earlier results, Engelstein et al could demonstrate significant higher rates of stone expulsion in the Rowatinex group (81% vs 59%, $p < 0.05$). Engelstein et al also reported data on adverse reaction, showing good tolerability of Rowatinex, with a total of seven patients experiencing mild nausea or abdominal pain.

Reference-controlled results were presented by Aldemir et al. [24]. Ninety patients with distal ureteral <10 mm stones were randomized into three groups, comparing efficacy and spontaneous stone expulsion rate among tamsulosin, Rowatinex, and diclofenac. With comparable demographic data and stone size in all three groups, the stone expulsion rate was significantly higher in the tamsulosin group compared to Rowatinex and/or diclofenac (80.6% vs 43.3% vs 37.9%, $p = 0.002$ and $p = 0.001$, respectively). In addition, the mean time to stone expulsion was shorter in the tamsulosin group and the need for additional analgesic drugs was reduced. No significant difference was detected in terms of the incidence of renal or ureteral colic among the three groups.

3.6. *Rowatinex following shock wave lithotripsy*

Two prospective randomized controlled trials investigate the effect of Rowatinex on stone passage and stone-free rates after SWL. In 2009, Djaladat et al. [25] reported a series of 100 patients after uncomplicated SWL who were randomized into a Rowatinex group and a placebo group. All patients were treated because of renal calculi between 10 and 20 mm in size. Patients had been followed for stone expulsion at intervals after 14 and 28 d. Although the overall stone-free rate was comparable between both groups after 28 d, the patients who received Rowatinex seemed to demonstrate accelerated stone passage. After 2 wk, only 4% of the patients in the control group were considered stone free, whereas 18% of the Rowatinex group had passed their fragments completely ($p = 0.02$). The authors concluded that despite missing advantages in overall stone-free status after 4 wk, the treatment with Rowatinex may lead to accelerated stone expulsion.

Recently, Romics et al. [26] published a prospective randomized trial of >200 patients receiving SWL and postoperative expulsion supportive therapy with either Rowatinex or placebo. This group found significantly higher rates of stone-free patients in the Rowatinex group within a 12-wk interval. Complications and adverse events were comparable in both groups.

4. Conclusions

Rowatinex is a combination of seven naturally appearing essential oils (terpenes). Due to the pharmacologic nature of the utilized terpenes, Rowatinex is used as a supportive drug in conservative stone management and stone expulsive therapy. Despite market introduction as early as 1954, only a small number of studies on efficacy and tolerability exist. Most of the reports published on Rowatinex efficacy are case reports and, due to varying indications, are hardly comparable. A total of five randomized controlled trials have been published within the last 23 yr. Four of these trials show superiority of Rowatinex-treated patients over placebo in terms of stone-free rates in conservative stone management or stone expulsive therapy following SWL, in combination with good tolerability. Especially following SWL, Rowatinex seems to provide faster and more efficient stone expulsion. However, large-scale trials comparing Rowatinex not only to placebo but to alternative pharmacologic promoters of stone expulsion (eg, tamsulosin) are missing.

Funding support

The publication of this review was supported by ROWA Wagner GmbH & Co. KG, Germany.

Conflict of interest

The author has received consultancy or lecturer honoraria from Rowa Pharmaceuticals.

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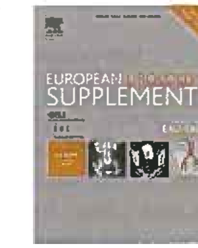

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Improving Stone Clearance After Extracorporeal Shock Wave Lithotripsy in Urolithiasis Patients by a Special Terpene Combination (Rowatinex®): Results of a Placebo-Controlled, Randomized Trial

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Article info

Keywords:
Extracorporeal shock wave lithotripsy
Urolithiasis
Kidney stones
Terpenes
Rowatinex®

Abstract

Background: Extracorporeal shockwave lithotripsy (ESWL) is the first-choice treatment for most renal stones. Rowatinex®, a special terpene combination, has been used therapeutically in the supportive treatment of urolithiasis and for assistance in the expulsion of stones of the renal system for many years.
Objective: The aim of the study was to investigate the safety and efficacy of Rowatinex® in the treatment of patients with urolithiasis after ESWL.
Design, setting, and participants: In a randomized, double-blinded, placebo-controlled, multicenter trial, 222 patients with clinically unapparent kidney or ureter stones who had undergone complication-free ESWL were included between June 2003 and December 2006. The study consisted of a 12-wk active treatment phase and a 2-wk follow-up phase. All patients underwent physical examination, and diagnosis of kidney stones was made by x-ray, intravenous pyelogram (IVP), or ultrasound at weeks 1, 4, 8, and 12 as well as after 2 wk of follow-up.
Intervention: Patients were randomized to receive either 3 × 2 Rowatinex® capsules per day or placebo.
Measurements: The primary end point was the rate of stone-free patients (without any fragments) after 12 wk of treatment.
Results and limitations: Significantly more patients treated with the terpene combination were stone free at the end of the study compared to placebo (intention-to-treat [ITT]—verum vs placebo: 72 patients [67.9%] vs 49 patients [50.0%]; $p = 0.0009$; per-protocol [PP]—verum vs placebo: 69 patients [78.4%] vs 48 patients [52.2%]; $p = 0.0004$). The treatment was even more effective when analyzed with respect to the size of the treated stone. In addition, the terpene combination treatment significantly reduced the median time to stone-free status (ITT—placebo vs verum: 85.0 d vs 56.0 d; $p = 0.0061$; PP—placebo vs verum: 85.0 d vs. 49.5 d; $p = 0.0028$). Tolerability was excellent.
Conclusions: The terpene combination Rowatinex® was found to be an efficacious, well-tolerated, and safe treatment for eliminating calculi fragments generated by ESWL compared to placebo.

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1569-9056/$ – see front matter © 2010 Published by Elsevier B.V. on behalf of European Association of Urology. doi:10.1016/j.eursup.2010.11.007

1. Introduction

Urolithiasis is a common condition that affects approximately 5–12% of the population worldwide [1–3]. At present, extracorporeal shockwave lithotripsy (ESWL) is the first-choice treatment for most renal stones, and success rates >90% have been reported [4–6]. Interpretation of results is complicated by variable definitions for the success of lithotripsy [4]. The current understanding is that *stone free* should mean exactly that and should not include those patients with asymptomatic (clinically insignificant residual stones) fragments < 4 mm in size [7,8].

The therapeutic use of the special terpene combination Rowatinex® (an essential oil preparation composed of 31% pinene, 15% camphene, 10% borneol, 4% anethol, 4% fenchone, and 3% cineol in olive oil that was developed at the beginning of the second half of the last century) in the supportive treatment of urolithiasis (renal and/or urethral calculi)—particularly in conditions with spasm and/or inflammation associated with urolithiasis—and for assistance in the expulsion of stones of the renal system has a 50-yr history as a registered drug in >60 countries. The aim of this multicenter, randomized, double-blind (investigator and patient), therapeutic, parallel-group trial was to demonstrate the superiority of Rowatinex® compared to placebo with respect to the status of stone-free patients during 12 wk of treatment after ESWL.[1]

2. Patients and methods

This outpatient study was designed according to European Association of Urology guidance [9] for active removal of stones in the kidney or ureter by ESWL. ESWL was performed with a Dornier Compact Delta (Wessling, Germany). The study was also performed in accordance with Hungarian laws and approved by Országos Gyógyszerészeti Intézet (OGYI—National Institute of Pharmacy[2]) regulations along with the guidelines of the International Conference on Harmonization (Good Clinical Practice) and the Declaration of Helsinki (2000). The Independent Ethics Committee of the participating hospitals approved the study design, and participating patients gave their informed consent.

The study evaluated the safety and efficacy of the terpene combination Rowatinex® (3 × 2 capsules/d) in patients with clinically stable kidney or ureter stones. Inclusion criteria were (1) complication-free ESWL indicated by complication-free calculus; (2) no urinary deviation; (3) calculus diameter ≤20 mm; (4) no previous endourologic intervention (eg, nephrostoma, endosplint) before ESWL; (5) no urinary tract obstruction; (6) no other severe, untreated associated disease; (7) age >18 yr; and (8) signed informed consent. Patients were excluded if they had kidney stones with complications (eg, severe colic, anuria, or severe urinary tract infection), were pregnant or lactating, or had an allergy to the terpene combination or other components of Rowatinex®.

Patients were treated by the same investigator at each centre, with a treatment strategy of reaching disintegration of the calculus with ≤3,500 impulses or shock waves if the stone totally disintegrated earlier. The endpoint of ESWL was to reach fragments ≤4 mm in size. ESWL was repeated if no spontaneous stone elimination occurred. The study consisted of a screening phase, a 12-wk active treatment phase, and a 2-wk follow-up phase. Aside from analgesics (the usual medication was 500-mg metamizol tablets) and spasmolytics (40-mg drotaverine HCl injection or tablets) as needed, no other concomitant treatment of residual stones after ESWL was foreseen or permitted.

The primary end point of the study was the total elimination of the fragments of calculi generated by ESWL after 3 mo of treatment (rate of stone-free patients). Stone-free status was determined by x-ray of the kidney–ureters–bladder (KUB) and ultrasound. Based on these findings and considering no dilatation in the urinary tract, the patient was declared symptom free. Following the screening phase, subjects eligible for the study who had signed the informed consent were enrolled in the 12-wk active treatment phase in a randomized manner.

In all, 223 patients with clinically stable kidney stones were screened at six centers between June 26, 2003, and December 1, 2006. As one patient withdrew informed consent prior to start of treatment with study medication, 222 patients were randomized. This number was expected to provide 80% power to detect 20% group difference in the proportion of stone-free status at week 12, with a 5% probability of type 1 error rates while assuming a 70% success rate in the Rowatinex® group.

All patients underwent physical and laboratory examination (hemoglobin, hematocrit, red blood cell count [RBC], white blood cell count [WBC], platelet count, prothrombin [at screening only], serum calcium, blood glucose, uric acid, serum bilirubin, serum creatinine, alkaline phosphatase, aspartate amino transferase, and alanine amino transferase), urinalysis (pH, WBC, RBC, urine culture), and a urinary pregnancy test performed at screening and at follow-up for females with child-bearing potential. Diagnosis of kidney stones was made by KUB with the x-ray equipment available in the hospital, intravenous pyelogram (IVP—only at baseline), with expositions 10 and 20 min after the administration of contrast liquid, and/or ultrasound with a 3.5-MHz abdominal head. Patients were questioned about their previous medical history and concomitant medications.

The administration of the terpene combination Rowatinex® (ROWA Pharmaceuticals, Bantry, Co. Cork, Ireland) or placebo started at the first day of the trial after ESWL in the morning. Patients were instructed to take 3 × 2 capsules per day, to drink 2.5 l of liquid before meals to achieve standard hydration, and to record dates of missed doses.

At each visit, the patient was asked whether he or she experienced had any problems since the last visit. All adverse events (AEs) were recorded in standard medical terminology on case report forms (CRFs). For all AEs, the investigator pursued and obtained information adequate both to determine the outcome of the AE and to assess whether it met the criteria for classification as a serious AE requiring immediate notification. Follow-up of the AE, even after the date of therapy discontinuation, was done if the AE persisted until the event had resolved or stabilized at a level acceptable to the investigator. The intensity of the AE was characterized as mild, moderate, or severe, and the relationship to or association with the study medication in causing or contributing to the AE was characterized as unrelated, unlikely, possible, probable, or highly probable.

Randomization lists were generated centrally by the biometrical department of Rowa Pharmaceuticals; using the random number function of a Sharp scientific calculator, study medications were assigned to individual patients. Study medication was delivered in blocks to the sites. At baseline, patient numbers were sequentially assigned to newly included patients by the investigators in an ascending order.

The safety-analyzable population (or *safety population*) consisted of all randomized patients who had safety data after the first dose of the study drug. Note that if a patient had no AE, this defined a safety statement. The intent-to-treat (ITT) population consisted of all randomized patients with at least one postrandomization (on-drug) efficacy evaluation. Patients who were stone free after ESWL were excluded from the ITT population and any other populations to evaluate efficacy. The per-protocol (PP) population consisted of all patients of the ITT population who completed the study without major protocol violations. Protocol deviations were defined and assessed prior to unblinding in a blind data review. The evaluable population for the primary efficacy analysis in this study was the ITT population. Additional analyses in the PP or PP completer set population have been performed to evaluate the robustness of the effects observed in the ITT population.

The number of patients with or without residual stones was compared between both treatment groups using the Fisher exact test. Continuous data were compared with two-sample Wilcoxon or student *t* tests, with further categorical data by χ^2 contingency tests or logistic regression models fitting terms for treatment group and centre. Time to stone-free status was compared between the two treatment groups using Kaplan-Meier life-table analysis with log-rank statistics. In addition, ESWL complications and clinical symptoms (headache, vertigo, nausea, vomiting, eruption) specified in the CRFs were compared descriptively.

[1] This clinical study was first published in Urol Int. (DOI: 10.1159/000320999).

[2] Trial Registration: OGYI 11005/40/2000; TUKEB 161-1/2002.

3. Results

3.1. Patient characteristics

Fifteen patients were stone free already at the baseline visit. In addition, one patient had no postbaseline efficacy values because of discontinuation of the study at day 1, and two further patients were excluded, as they had no postbaseline efficacy values after ESWL. Thus, these 18 patients were excluded from the ITT population. In the ITT population, 98 patients (89.1%) under placebo and 106 patients (94.6%) under the terpene combination were evaluable for efficacy.

Twenty-four patients in the ITT population (6 patients under placebo and 18 patients under the terpene combination) were excluded from the PP population, because they dropped out before the fifth visit (V-5 at week 12). The PP population, therefore, consisted of 180 patients: 92 patients in the placebo group and 88 patients in the terpene combination group. Demographic and other baseline characteristics displayed for the ITT population are provided in Table 1.

3.2. Stone characteristics and treatment parameters

The affected side of treated stones was slightly more frequently the right (55.9%) than the left (44.6%). The distribution of the position was fairly similar in both treatment groups, even if a slightly higher rate of occurrence in the lower calyx was observed for the terpene combination group. In summary, the highest number of patients had treated stones in the lower calyx (approximately 20%; see Table 1). No difference in the size of treated stone was observed between both treatment groups. This is also true for the largest stone size after ESWL (ie, at day 1, where the residual stone measurement by ultrasound revealed a median of 5.0 mm [range: 2–34] and 4.0 mm [range: 2–24] and a mean plus or minus standard deviation of 6.2 ± 5.1 mm and 5.5 ± 4.2 mm for the patients on placebo and on the terpene combination, respectively).

Overall, there were slightly fewer real numbers of shock waves in the terpene combination group compared to the placebo group (2968 ± 708.4 vs 3068 ± 646.8). Consequently, there were no significant differences between the treatment groups with respect to the number of ESWL treatments ($p = 0.9719$; student *t* test) and the maximum intensity of ESWL ($p = 0.5740$; student *t* test). However, a higher rate of patients under placebo was treated with ESWL under anesthesia (24.5% vs 17.0%).

3.3. Efficacy

At the end of the double-blind study period (ie, at week 12), significantly more patients under the terpene combination in the ITT and the PP population were stone free compared to placebo (see Fig. 1). Table 2 shows the cumulative

Table 1 – Demographic, baseline, and treated stone characteristics (intent-to-treat population)*

	Placebo	Terpene combination	Total
Demographic data			
Gender			
Male, No. (%)	53 (54.1)	62 (58.5)	115 (56.4)
Female, No. (%)	45 (45.9)	44 (41.5)	89 (43.6)
Total, No.	98	106	204
Age, yr, median (range)	48 (18–78)	51.0 (18–82)	50 (18–82)
Characteristics of treated stone data (ITT)			
Right side, No. (%)	59 (60.2)	55 (51.9)	114 (55.9)
Position, No. (%)			
Upper calyx	7 (7.1)	5 (4.7)	12 (5.9)
Lower calyx	19 (19.4)	26 (24.5)	45 (22.1)
Middle calyx	14 (14.3)	11 (10.4)	25 (12.3)
Pyelum passage	10 (10.2)	9 (8.5)	19 (9.3)
Size, mm, median (range)	8.0 (3–20)	7.0 (3–19)	8.0 (3–20)
Left side, No. (%)	40 (40.8)	51 (48.1)	91 (44.6)
Position, No. (%)			
Upper calyx	7 (7.1)	7 (6.6)	14 (6.9)
Lower calyx	16 (16.3)	24 (22.6)	40 (19.6)
Middle calyx	9 (9.2)	7 (6.6)	16 (7.8)
Pyelum passage	4 (4.1)	8 (7.5)	12 (5.9)
Size, mm, median (range)	6.5 (3–20)	6.5 (2–17)	6.5 (2–20)

ITT = intent to treat.

* The table shows the number and percent (in parentheses) of patients or stones in each group and in total. The chemical composition was only known for 44 patients.

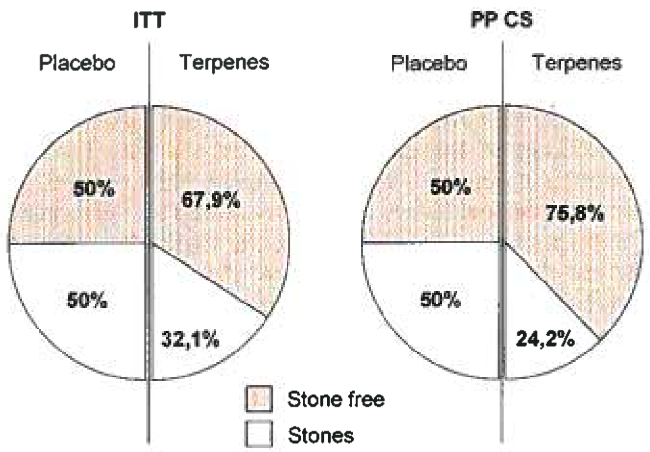

Fig. 1 – Rate of patients with stone-free status within 12 wk after extracorporeal shock wave lithotripsy in the intent-to-treat and per-protocol completer set population.
ITT = intent-to-treat; PP CS = per-protocol completer set.

numbers of stone-free patients in the placebo and terpene combination groups for the ITT, PP, and PP completer set population. It can be seen that the rates of stone-free patients were significantly higher ($p = 0.0009$, $p < 0.0001$, and $p = 0.0004$, respectively) in the terpene combination group compared to the placebo group (see all three populations).

Survival distribution function analyses revealed that the terpene combination significantly reduced the median time to stone-free status from 85.0 d to 56.0 d (log-rank test; $p = 0.0061$) and from 85.0 d to 49.5 d (log-rank test; $p = 0.0028$) in the ITT and PP population, respectively (see Fig. 2).

The terpene combination was more effective when analyzed with respect to the size of the treated stone (see Table 3). In both subgroups (≤8 mm or >8 mm), the efficacy of the terpene combination was demonstrated in an even more pronounced fashion in the PP (see Table 3). In addition, the terpene combination seemed to be more effective in stones in the upper and lower left and right calyx.

Table 2 – Number of stone-free patients (cumulative)

	Placebo			Terpene combination		
	ITT $n = 98$	PP $n = 92$	PP (CS) $n = 74$	ITT $n = 106$	PP $n = 88$	PP (CS) $n = 66$
ITT						
Day 1, week 1, No. (%)	14 (14.3)	14 (15.6)	9 (12.2)	22 (20.8)	21 (23.9)	15 (22.7)
Day 1, week 4, No. (%)	29 (29.6)	28 (30.4)	19 (25.7)	47 (44.3)	44 (50.0)	28 (42.4)
Day 1, week 8, No. (%)	42 (42.9)	41 (44.6)	31 (41.9)	59 (55.7)	56 (63.6)	39 (59.1)
Day 1, week 12, No. (%)	49 (50.0)	48 (52.2)	37 (50.0)	72 (67.9)	69 (78.4)	50 (75.8)
Day 1, week 14, No (%)	53 (54.1)	52 (56.5)	41 (55.4)	76 (71.7)	72 (81.8)	53 (80.3)

ITT = intent to treat; PP = per-protocol; CS = completer set.

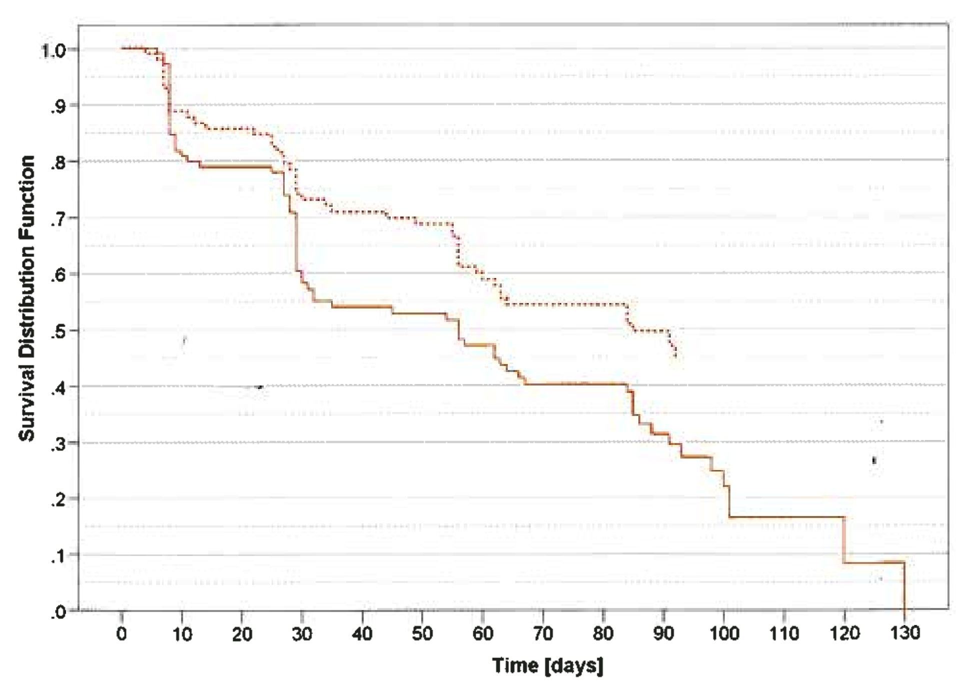

Fig. 2 – Survival distribution functions of the intent-to-treat population; time to stone-free status. Dashed line: placebo; solid line: the terpene combination group (log-rank test; $p = 0.0061$).

Table 3 – Number of stone-free patients stratified by size of treated stone side and position of treated stone

	Placebo		Terpene combination	
	ITT ($n = 98$)	PP ($n = 92$)	ITT ($n = 106$)	PP ($n = 88$)
Size:				
≤8 mm, No. (%)	35 (55.6)	35 (57.4)	55 (73.3)	53 (82.8)
>8 mm, No. (%)	14 (40.0)	13 (41.9)	16 (53.3)	15 (65.2)
Total, No. (%)	49 (50.0)	48 (52.2)	71 (67.6)	68 (78.1)

ITT = intent to treat; PP = per-protocol.

3.4. *Pain measured by a visual analog scale*

The analysis of the course of pain during the study showed that pain at baseline was very low and statistically insignificantly different between the terpene combination and placebo groups (ITT: 2.1 ± 2.6 vs 2.1 ± 2.3). Because of this floor effect, no differences between the two treatments could be detected.

3.5. *Adverse events*

Seven mild to moderate AEs occurring in four patients (3.6%) were assessed as drug related in the terpene combination group (diarrhea [$n = 3$], nausea, vomiting, headache, vertigo), and two mild AEs (diarrhea [$n = 2$]) occurred in two patients (1.8%) in the placebo group. In conclusion, the tolerability of Rowatinex® was excellent.

Only two and three patients in the placebo and terpene combination group, respectively, in the ITT population (PP: 2 vs 1) experienced ESWL complications. Observed ESWL complications were hematuria, fever, pyelonephritis, and occlusions.

4. Discussion

ESWL has revolutionized the treatment of kidney stones. Improved ESWL efficiency occurs at slower shock wave rates [10]. Despite favoring placebo, where a lower ESWL intensity may have increased the rate of stone-free patients, significantly greater success in the patients treated with the terpene combination was observed.

The so-called clinically insignificant residual fragments have the potential to cause obstruction and are important risk factors for stone recurrence and regrowth. Secondary procedures are advised in those patients who have significant symptoms of obstruction associated with the residual stone [8]. El-Nahas et al (2006) determined the predictors of the clinical outcome of residual fragments after ESWL in 99 male and 55 female patients (mean age: 43.1 yr) with residual fragments ≤5 mm for >3 mo after ESWL for renal stones. Stone-free status, regrowth of fragments, and persistence of fragments of the same size were present in 21 (13.6%), 52 (33.8%), and 81 (52.6%) patients, respectively. Significant independent predictors of a clinically significant outcome were fragment size ≥4 mm and history of recurrent stone disease ($p < 0.001$). According to the authors, the term *clinically insignificant residual fragments* is not appropriate for all patients with post-ESWL fragments, as 48.7% of patients in their study had fragments that became clinically significant. In addition, the authors concluded that fragments of 4–5 mm in size and recurrent stone disease predict clinical significance [11]. They confirmed the earlier findings of Khaitan et al [12], who revealed a 50% rate of previous insignificant residual stones becoming clinically significant with one or more complication. Therefore, it is important to define stone-free status as truly stone free and not to include clinically insignificant residual stones ≤4 mm.

The terpene combination was statistically and clinically superior to placebo, with a difference of 17.9% in the rate of patients with stone-free status in the ITT population (67.9% in the terpene combination group vs 50% in the placebo group). Based on this difference, the number needed to treat (NNT) was 5.6, which is clinically relevant. The more favorable efficacy of the terpene combination was even more pronounced in the PP population, with a difference of 26.1% more responders and a clinically highly significant NNT of 3.8. From the Kaplan-Meier-analyses, the median time for patients to become stone free was 56 d in the terpene combination group and 85 d in the placebo group. This difference of approximately 1 mo was statistically significant ($p = 0.0061$). The analysis of the numbers of stone-free patients with an initial size of the treated stone of ≤8 mm or >8 mm showed no difference in the efficacy of the terpene combination, which was clearly superior compared to placebo in both subgroups but was more pronounced in patients with smaller stones at baseline.

The results with the terpene combination in the presented study are in line with those of a previous open, noncontrolled, prospective study evaluating whether the terpene combination facilitated the elimination of stone fragments or debris generated by ESWL. Out of 50 patients (28 men, 22 females; age range: 22–80 yr of age; average age: 44 yr of age), 30 (60%) and 41 (82%) patients on day 14 and on day 28, respectively, became stone free [13].

In addition, a benefit of the terpene combination Rowatinex® over placebo was already demonstrated in one prospective, randomized, double-blind, placebo-controlled study in 87 patients with ureterolithiasis [14], from which a subset of data was published in advance [15]. The goal of the study of Engelstein et al was to assess the value of Rowatinex® in both spontaneous expulsion of ureteral stones and/or disappearance of pretreatment dilatation of the collecting system, indicating stone expulsion. The efficacy of the terpene combination in the alleviation of symptoms associated with nephrolithiasis/urolithiasis was previously described in open studies [16,17].

These early findings on the clinical efficacy of the terpene combination on a wide variety of symptoms associated with illnesses of the kidney and the urinary tract collecting system rely on the antilithogen, antibacterial, anti-inflammatory, spasmolytic, and analgesic activities of the special terpene combination of Rowatinex®, which have been confirmed in preclinical experiments. These preclinical studies demonstrated primary pharmacodynamic effects with a consistent picture of the inhibition of stone formation [18–22]. The finding of an antilithogenic influence on renal oxalate lithogenesis is of particular importance because most of the renal or ureteral stones are composed of calcium oxalate aggregates and because inhibition of stone formation originating from clinically insignificant residual stones generated by ESWL might increase the long-term success rate of ESWL. In addition, Rowatinex® showed antibacterial effects against a variety of pathogens (eg, *Bacillus subtilis, Escherichia coli, Proteus vulgaris, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus faecalis, Enterococcus, Salmonella typhi, Saccharomyces cervisiae*) [23–25].

The spasmolytic activities of Rowatinex® and of its single terpenes like camphene, 1,8-cineole, and borneol were seen with the classical methods for showing antispasmodic efficiency in smooth muscle preparations (intestine, bladder, aorta) of guinea pigs, cats, and rabbits [26] and correspond to the findings in toxicity studies representing effects like vasodilatation and hyperemic status [18]. Together with anti-inflammatory and analgesic properties (ie, by 1,8 cineole, anethol [27,28]), the pharmacodynamic spectrum of the special terpene combination of Rowatinex® mirrors the clinically important pathophysiologic changes in patients with nephrolithiasis/urolithiasis with spasm, inflammation, pain, and infection, especially if it is considered that the excreted terpene glucuronides are still active, impeding further complications in the ureter and lower urinary tract. In summary, the properties of Rowatinex® represent a valuable drug used in the prophylaxis and metaphylaxis of urolithiasis. In relation to α-blockers (eg, tamsulosin), which have been shown to support stone expulsion, especially of ureteral stones with a diameter >5 mm [29], the advantages versus control in the rate of stone-free patients and time to stone-free status are comparable. However, because Rowatinex® has spasmolytic and anti-inflammatory properties, it is more similar to the combination of α-blocker and corticosteroid.

5. Conclusions

Overall, this randomized, double-blind, placebo-controlled, multicenter study demonstrates the superiority of the terpene combination compared to placebo with respect to the rate of stone-free patients and the time of stone-free status during 12 wk of treatment after ESWL. The terpene combination was well tolerated and safe.

Conflicts of interest

In recent years, the authors have received clinical trial, consultancy, or lecturer honoraria from Rowa Pharmaceuticals.

Funding support

None.

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