ORIGINAL INVESTIGATION

Tamsulosin Hydrochloride vs Placebo for Management of Distal Ureteral Stones

A Multicentric, Randomized, Double-blind Trial

Sébastien Vincendeau, MD; Eric Bellissant, MD, PhD; Alain Houlgatte, MD; Bertrand Doré, MD; Franck Bruyère, MD; Alain Renault, MS; Catherine Mouchel, PharmD; Karim Bensalah, MD; François Guillé, MD; for the Tamsulosin Study Group

Background: α-Blockers induce selective relaxation of ureteral smooth muscle with subsequent inhibition of ureteral spasms and dilatation of the ureteral lumen. The aim of the study was to evaluate the efficacy and safety of the α-blocker tamsulosin hydrochloride in patients with ureteral colic owing to a distal ureteral stone.

Methods: This was a multicenter, placebo-controlled, randomized, double-blind study. Patients with emergency admission for ureteral colic with a 2- to 7-mm-diameter radio-opaque distal ureteral stone were included in the study. They received tamsulosin (0.4 mg/d) or matching placebo until stone expulsion or day 42, whichever came first. The main end point was time to stone expulsion between inclusion and day 42. Sequential statistical analysis was performed using the triangular test.

Results: A total of 129 patients with acute renal colic were recruited from emergency wards between February 1, 2002, and December 8, 2006, in 6 French hospitals. Of these 129 randomized patients (placebo, 63; tamsulosin, 66), 7 were excluded from analyses: 5 for major deviations from inclusion criteria, 1 for stone expulsion before the first treatment administration, and 1 for consent withdrawal. At inclusion, mean (SD) stone diameters were 3.2 (1.2) and 2.9 (1.0) mm in the placebo and tamsulosin groups, respectively ($P = .23$). Expulsion delay distributions during 42 days did not show any difference ($P = .30$). The numbers of patients who spontaneously expelled their stone within 42 days were 43 of 61 (70.5%) and 47 of 61 (77.0%) in the placebo and tamsulosin groups, respectively ($P = .41$). Corresponding delays were 10.1 (10.0) and 9.6 (9.8) days ($P = .82$). Other secondary end points and tolerance were not different between groups.

Conclusion: Although well tolerated, a daily administration of 0.4 mg of tamsulosin did not accelerate the expulsion of distal ureteral stones in patients with ureteral colic.

Trial Registration: clinicaltrials.gov Identifier: NCT00151567

Arch Intern Med. 2010;170(22):2021-2027

Author Affiliations: Departments of Urology (Drs Vincendeau, Bensalah, and Guillé) and Clinical Pharmacology and INSERM CIC 0203 Clinical Investigation Centre (Drs Bellissant and Mouchel and Mr Renault), University Hospital, Rennes 1 University, Rennes, France; and Departments of Urology, Val de Grâce Hospital, Paris (Dr Houlgatte) and University Hospital, Poitiers University, Poitiers (Dr Doré) and University Hospital, Tours University, Tours, France (Dr Bruyère).
Group Information: Members of the Tamsulosin Study Group are given at the end of the article.

URINARY STONE DISEASE IS A common and increasing condition that affects 5% to 15% of the population in Europe and North America.[1-3] Its optimal management is usually based on the site and size of the stone.[4,5] Most ureteral calculi are small (<5 mm) and located in the distal ureter.[5] For these patients, spontaneous passage rates of 71% to 98% have been reported.[5] Thus, conservative therapy is indicated if pain can be controlled and if there is no evidence of infection. Medical expulsive therapy, using calcium channel blockers or adrenergic α-blockers, has also been proposed as a way to enhance ureteral stone passage.[6] Indeed, ureteral smooth muscle relaxes in response to calcium channel blockers, and high densities of α_{1a}-receptors and α_{1d}-receptors have been shown in the distal third and ureterovesical junction of the ureteral smooth muscle.[7-9] Therefore, α-adrenergic receptor antagonists decrease intraureteral pressure and increase fluid transport. Among these antagonists, tamsulosin hydrochloride seems to be selective and particularly interesting for medical expulsive therapy.[10,11]

Several randomized but nonmasked trials have been conducted on small cohorts of patients. Three meta-analyses[12-14] suggested that medical expulsive therapy could facilitate urinary stone passage. However, 2 of them[12,14] emphasized that their results were probably limited by a publication bias, which may have led to an overestimation of treatment effect and clearly advocated for a large, well-performed randomized clinical trial (RCT). More recently, 2 monocentric, placebo-controlled, randomized double-blind trials reported, for the first time, negative results with α-blockers,[15,16] reactivating the debate regarding the efficacy of these drugs for the management of distal ureteral stones.[17] Lately, similar negative results were also observed in another monocentric open study in which patients were randomized to receive ibuprofen and oxycodone hydrochloride plus tamsulosin or only ibuprofen and oxycodone.[18]

In this article, we report the results of a prospective, multicentric, placebo-controlled, randomized double-blind study on 2 parallel groups to evaluate the efficacy and safety of tamsulosin, 0.4 mg/d, in patients with acute renal colic owing to a small distal ureteral stone. The study was planned, monitored, and analyzed using a sequential method, the triangular test.[19]

METHODS

STUDY PARTICIPANTS

The protocol was approved by the Committee for Human Investigation (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale) of Rennes, France, on July 6, 2001 (registration number 01/19-340). All participants gave written informed consent.

Patients older than 18 years who were hospitalized in emergency wards of participating centers for acute renal colic were eligible for study inclusion. They needed to have a radio-opaque, distal ureteral stone between 2 and 7 mm in diameter and to agree to a 6-week follow-up. Pregnant or breastfeeding women, patients receiving α- or β-blockers, those with transient hypotension, those with liver impairment, and those requiring a surgical procedure because of infection or continuation of pain after medical treatment were excluded. Patients with spontaneous passage before randomization were also excluded.

RANDOMIZATION

Randomization was centrally performed, concealed, and stratified by center in blocks of 4 according to a computer-generated random number table. In each center, sequentially numbered boxes containing the whole treatment for each patient were delivered to the investigator by the pharmacist following the order of the randomization list. All patients, health medical and nursing staffs, and pharmacists remained masked throughout the study period. The randomization day was considered day 1 of the study.

INTERVENTION

In the emergency ward, patients received a first-line treatment with ketoprofen, 50 mg, and phloroglucinol, 80 mg, intravenously. As soon as renal colic resolution was achieved, patients underwent a complete physical examination, serum creatinine and hepatic enzymes determination, urinary stick test, plain abdominal radiography, and abdominal ultrasonography and/or spiral tomodensitometry for stone identification. They were given an informational letter describing the protocol; the treatment modalities and the absolute necessity of systematically filtering urine during the follow-up were fully explained before obtaining valid informed consent. Patients were then admitted to the urology department and randomized, and treatment was continued orally with ketoprofen, 50 mg (3 capsules daily), and phloroglucinol, 80 mg (6 tablets daily), for 5 days and tamsulosin, 0.4 mg, or matching placebo (both provided by Yamanouchi Pharmaceutical Co Ltd, Paris, France) until stone expulsion or day 42, whichever came first. Systematic urinary filtering was started. After 1- or 2-day hospitalization, patients who reported no pain were discharged and given a booklet in which they were asked to report all events (eg, pain relapses, type and date of adverse effects, and date of stone expulsion) occurring during the follow-up period. They were also asked to drink 2 L of water daily and to filter urine (free strainers were provided).

All patients were evaluated at day 7 and every 7 days thereafter until day 42 by investigators with physical examination and plain abdominal radiography except on days 21 and 35, for which there was only telephone contact. The adverse effects of the medical expulsive therapy were recorded at each follow-up visit.

END POINTS

The primary end point was time to stone expulsion between inclusion and day 42 (censored criterion). When the expulsion was detected by the patient, its date and time were recorded. In case of any doubt, expulsion was required to be confirmed as soon as possible by plain abdominal radiography and by spiral tomodensitometry. When the expulsion was not detected by the patient, the date taken for the analysis was the date of the first investigation that did not show the stone anymore. Secondary end points were the rates of stone expulsion at each visit, globally and according to stone size (2-3 or 4-7 mm) and patient sex, the delay of expulsion in days in patients with spontaneous expulsion, the percentage of patients who required surgery and time to surgery (censored criterion), the percentage of patients with pain relapses and time to the first pain relapse (censored criterion), the percentage of patients who required steroids and/or morphine and time to their first administration (censored criterion), and the percentage of patients who reported predetermined adverse effects (headache, asthenia, orthostatic hypotension, palpitation, nausea or vomiting, or other gastrointestinal disorder).

COMMITTEES

A Diagnosis and Main Endpoint Validation Committee was set up before the beginning of the protocol. This committee met before each sequential analysis and performed a masked review of the data of all included patients. The committee was required to validate inclusion and exclusion criteria, measure the size of the stone, and validate the date of stone expulsion based on the analysis of all available investigations. If necessary, this committee could ask the investigators to provide all additional information required to validate patients' data.

An independent data and safety monitoring board (DSMB) was also set up. This committee was required to analyze the conduct of the study, discuss the results of sequential analyses, and review serious adverse events.

STATISTICAL ANALYSIS

We estimated, from data previously available in our center, that the median time to stone expulsion would be 16 days. To discontinue the study as soon as sufficient information was collected, we used a sequential method, the single triangular test.[19] The test was designed to allow detection on the primary end point of a hazard ratio of 2 (corresponding to an expected reduction of the median time to stone expulsion of 8 days) with 95% power, while the type I error (2-sided) was set at 5%. We chose the single triangular test in its 2-sided version, rather than the double triangular test, to allow for a 2-sided conclusion while reducing the sample size.[20] This methodological option was acceptable be-

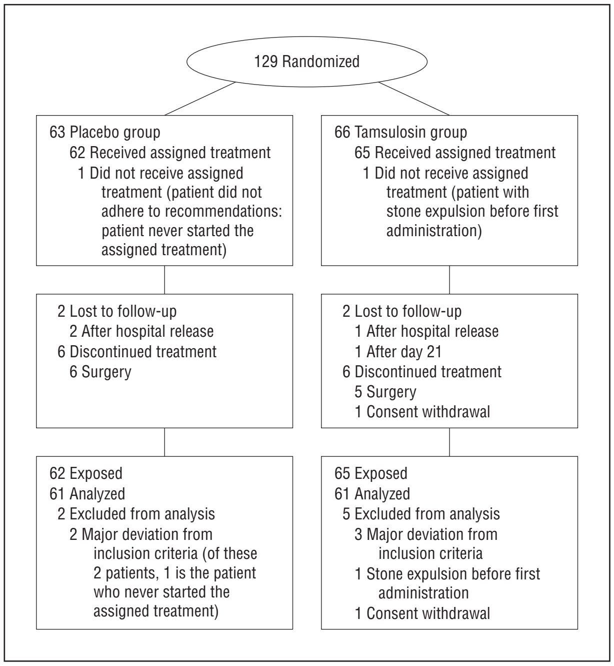

Figure 1. Study flowchart.

cause the control group received a placebo, and we were not interested in demonstrating the inferiority of tamsulosin with a power similar to that required for demonstrating its superiority.[20] Under these conditions, using PEST 3.0 statistical software (Reading University, Reading, England), we determined that the average number of events required to discontinue the study was 49 (90th percentile, 80 events) under the null and alternative hypotheses and 65 (90th percentile, 101 events) right between the null and alternative hypotheses, and the maximum number of events (corresponding to the apex of the triangle) was 154. We also computed that the equivalent fixed sample design would have required 91 events.

Statistical analyses were performed on intent to treat. Reported values are expressed as mean (SD) (continuous variables) or as frequencies and corresponding percentages (categorical variables).

Sequential analyses using PEST were performed on the primary end point after the evaluation of groups of 20 patients each. For the patients who had to be censored, time to censure was defined according to written rules (eAppendix 1; http://www.archinternmed.com). Once the trial was discontinued, the final analysis on the primary end point was also performed using PEST. Cumulative event curves were constructed using the Kaplan-Meier method.

Final analyses on secondary end points were performed with SAS statistical software (SAS Institute Inc, Cary, North Carolina). The *t* test was used for the comparison of continuous variables, the χ^2 test (or Fisher exact test when appropriate) was used for the comparison of categorical variables, and the log rank test was used for the comparison of censored variables.

RESULTS

A total of 129 patients with acute renal colic were recruited from emergency wards between February 1, 2002, and December 8, 2006, in 6 French hospitals. Among the 6 centers, 1 of them, which had only included 2 patients, was excluded from all analyses because of good clinical practice deficiencies. The DSMB met on July 26, 2005, and December 11, 2006, after the fifth and sixth sequential analyses, respectively. After the fifth analysis, the DSMB advised continuation of the study. After the sixth analysis, it recommended discontinuation of the study.

Table 1. Participant Characteristics at Study Inclusion[a]

Characteristic	Placebo (n=61)	Tamsulosin Hydrochloride (n=61)	Overall (n=122)	*P* Value
Age, mean (SD), y	39.0 (11.4)	38.9 (13.4)	38.9 (12.4)	.97
Sex, No. (%)				.05
Male	52 (85.2)	43 (70.5)	95 (77.9)	
Female	9 (14.8)	18 (29.5)	27 (22.1)	
Height, mean (SD), cm	173.0 (7.5)	171.4 (8.6)	172.2 (8.1)	.29
Weight, mean (SD), kg	73.9 (10.2)	73.2 (13.7)	73.5 (12.0)	.76
Temperature, mean (SD), °C	36.9 (0.5)	36.9 (0.6)	36.9 (0.5)	.46
Heart rate, mean (SD), beats/min	75 (12)	75 (12)	75 (12)	.83
Stone side, No. (%)				.72
Right	29 (47.5)	31 (50.8)	60 (49.2)	
Left	32 (52.5)	30 (49.2)	62 (50.8)	
Stone size, mm	3.2 (1.2)	2.9 (1.0)	3.1 (1.1)	.23
Stone size, No. (%)				.88
2-3 mm	44 (72.1)	44 (73.3)	88 (72.7)	
4-7 mm	17 (27.9)	16 (26.7)	33 (27.3)	

[a] Height and weight were not measured in 1 patient in each group. Temperature was not measured in 1 patient in the tamsulosin group. Heart rate was not measured in 1 patient in the placebo group. Stone size was impossible to measure precisely because of the superposition of different structures on plain abdominal radiography in 1 patient in the tamsulosin group. The *t* test was used for the comparison of continuous variables, and the χ^2 test (or Fisher exact test when appropriate) was used for the comparison of categorical variables. Percentages may not total 100 because of rounding.

STUDY POPULATION

Figure 1 shows the study flowchart. Seven patients were excluded from efficacy analyses: 5 for major deviations from selection criteria (2 patients without stones but with phlebolith, 2 patients with proximal ureteral stones, and 1 patient with a non–radio-opaque stone), 1 for stone expulsion before first treatment administration, and 1 for consent withdrawal. Among these patients, the 2 with proximal ureteral stones had been included in the center excluded for good clinical practice deficiencies. For 1 of these 2 patients, the box containing the treatment kit was found intact by the clinical research assistant in charge of data monitoring, demonstrating that the patient never started the treatment. Safety analyses were performed on the 126 patients who had been included in the 5 other centers and who had received at least 1 dose of treatment.

No significant difference was found between groups in patient characteristics at inclusion except sex, for which there was a higher rate of women in the tamsulosin group (**Table 1**). No significant difference was found between groups in the results of physical examination, serum creatinine and hepatic enzymes, and urinary stick test (data not shown). In addition, no significant differ-

Table 2. Delays Between Hospital Admission and First Treatment Administration, Delays Between First Treatment Administration and Hospital Discharge, and Duration of Hospitalization[a]

Variable	No. (%) of Patients: Placebo (n=60)[b]	Tamsulosin Hydrochloride (n=59)[c]	Overall (n=119)[d]	*P* Value
Delay between hospital admission and first treatment administration, h				.96
0-12	18 (30.0)	20 (33.9)	38 (31.9)	
>12-24	25 (41.7)	22 (37.3)	47 (39.5)	
>24-48	14 (23.3)	14 (23.7)	28 (23.5)	
>48	3 (5.0)	3 (5.1)	6 (5.0)	
Total delay, mean (SD), h	20 (17)	20 (19)	20 (18)	.99
Delay between first treatment administration and hospital discharge, h				
Administration after discharge	4 (6.7)	5 (8.5)	9 (7.6)	.58
0-12	13 (21.7)	18 (30.5)	31 (26.1)	
>12-24	21 (35.0)	15 (25.4)	36 (30.3)	
>24-48	15 (25.0)	17 (28.8)	32 (26.9)	
>48	7 (11.7)	4 (6.8)	11 (9.2)	
Total delay, mean (SD), h	23 (20)	20 (20)	22 (20)	.38
Duration of hospitalization, h				.64
0-24	14 (23.3)	13 (22.0)	27 (22.7)	
>24-48	24 (40.0)	30 (50.8)	54 (45.4)	
>48-72	13 (21.7)	10 (16.9)	23 (19.3)	
>72	9 (15.0)	6 (10.2)	15 (12.6)	
Total duration, mean (SD), h	44 (26)	40 (30)	42 (28)	.52

[a] Percentages may not total 100 because of rounding.
[b] Data missing in 1 patient.
[c] Data missing in 2 patients.
[d] Data missing in 3 patients.

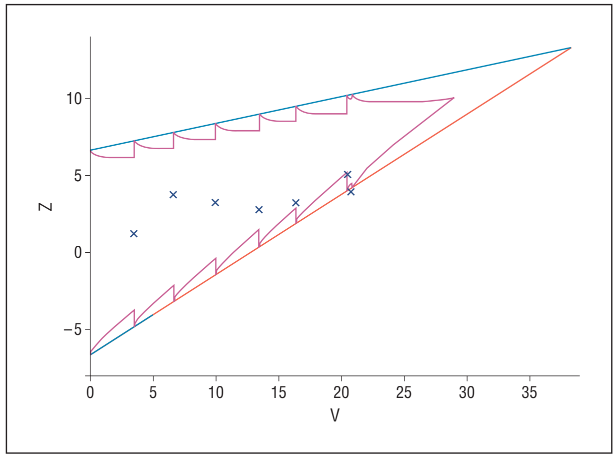

Figure 2. Triangular test and sample path. Sequential analyses were performed on July 1, 2002 (20 patients), December 1, 2002 (40 patients), January 28, 2004 (60 patients), October 25, 2004 (80 patients), July 6, 2005 (100 patients), December 6, 2006 (120 patients), and July 20, 2007 (122 patients; final analysis).

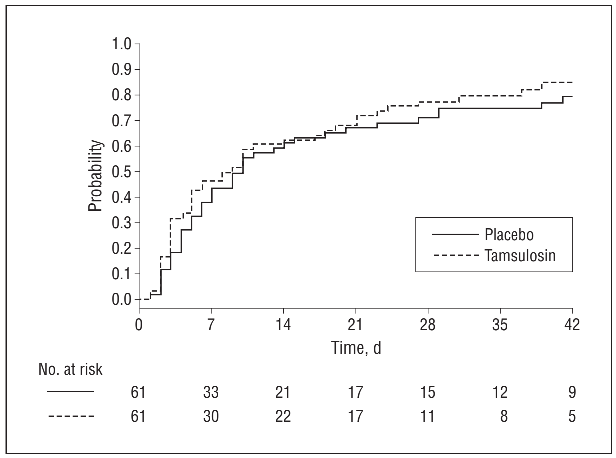

Figure 3. Probability of stone expulsion within the 42 days of follow-up. *P*=.30 for the final sequential analysis.

ence was found between groups in stone characteristics on plain abdominal radiography (Table 1). Overall, stone size was 3.1 (1.1) mm (first quartile: 2 mm; median, 3 mm; third quartile: 4 mm). In each case, the distal ureteral localization of the stone was confirmed by echography and/or tomodensitometry. The delay between hospital admission and first administration of tamsulosin or placebo was 20 (18) hours, with no significant difference between groups (*P*=.99). The delay between first administration of tamsulosin or placebo and hospital discharge and the duration of hospitalization were 22 (20) and 42 (28) hours, respectively, with no significant differences between groups (*P*=.38 and .52, respectively) (**Table 2**).

PRIMARY END POINT (SEQUENTIAL ANALYSIS)

Figure 2 shows the triangular test and the corresponding sample path (ie, the path made by the successive points defined by the 2 test statistics, V and Z, computed at each sequential analysis; also, eAppendix 2). The trial was discontinued after the sixth analysis with acceptance of the null hypothesis. When the result of this analysis became available, 2 more patients had been enrolled in the study. These patients were included in the final sequential analysis with the use of the overrunning procedure. **Figure 3** shows Kaplan-Meier probabilities of stone expulsion. At the end of the study, the estimated hazard ratio, resulting from the comparison of time to stone expulsion distributions between randomization and day 42 in the placebo and tamsulosin groups, was 1.27 (95% confidence interval, 0.81-2.04; *P*=.30; unbiased estimate and significance level taking into account the sequential nature of the analysis). To take into account the imbalance with regard to sex, we also analyzed the main end point using a Cox model, and the hazard ratio decreased to 1.15 (95% confidence interval, 0.76-1.75; *P*=.51).

SECONDARY END POINTS (FINAL ANALYSIS)

Spontaneous expulsion at day 42 was observed in 90 of 122 patients (73.8%) with no significant difference between groups (placebo: 43 of 61 [70.5%]; tamsulosin: 47

Table 3. Time to Stone Expulsion Rates, According to Stone Size[a]

Time to Stone Expulsion, d	No. (%) of Patients: Placebo (n=61)	Tamsulosin Hydrochloride (n=60)	Overall (n=121)	*P* Value
2- to 3-mm Stones				
1	1/44 (2.3)	2/44 (4.5)	3/88 (3.4)	>.99
7	22/44 (50.0)	19/44 (43.2)	41/88 (46.6)	.52
14	27/44 (61.4)	28/44 (63.6)	55/88 (62.5)	.83
21	28/44 (63.6)	30/44 (68.2)	58/88 (65.9)	.65
28	29/44 (65.9)	32/44 (72.7)	61/88 (69.3)	.49
35	31/44 (70.5)	33/44 (75.0)	64/88 (72.7)	.63
42	33/44 (75.0)	34/44 (77.3)	67/88 (76.1)	.80
4- to 7-mm Stones				
1	0/17 (0.0)	0/16 (0.0)	0/33 (0.0)	>.99
7	3/17 (17.6)	7/16 (43.8)	10/33 (30.3)	.14
14	7/17 (41.2)	7/16 (43.8)	14/33 (42.4)	.88
21	9/17 (52.9)	10/16 (62.5)	19/33 (57.6)	.58
28	10/17 (58.8)	11/16 (68.8)	21/33 (63.6)	.55
35	10/17 (58.8)	11/16 (68.8)	21/33 (63.6)	.55
42	10/17 (58.8)	12/16 (75.0)	22/33 (66.7)	.32

[a]The total number of participants in the tamsulosin group is 60 instead of 61 because stone size was impossible to measure precisely at inclusion in 1 patient (Table 1) and stone expulsion spontaneously occurred at day 4 before another plain abdominal radiography was performed. The χ^2 test (or Fisher exact test when appropriate) was used for the comparison of variables.

of 61 [77.0%]; *P*=.41). No significant difference was found in spontaneous expulsion delays between groups with an average time to stone passage of 9.9 (9.8) days (placebo: 10.1 [10.0] days; tamsulosin: 9.6 [9.8] days; *P*=.82). No significant difference was found in expulsion rates during the follow-up, even when considering stone size (**Table 3**) and sex (**Table 4**).

A total of 10 of 122 patients (8.2%) required urgent hospitalization and ureteroscopy during follow-up (placebo: 6 of 61 [9.8%]; tamsulosin: 4 of 61 [6.6%]; *P*=.51). No significant difference was found between the probability distributions of time to surgery (*P*=.51, log-rank test).

Pain relapses were noted in 63 of 119 patients (52.9%) during follow-up (placebo: 35 of 59 [59.3%]; tamsulosin: 28 of 60 [46.7%]; *P*=.17), with the number of relapses being 2.6 (2.0) (placebo: 2.6 [1.9]; tamsulosin: 2.6 [2.1]; *P*=.93). No significant difference was found between the probability distributions of the first pain relapse (*P*=.15, log-rank test).

Morphine requirement was observed in 11 of 122 patients (9.0%) during the follow-up (placebo: 7 of 61 [11.5%]; tamsulosin: 4 of 61 [6.6%], *P*=.34). No significant difference was found between the probability distributions of the first morphine administration (*P*=.32, log-rank test). One patient (tamsulosin group) took steroids (methylprednisolone, 5 mg/kg) during 1 day at 1 month after inclusion.

TREATMENT SAFETY

No serious adverse event that could be imputed to tamsulosin or placebo was observed during the study period. The single consent withdrawal (tamsulosin group) was in relation to asthenia between day 1 and day 7. All types of predetermined adverse events were observed, but their percentages were not significantly different between groups (**Table 5**). In addition, 4 patients (tamsulosin group) reported retrograde ejaculation and 1 patient (placebo group) reported a skin reaction.

Table 4. Time to Stone Expulsion Rates, According to Sex[a]

Time to Stone Expulsion, d	No. (%) of Patients: Placebo (n=61)	Tamsulosin Hydrochloride (n=61)	Overall (n=122)	*P* Value
Male				
1	1/52 (1.9)	1/43 (2.3)	2/95 (2.1)	>.99
7	20/52 (38.5)	17/43 (39.5)	37/95 (38.9)	.92
14	28/52 (53.8)	23/43 (53.5)	51/95 (53.7)	.97
21	30/52 (57.7)	27/43 (62.8)	57/95 (60.0)	.61
28	32/52 (61.5)	29/43 (67.4)	61/95 (64.2)	.55
35	34/52 (65.4)	30/43 (69.8)	64/95 (67.4)	.65
42	36/52 (69.2)	32/43 (74.4)	68/95 (71.6)	.58
Female				
1	0/9 (0.0)	1/18 (5.6)	1/27 (3.7)	>.99
7	5/9 (55.6)	10/18 (55.6)	15/27 (55.6)	>.99
14	6/9 (66.7)	13/18 (72.2)	19/27 (70.4)	>.99
21	7/9 (77.8)	14/18 (77.8)	21/27 (77.8)	>.99
28	7/9 (77.8)	15/18 (83.3)	22/27 (81.5)	>.99
35	7/9 (77.8)	15/18 (83.3)	22/27 (81.5)	>.99
42	7/9 (77.8)	15/18 (83.3)	22/27 (81.5)	>.99

[a]The χ^2 test (or Fisher exact test when appropriate) was used for the comparison of variables.

Table 5. Predetermined Adverse Effects[a]

Adverse Effect	No. (%) of Adverse Effects: Placebo (n=62)	Tamsulosin Hydrochloride (n=64)	*P* Value
Headache	7 (11.3)	7 (10.9)	.95
Asthenia	18 (29.0)	21 (32.8)	.65
Orthostatic hypotension	3 (4.8)	6 (9.4)	.49
Palpitation	1 (1.6)	3 (4.7)	.62
Nausea or vomiting	7 (11.3)	12 (18.8)	.24
Other gastrointestinal disorder	10 (16.1)	16 (25.0)	.22

[a]Data belong to the 126 participants included in the 5 centers kept in the analyses (1 center was excluded because of good clinical practices deficiencies) and who received at least 1 dose of treatment. The χ^2 test (or Fisher exact test when appropriate) was used for the comparison of variables.

COMMENT

The question explored by this trial is important because of the number of people affected each year by ureteral stones in Western countries, their ages, and the economic consequences of their treatment, which often include work stoppage. Many clinical trials have been conducted so far, but their conclusions remain uncertain owing to methodologic flaws (lack of control group, randomization, masking conduct and assessment, and/or sample size determination based on statistical hypotheses). Moreover, meta-analyses showed important clinical heterogeneity in terms of population (percentage of women, mean stone sizes) and treatments (associations in study arms, treatment in control arms).[12-14] Among the randomized trials selected for meta-analyses, most were not masked (none for α-blockers) and did not describe the randomization procedure in detail. Mean times to expulsion and follow-up were short, and sample sizes were often small. In this context, these meta-analyses could not reach definite conclusions, leading Hollingsworth et al[12] to state in their discussion in 2006 that "a definitive high-quality randomised controlled trial is necessary to confirm the efficacy of calcium-channel blockers and α-blockers in patients with urolithiasis,"[12,(p1177)] and Singh et al[14] to conclude in 2007 that "the results of this meta-analysis are encouraging for the use of an α-antagonist or calcium-channel blocker to facilitate stone expulsion of moderately-sized distal ureteral calculi; however, because of the limitations of methodologic quality within the studies reviewed, a large, well-done, randomized, clinical trial is needed to confirm these results before uniform adoption can be recommended."[14,(p561)]

At the same time, the joint European Association of Urology–American Urological Association Nephrolithiasis Guideline Panel performed a systematic review of the English-language literature published since 1997 and released recommendations in 2007.[6] The panel's conclusions were in total agreement with those of Hollingsworth et al[12] and Singh et al[14]: "The Panel encountered a number of deficits in the literature. While the management of ureteral stones remains commonly needed, few RCTs were available for data extraction. The data were inconsistent, starting from the definition of stone sizes and ending with variable definitions of a stone-free state. These limitations hinder the development of evidence-based recommendations. To improve the quality of research, the Panel strongly recommends the following: . . . conducting pharmacological studies of stone-expulsion therapies as double-blinded RCTs."[6,(p1627)]

Of interest, more recently, 3 monocentric, randomized studies with alfuzosin hydrochloride[15] and tamsulosin[16,18] did not confirm the ability of α-antagonists to improve spontaneous stone passage rate. The first study only showed that the mean (SD) time needed to pass the stone was 8.54 (6.99) days for placebo vs 5.19 (4.82) days for alfuzosin ($P = .003$). The second study only found that patients in the tamsulosin arm required significantly fewer analgesics than patients in the placebo arm (median: 3 vs 7, $P = .01$). The editorial comment on this study[17] focused on some limitations, especially the monocentric design and small sample size, and advocated for a multicentric trial. Finally, the third study did not show any statistically significant difference between groups for any secondary outcome (time to stone passage, self-reported pain scores, number of colicky pain episodes, unscheduled return to emergency department, number of days of missed work, or amount of analgesics used) at 2-, 5-, and 14-day follow-up.[18]

In our multicentric, placebo-controlled, randomized double-blind study, we did not find that the α-blocker tamsulosin, 0.4 mg/d, improved stone passage rate, shortened time to stone expulsion, or reduced the number of episodes of ureteral colic. Of importance, we systematically used, in both groups, nonsteroidal anti-inflammatory drugs, which are highly effective in the symptomatic relief of acute renal colic.[21] Although the hazard ratio computed on the main end point was above 1, expressing a tendency toward better efficacy of tamsulosin compared with placebo, the *P* value was far from being significant, and this tendency partly resulted from the imbalance with regard to sex observed at randomization. When this imbalance was taken into account using a Cox model, the hazard ratio decreased to a value close to 1 and the *P* value increased accordingly. Moreover, subgroup analyses according to stone size and sex did not show any benefit in the treatment arm in either subgroup considered.

Because our results contrast with those of most previously published studies, the methodologic aspects of our trial must be discussed. The first reason for such a negative result could be insufficient power. This is not likely because (1) the sample size of our study is the second largest for a clinical trial on that topic (the largest was for a monocentric, randomized, nonmasked study in 3 groups of 70 patients who received phloroglucinol, tamsulosin, or nifedipine)[22] and (2) the trial was designed to allow the detection for the primary end point of a hazard ratio of 2 (corresponding to an expected reduction of the median time to stone expulsion from 16 to 8 days) with 95% power. With this high power, we had a reasonable probability to detect smaller benefits. We computed that, making the hypothesis that the observed difference would be true (hazard ratio of 1.27), the observation of 990 events (1240 patients, considering the observed expulsion rates) would be necessary to reject the null hypothesis. On the basis of the comparison of the observed expulsion rates at day 42 (77.0% vs 70.5%), 2376 patients would be necessary. In this context, the triangular test, which allowed cessation of the study on the basis of the futility of continuation, was particularly well adapted.[23] A second reason for such a negative result could be uncertainties with regard to the population included or with regard to the main end point. To prevent such flaws, the patients included were fully characterized and validated in terms of inclusion criteria and results on the main end point by our Diagnosis and Main Endpoint Validation Committee, which was masked to treatment assignment. Finally, statistical analyses with regard to efficacy and safety were performed on intent to treat and were assessed and validated by an independent DSMB, which recommended discontinuing the trial when the results were sufficiently convincing to accept the null hypothesis. These methodologic characteristics allow a high degree of confidence in our results.

The rate for stone passage in the control group in the present study was substantially higher than the mean for the α-blocker studies in the meta-analysis by Hollingsworth et al,[12] whereas the rate in the treatment group was nearly the same. In the recent single-center RCTs, the passage rates in the control arm were similar to or higher than those in the current study and higher than those in the meta-analysis. This is a consequence of the fact that the 9 trials included in the meta-analysis had included patients with larger stones than those in the trials performed in more recent years. Among these trials, the 5 that had assessed the effect of α-blockers vs different types of controls had been performed in Turkey (4 studies, with mean stone sizes between 5 and 8 mm) and in Iran (1 study, with a mean stone size of 7 mm), which do not have the same profile of patients as those performed in Western countries. Notably, the only trial included in the meta-analysis that was performed in the United States had a mean stone size of less than 4 mm. Another explanation could be linked to enrollment sites, which appear to be, as reported in publications, urology clinics rather than emergency departments, with a probable selection bias inducing the inclusion of patients with larger stones. In fact, our patients are those commonly encountered in the emergency wards of Western countries, and we think that our results are transferrable to these populations. This is all the more important to consider because the current American[24] and European[25] guidelines recommend the use of medical expulsive therapy using α-blocking drugs without any restriction concerning the size of stones smaller than 10 mm.

In conclusion, although well tolerated, a daily administration of 0.4 mg of tamsulosin did not improve the stone passage rate. It also did not shorten the time to stone expulsion in patients with distal ureteral stones.

Accepted for Publication: June 1, 2010.
Correspondence: Eric Bellissant, MD, PhD, Service de Pharmacologie Clinique, CHU de Rennes, Hôpital de Pontchaillou, 2 rue Henri Le Guilloux, 35033 Rennes CEDEX 09, France (Eric.Bellissant@univ-rennes1.fr).
Author Contributions: *Study concept and design:* Vincendeau, Bellissant, and Guillé. *Acquisition of data:* Vincendeau, Houlgatte, Doré, Bruyère, Bensalah, and Guillé. *Analysis and interpretation of data:* Vincendeau, Bellissant, Renault, Mouchel, and Guillé. *Drafting of the manuscript:* Vincendeau, Bellissant, Renault, Mouchel, and Guillé. *Critical revision of the manuscript for important intellectual content:* Vincendeau, Bellissant, Houlgatte, Doré, Bruyère, and Bensalah. *Statistical analysis:* Bellissant and Renault. *Obtained funding:* Vincendeau, Bellissant, and Guillé. *Study supervision:* Bellissant and Guillé.
Tamsulosin Study Group: *Steering Committee:* Drs Vincendeau, Bellissant, and Guillé; *Diagnosis and Main Endpoint Validation Committee:* Drs Vincendeau, Bellissant, Mouchel, and Guillé and Mr Renault; *Quality assurance:* Dr Mouchel; *Pharmacy:* Catherine Hamon, PharmD; *Data monitoring:* Christelle Tual, MS; *Pharmacovigilance:* Dr Mouchel; *Data management:* Hélène Danjou, BS, and Mr Renault; *Statistician:* Mr Renault; *Independent DSMB:* Jacques Irani, MD, PhD; Elisabeth Polard, PharmD; Véronique Sébille, PhD, and Arnauld Villers, MD, PhD.
Financial Disclosure: Dr Vincendeau is an investigator for Astellas Pharma Inc, AstraZeneca, Beckman-Coulter/Hybritech Inc, and Pfizer Incorporated.
Funding/Support: This study was conducted with financial support from the French Ministry of Health (Programme hospitalier de recherche clinique [PHRC] 2000) and Yamanouchi Pharmaceutical Co Ltd. Yamanouchi Pharmaceutical Co Ltd also supplied the tamsulosin and placebo.
Role of the Sponsors: The PHRC and Yamanouchi Pharmaceutical Co Ltd had no role in the planning of the protocol; in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.
Online-Only Material: The eAppendices are available at http://www.archinternmed.com.
Additional Information: Drs Vincendeau and Bellissant, as co–first authors, contributed equally to this work.

REFERENCES

1. Stamatelou KK, Francis ME, Jones CA, Nyberg LM, Curhan GC. Time trends in reported prevalence of kidney stones in the United States: 1976-1994. *Kidney Int.* 2003;63(5):1817-1823.
2. Tiselius HG. Epidemiology and medical management of stone disease. *BJU Int.* 2003;91(8):758-767.
3. Pearle MS, Calhoun EA, Curhan GC; Urologic Diseases of America Project. Urologic diseases in America project: urolithiasis. *J Urol.* 2005;173(3):848-857.
4. Hübner WA, Irby P, Stoller ML. Natural history and current concepts for the treatment of small ureteral calculi. *Eur Urol.* 1993;24(2):172-176.
5. Segura JW, Preminger GM, Assimos DG, et al; The American Urological Association. Ureteral Stones Clinical Guidelines Panel summary report on the management of ureteral calculi. *J Urol.* 1997;158(5):1915-1921.
6. Preminger GM, Tiselius HG, Assimos DG, et al; American Urological Association Education and Research, Inc; European Association of Urology. 2007 Guideline for the management of ureteral calculi. *Eur Urol.* 2007;52(6):1610-1631.
7. Sigala S, Dellabella M, Milanese G, et al. Evidence for the presence of α_1 adrenoceptor subtypes in the human ureter. *Neurourol Urodyn.* 2005;24(2):142-148.
8. Davenport K, Timoney AG, Keeley FX. A comparative *in vitro* study to determine the beneficial effect of calcium-channel and α_1-adrenoceptor antagonism on human ureteric activity. *BJU Int.* 2006;98(3):651-655.
9. Troxel SA, Jones AW, Magliola L, Benson JS. Physiologic effect of nifedipine and tamsulosin on contractility of distal ureter. *J Endourol.* 2006;20(8):565-568.
10. Kenny BA, Miller AM, Williamson IJR, O'Connell J, Chalmers DH, Naylor AM. Evaluation of the pharmacological selectivity profile of α_1 adrenoceptor antagonists at prostatic α_1 adrenoceptors: binding, functional and *in vivo* studies. *Br J Pharmacol.* 1996;118(4):871-878.
11. Muramatsu I, Taniguchi T, Okada K. Tamsulosin: α_1-adrenoceptor subtype-selectivity and comparison with terazosin. *Jpn J Pharmacol.* 1998;78(3):331-335.
12. Hollingsworth JM, Rogers MAM, Kaufman SR, et al. Medical therapy to facilitate urinary stone passage: a meta-analysis. *Lancet.* 2006;368(9542):1171-1179.
13. Parsons JK, Hergan LA, Sakamoto K, Lakin C. Efficacy of α-blockers for the treatment of ureteral stones. *J Urol.* 2007;177(3):983-987.
14. Singh A, Alter HJ, Littlepage A. A systematic review of medical therapy to facilitate passage of ureteral calculi. *Ann Emerg Med.* 2007;50(5):552-563.
15. Pedro RN, Hinck B, Hendlin K, Feia K, Canales BK, Monga M. Alfuzosin stone expulsion therapy for distal ureteral calculi. *J Urol.* 2008;179(6):2244-2247.
16. Hermanns T, Sauermann P, Rufibach K, Frauenfelder T, Sulser T, Strebel RT. Is there a role for tamsulosin in the treatment of distal ureteral stones of 7 mm or less? *Eur Urol.* 2009;56(3):407-412.
17. Giannarini G, Autorino R. Recommending medical expulsive therapy for distal ureteric calculi: a step back? *Eur Urol.* 2009;56(3):413-417.
18. Ferre RM, Wasielewski JN, Strout TD, Perron AD. Tamsulosin for ureteral stones in the emergency department: a randomized, controlled trial. *Ann Emerg Med.* 2009;54(3):432-439, e1-e2. doi:10.1016/j.annemergmed.2008.12.026.
19. Whitehead J. *The Design and Analysis of Sequential Clinical Trials.* Rev 2nd ed. Chichester, England: John Wiley & Sons, Inc; 1997.
20. Sébille V, Bellissant E. Comparison of the two-sided single triangular test to the double triangular test. *Control Clin Trials.* 2001;22(5):503-514.
21. Holdgate A, Pollock T. Systematic review of the relative efficacy of non-steroidal anti-inflammatory drugs and opioids in the treatment of acute renal colic. *BMJ.* 2004;328(7453):1401.
22. Dellabella M, Milanese G, Muzzonigro G. Randomized trial of the efficacy of tamsulosin, nifedipine and phloroglucinol in medical expulsive therapy for distal ureteral calculi. *J Urol.* 2005;174(1):167-172.
23. Sébille V, Bellissant E. Sequential methods and group sequential designs for comparative clinical trials. *Fundam Clin Pharmacol.* 2003;17(5):505-516.
24. American Urological Association. Clinical Guidelines. American Urological Association Web site. http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines.cfm. Accessed May 8, 2010.
25. European Association of Urology. Online Guidelines. European Association of Urology Web site. http://www.uroweb.org/guidelines/online-guidelines. Accessed May 8, 2010.