The effect of drotaverine hydrochloride in acute colicky pain caused by renal and ureteric stones

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OBJECTIVE

To assess the spasmolytic effect of drotaverine hydrochloride in colicky pain caused by renal and ureteric stones.

PATIENTS AND METHODS

In a placebo-controlled, multicentre, multinational, randomized, double-blind study changes in the intensity of pain were recorded using a visual analogue scale (VAS), a four-grade (five points) pain intensity (PI) scale and a pain-relief scale. The primary endpoint was the evaluation of the antispasmodic effect of drotaverine during a 3-h study period, to confirm that drotaverine abolished or significantly decreased the intensity of pain in renal colic. The painkilling effect was defined as a decrease by at least half in the PI scale, and/or a ≥40% decrease in the VAS 40 min after either the first or the second injection of 80 mg drotaverine or placebo (if necessary the dose could be repeated once). In all, 140 patients were enrolled but 38 withdrew, leaving 102 patients for analysis (48 drotaverine, 54 placebo; mean age 42.5 years, SD 11.25, and 41.7, SD 10.79).

RESULTS

Drotaverine was effective in 79% of patients and placebo in only 46% ($P < 0.001$). There were no serious adverse effects. There were 20 minor side-effects in the drotaverine and four in the placebo group; none of the patients required treatment. The most frequent side-effects were a transitory decrease in blood pressure, vertigo, nausea or vomiting.

CONCLUSION

Intravenous drotaverine provides effective pain relief in more than two-thirds of patients with renal colic, with no serious side-effects.

KEYWORDS

drotaverine hydrochloride, spasmolytic treatment, renal colic, ureteric stones, pain

INTRODUCTION

Urinary calculus may occur in every part of the urinary tract and is a common cause of pain, blockage of urine passage and secondary UTI. The incidence of renal stones at autopsy is 1%, but 80% of ureteric stones are eliminated spontaneously, although such elimination is often preceded by spasm. The most frequent symptom of pelvi- and ureterolithiasis is pain. The main factors inducing pain in visceral structures are abnormal distension and contraction of hollow structures, stretching of the capsule of solid visceral organs, ischaemia of visceral musculature, accommodation of algogenic substances, and traction or compression of ligaments, vessels and mesentery. The innervation of the kidney is by sympathetic, parasympathetic and sensory fibres. Pre-ganglionic sympathetic fibres from T10-L2 convey information via the white rami and paravertebral ganglia and synapses in coeliac and aorticoronal ganglia. Post-ganglionic fibres pass to the renal plexus. Parasympathetic fibres from the vagus traverse the coeliac plexus and synapse in the renal plexus. Sensory afferent pain fibres mainly travel with kidney sympathetic fibres via thoracic spinal nerves T10-T12 to the dorsal horn neurones, some of them following the vagus. The upper half of the ureter receives the same nerve supply as the kidney. The lower half is innervated by lumbar splanchnic nerves via the aortic and superior hypogastric plexus. Parasympathetic innervation from S2–S4 travels with the pelvic splanchnic nerves via the inferior hypogastric plexus to the ureter. Sensory fibres travel with the sympathetic neurones to T12–L1 to the spinal cord.

Stones inhibiting the flow of urine cause urinary stasis, and thereby tension of the renal capsule, which is accompanied by intense pain. In such situations the first step is to relieve pain and spasm, or at least reduce the intensity. The parasympathetic symptoms accompanying spasm, e.g. nausea, vomiting, feeling of collapse, impulse to urinate and defecate, debilitate the patient, who must be examined in a state free of spasm [1]. It is only thereafter that the mode of treating the stone can be selected, i.e. whether to wait for spontaneous passage or to remove it by endoscopy or ESWL. If there is cumulative spasm, endoscopic removal is justified, even if the stone otherwise would be suitable for spontaneous evacuation. After ESWL passage of the stone fragments may also be accompanied by spasms. Spasmolysis is a challenge which may be faced with equal frequency by the family doctor, the first-aid officer, the urologist, or other specialists [2,3].

In Hungary, for four decades the most widely used spasmolytic has been drotaverine hydrochloride, which is currently used successfully in many countries [4–6]. There were many open studies with this drug in the 1960s but to date there is no study complying with the actual prescription [7–12]. Thus our aim was to verify the empirical results in a multicentre, multinational, placebo-controlled, randomized, double-blind study, complying with the principles of Good Clinical Practice.

PATIENTS AND METHODS

The study was conducted in 11 centres in four countries between 21 June 1999 and 13 June 2000 (Appendix 1). Patients of both sexes and

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with renal spasm were enrolled, and further inclusion criteria were: typical physical complaints; a pain intensity of ≥ 50% on a 10 cm visual analogue scale (VAS) marked by the patient; a ureteric or kidney stone verified by ultrasonography and/or native abdominal X-ray; informed consent by the patient; and in women of fertile age, the apparent use of efficient contraception. The exclusion criteria were: allergy to drotaverine; any contraindication to intravenous drug administration; any known contraindication to drotaverine; need for immediate surgical or other intervention; spasmolytic or analgesic therapy given within 3 h (the list of forbidden premedication compiled according to the pharmacopoeias of the participating countries); tranquillising or muscle-relaxant therapy used within 3 days; second- or third-degree arteriovenous block; known or suspected pregnancy; known progressive malignant disease; clinically unstable renal, hepatic or cardiac insufficiency (serum glutamate-oxalacetate transaminase >180 U/L, creatinine >250 μmol/L).

After the patients provided informed consent they underwent a general physical examination, electrocardiography, ultrasonography, and plain abdominal X-ray, and urine and blood samples were drawn. If the patient complied with the inclusion criteria, two ampoules (2 × 40 mg) of drotaverine or two (4 mL) of placebo were administered according to the randomization, as a slow intravenous injection of ≈5 min. If the pain did not decrease within 20 min the same dose was repeated once. If after the next 20 min the pain did not cease, the patient was given another spasmolytic. If within this period either the patient requested or the physician judged that the patient required another spasmolytic or analgesic treatment, the study drug was considered ineffective.

The assessment continued for 3 h after the first injection, during which the patients were under strict observation, with possible side-effects continuously monitored, and the pulse rate and blood pressure recorded at 30-min intervals. At the end of this period the physical examination and ultrasonography were repeated.

The aim and primary endpoint of the study was to evaluate the antispasmodic effect of drotaverine over the 3-h study period, to confirm that drotaverine resolved or significantly decreased the pain intensity in renal colic. The secondary endpoints were: to assess the efficacy using two five-point pain scales; to evaluate the relief of pain by the patient on a VAS (0–10 cm), according to a diary completed by the patient every 20 min during the 3-h study period and at the end of the study; to assess the time to re-medication; to obtain the patients' opinion of the treatment; and to ascertain the physician and the patient overall assessment of tolerability.

The relief of pain was evaluated by the patient using the VAS and by the investigator considering the patients' opinions on a pain intensity (PI) and a pain-relief scale (PRS) [13]. From these were calculated the pain intensity difference (PID), the total pain intensity difference (SPID), the pain relief (PR) and total pain relief (TPR). The PI and PRS were assessed by the patient and the investigator on a four-grade scale (0, no pain, to 4, unbearable pain; and 0, no pain relief, to 4, complete cessation of pain). The investigators registered the relevant data by questioning the patient at 20-min intervals. The PID and PR were the difference between the initial and recorded values; the SPID and TPR were then calculated as the area bordered by the PID and PR curves and the time axis.

The question for the primary endpoint ('Is the treatment effective?') was answered as 'yes' or 'no' by the investigator and checked in the study from all the documents supervised by the sponsor's representative. The treatment was considered efficient if the pain ceased or its intensity decreased on the VAS by ≥40% and/or on the PI by at least half within 40 min after either the first or the second injection. The study drug was considered ineffective if the pain-killing effect developed after either the first or the second injection, but the pain recurred within 1 h, or if there was no painkilling effect. The tolerability was evaluated by the investigators and patients, and was supervised by the sponsor's representative, considering the observed adverse events.

For statistical analyses double-data recording was applied. For continuous variables with a normal distribution a two-sample *t*-test was used, and with an abnormal distribution the Mann–Whitney *U*-test was used to assess differences between groups. For discrete data the chi-square test, Fisher's exact test or the Mann–Whitney *U*-test were used to determine the differences between the groups. Wilcoxon's test and a one-sample *t*-test were applied to determine the efficacy of the therapy compared with the baseline, for normal and abnormal distributions, respectively. The VAS scale was evaluated using an ANOVA (general linear model) function.

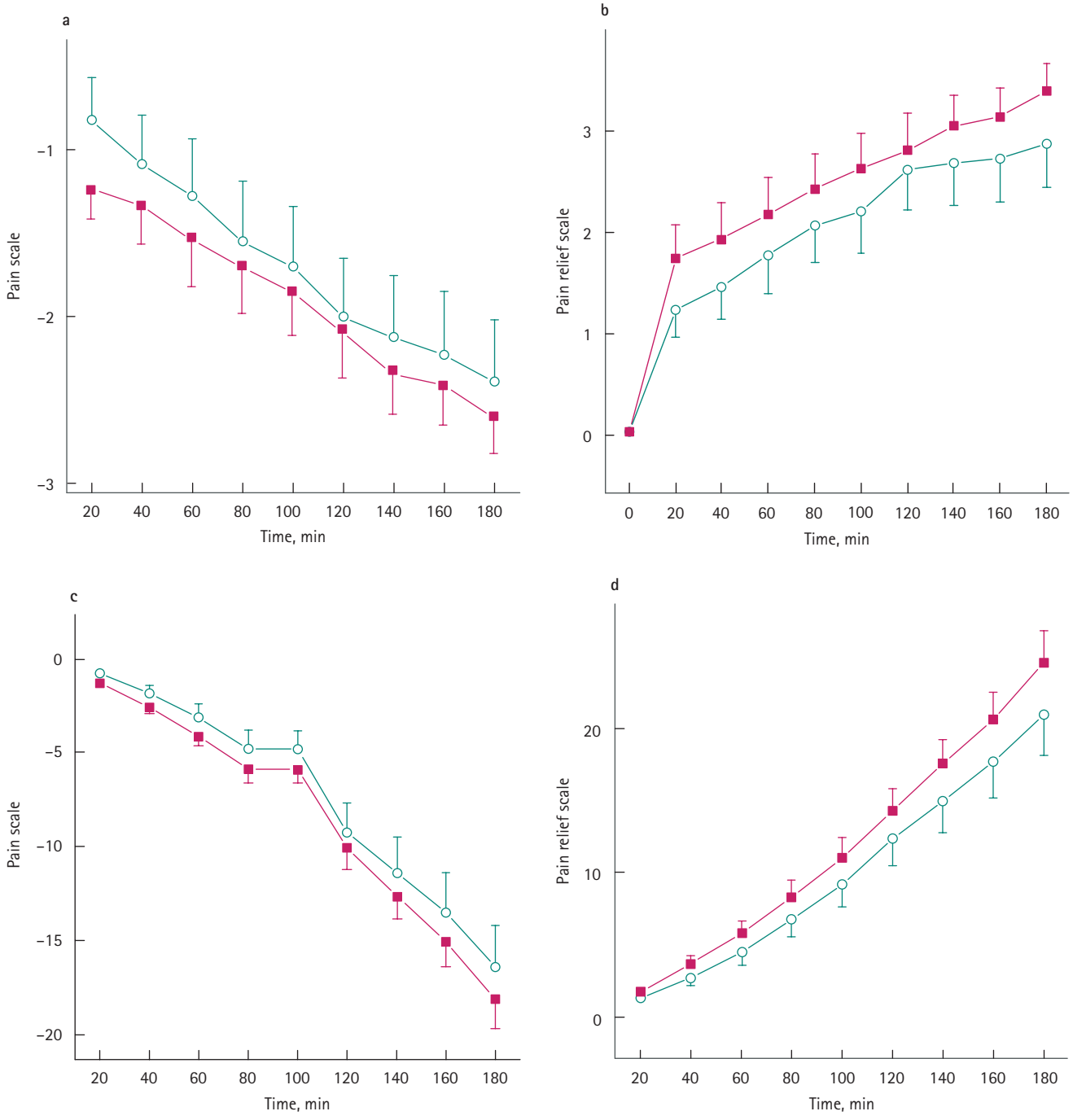
RESULTS

The inclusion of 150 patients into the study was planned but interim analysis of the data of 102 patients showed a significant difference in the benefit of drotaverine, and therefore the board of supervision decided to terminate the study early. Thus 140 patients were enrolled; 38 withdrew and thus the data of 102 were analysed, 48 of whom were treated with drotaverine and 54 with placebo. The mean (SD) age in the active group was 42.5 (11.25) years, i.e. 41.5 (11.27) for the men and 43.6 (11.36) for the women; the corresponding values for the placebo group were 41.7 (10.79), 40 (10.12) and 44.7 (11.59) years. There was a slightly higher proportion of men in the placebo group, at 64.8% vs 50%. There were significant differences between the groups for some patient characteristics (systolic and diastolic blood pressure; QRS duration in a 12-lead electrocardiogram; ESR, haematocrit and red blood cell values on haematology; creatinine level; frequency in urinary analyses). Although the differences were statistically significant they were not important medically and the imbalance had no effect on the study results.

Drotaverine was effective in 79% of the patients, but the placebo in only 46%; the difference was significant ($P = 0.001$). The PID showed significantly lower values with drotaverine than with placebo at 20, 40, 60, 140 and 180 min ($P = 0.049$–0.001) (Fig. 1a). The situation was similar for the PR, which logically mirrors the PID (Fig. 1b). The SPID for drotaverine was significantly higher than that for placebo at 20–120 min ($P = 0.03$–0.001) after injection (Fig. 1c). The TPR for drotaverine was also significantly higher that for placebo at all sample times ($P = 0.045$–0.006) after injection (Fig. 1d). For the VAS, the criterion for being deemed effective was a ≥40% decrease in the score for ≥1 h. There was a significant difference between the groups only at 20 min ($P = 0.043$; Fig. 1e).

The investigator asked the patient to assess the efficacy of the study drug; at the end of

*FIG. 1. The plots of **a,** PID, **b,** PR, **c,** SPID, **d,** TPR and **e,** relief of pain evaluated by the VAS. In each the placebo group is shown by the green open circles and the drotaverine group by the red closed squares. Each point is the mean (SD).*



the treatment 81% of those treated with drotaverine and 65% of those with placebo reported their state to be better than at the start of treatment. (Table 1).

Every patient was given the same initial dose of drotaverine (80 mg) or 4 mL of placebo, but as determined by the protocol a second dose of 80 mg was allowed; significantly fewer second injections were necessary in the drotaverine group ($P = 0.028$; Table 1). As assessed by the patient, 91% reported the placebo and 96% drotaverine to be good or very good (Table 1).

There were no serious side-effects but 20 patients in the drotaverine and four in the placebo group reported mild adverse effects; none required treatment and all were transitory. The most frequent side-effects were a transitory decrease in blood pressure, vertigo and nausea.

Fig. 1. Continued

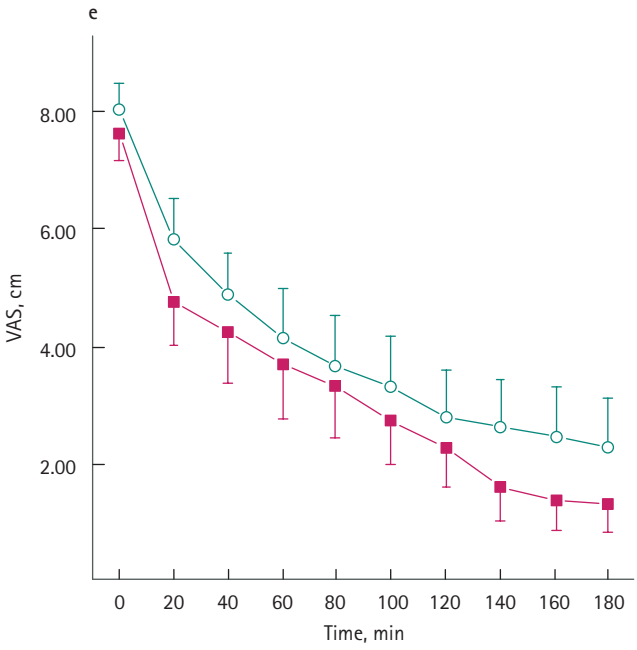


TABLE 1 The patients' opinion of the treatment, the number of doses given and the tolerability

Opinion	Drotaverine, n (%)	Placebo, n (%)
Total N	48	54
Worse	4 (8)	10 (19)
Same	5 (10)	9 (17)
Good	39 (81)	35 (65)
Drug dose		
Once	28 (58)	19 (35)*
Twice	20 (42)	35 (65)*
Tolerability (assessed by investigator)		
Poor	2 (4)	3 (6)
Fair	0	2 (4)
Good	20 (42)	8 (15)
Very good	26 (54)	41 (76)

**P < 0.05 (by chi-square test or Fisher's exact test).*

DISCUSSION

The relief of pain is a basic medical function; renal colic causes severe pain and is accompanied by general discomfort. The severity of the spasm is influenced by the size and form of the ureteric stone, the pressure in the ureter and any concomitant infection. Pain is caused by the dilatation of the renal pelvis and the ureteric wall, and by tension in the renal capsule. Drotaverine inhibits phosphodiesterases hydrolysing cAMP, thereby increasing cAMP concentration, decreasing Ca uptake of the cells and changing the distribution of calcium among the cells [14,15].

Drotaverine is an effective spasmolytic, inhibiting phosphodiesterase type IV in the smooth muscle cells, accompanied by a mild Ca-channel blocking effect with no anticholinergic effect. Drotaverine relieves smooth muscle spasm in all organs where phosphodiesterase type IV is present and does not specifically act on the smooth muscles of the kidney or ureter. Its effects have been confirmed for over 35 years by clinical studies on >10 000 patients. Open studies on urological patients were reported by Vecsey [16] and Wabrosch *et al.* [17]. In daily practice it is generally used in combination with an analgesic, thus potentiating the spasmolytic effect; it can be given orally, intramuscularly or intravenously.

In the present study it was administered alone as an intravenous injection. When choosing the efficacy variables and method of evaluation, we sought to measure the intensity of pain, which is known to be subjective even when assessed by the best 'objective' methods, and thus we used three different variables. This double-blind, placebo-controlled multicentre, multinational study confirmed the efficiency of drotaverine; 20–100 min after the injection almost all the variables assessed (PI, PID and PR) were significantly better with drotaverine, and remained so for up to 3 h, although not significantly so later for all. For those variables reflecting the relief of pain as a whole (SPID and TPR) the advantage of drotaverine remained significant throughout.

As this clinical study was undertaken in acute clinical circumstances there was no possibility to assess the internal diameter of the ureter with time. Consecutively, each patient's 'numerical expression' of spasmolysis should be replaced by a more subjective pain evaluation, but the drug is considered as a spasmolytic. Another study would be needed to evaluate its effect on dilatation of the appropriate part of the ureter (which would need a long series of ultrasonograms) and to measure the decrease in transit time of the stone through the ureter.

Considering that drotaverine was effective in relieving pain without eliminating the cause, i.e. the stone, in 79% of the patients the result must be rated as good. The effect obtained with placebo was unexpectedly high; even for tumorous pain, different authors report a 39–90% placebo effect [18].

There were no severe side-effects with drotaverine and in nearly 40 years' of using it no such events have been reported. There were mild adverse reactions with drotaverine in 20 of the present patients but they required no action or corrective therapy. Most mild adverse events (vertigo, decrease in blood pressure) were related to the blood pressure-lowering effect of intravenous drotaverine, and they can be prevented by using the recommended time of administration (3–5 min) or by applying drotaverine as a micro-infusion. As for other unwanted effects (nausea, vomiting) it is uncertain whether they are caused by drotaverine or by the underlying disease. Any unwanted effects, even if more than one occurred simultaneously, ceased with no intervention. Nevertheless, 96% of the treated patients considered it well or very well tolerated and only two patients (4%) rated it as unsatisfactory.

After open and single-blind studies, and based on the clinical experience over nearly four decades in >100 000 patients, the present double-blind, randomized study confirmed that for renal colic caused by renal and ureteric stones, intravenous drotaverine is an effective treatment in more than two-thirds

of patients, with no serious side-effects. The efficacy can be increased with the concomitant administration of novamidazophene or other NSAIDs, so in most cases narcotic analgesics (pethidine or morphine) can be avoided. A trial to confirm the advantage of combining drotaverine and NSAIDs is planned in the near future.

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Abbreviations: **VAS**, visual analogue scale; **PI**, pain intensity; **PRS**, pain-relief scale; **PID**, pain intensity difference; **SPID**, the total pain intensity difference; **PR**, pain relief; **TPR**, total pain relief.

APPENDIX 1

Study Centres

Croatia
KB 'Merkur', Zagreb
KBC 'Zagreb', Zagreb

Estonia
Tartu University Hospital Clinic of Surgery, Tartu
Mustamae Hospital Clinic of Surgery, Tallinn
Tallinn Central Hospital, Tallinn

Hungary
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Uzsoki utcai Kórház, Department of Urology, Budapest
Jahn Ferenc Délpesti Kórház, Department of Urology, Budapest

Latvia
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Liepāja Regional Hospital, Liepāja
Jeglava Regional Hospital, Jeglava