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Intrathecal Opioids and Lower Urinary Tract Function

A Urodynamic Evaluation

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Background: **Intrathecal administration of opioids may cause lower urinary tract dysfunction. In this study, the authors compared the effects of morphine and sufentanil administered intrathecally in a randomized double-blind fashion (two doses each) on lower urinary tract function in healthy male volunteers.**

Methods: **Urodynamic evaluation was performed before and every hour after drug administration up to complete recovery of lower urinary tract function using pressure and flow measurements recorded from catheters in the bladder and rectum. Sense of urge and urinary flow rates were assessed every hour by filling the bladder with its cystometric capacity and asking the patient to void. Full recovery was defined as a residual volume of less than 10% of bladder capacity and a maximum flow rate within 10% of the initial value.**

Results: **Intrathecal administration of both opioids caused dose-dependent suppression of detrusor contractility and decreased sensation of urge. Mean times to recovery of normal lower urinary tract function were 5 and 8 h after 10 or 30 μg sufentanil and 14 and 20 h after 0.1 or 0.3 mg morphine, respectively. This recovery profile can be explained by the spinal pharmacokinetics of both opioids.**

Conclusions: **Intrathecal opioids decrease bladder function by causing dose-dependent suppression of detrusor contractility and decreased sensation of urge. Recovery of normal lower urinary tract function is significantly faster after intrathecal sufentanil than after morphine, and the recovery time is clearly dose dependent.**

SINCE the first publication of Wang *et al.*[1] describing the analgesic effects of intrathecal morphine in humans, intrathecal administration of opioids has become popular in both perioperative analgesia and chronic pain treatment. Its use is mainly limited by side effects such as respiratory depression, itching, nausea, vomiting, and urinary retention.[2]

The mechanism by which opioids cause urinary retention is incompletely understood. The micturition reflex can be affected both on a spinal and on a supraspinal level. Most of the studies in this field were performed in experimental animals.[3–5] Most of the human studies[6–8] report only on the incidence of urinary retention after intrathecal opioid administration. Rawal *et al.*[8] found long-lasting urinary retention after epidural opioid administration, independent of the dosage used. In a previous study, we investigated the effects of a mixture of intrathecal lidocaine and sufentanil on lower urinary tract function in surgical patients. We found a pattern of micturition disturbance most likely caused by inefficient detrusor contraction and no increase in urethral resistance.

The current study was designed to further evaluate time-dependent changes in lower urinary tract function after intrathecally administered opioids (10 or 30 μg sufentanil and 0.1 or 0.3 mg morphine) without concomitant administration of local anesthetics in healthy male volunteers. A secondary objective was to compare the urodynamic recordings from these volunteers with data from pressure–flow studies from patients with known urologic diseases to gain insight in the pathophysiology of opioid-induced disturbances of micturition.

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

Materials and Methods

Approval from the Human Subjects Committee of the University Hospital, Utrecht, The Netherlands, was obtained, but the committee added a requirement that the level of participant discomfort was quantified. By way of advertising in a local newspaper, 45 healthy male volunteers aged between 18 and 60 yr were recruited. Volunteers were paid. Potential participants were first offered extensive written and verbal information about the aims of the study, the measurements, and the protocol.

Exclusion criteria were any contraindication to spinal puncture, use of any medication, a history of urologic disease, and known urologic problems. Potential participants received routine health screening similar to that used for patients scheduled to undergo elective outpatient surgery, including history and physical examina-

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tion. After a satisfactory preanesthetic evaluation and obtaining written informed consent, participants were admitted at 8:00 AM, having had nothing to eat or drink since midnight. First, a baseline urodynamic study was performed.

Urodynamic Measurements

Pressure–flow measurements involved introducing a small catheter to measure pressure within the bladder and to fill the bladder. Simultaneous flow rate measurements and detrusor pressure measurements provided information about the strength of the detrusor muscle and the resistance of the urethra to urine flow. Information about bladder capacity and residual volume were also obtained. After voiding, before cystometry, a urethral catheter was placed, and residual volume was measured. A residual volume greater than 10% of the cystometric capacity was defined as significant. The bladder was then filled. During filling and voiding, the pressure in the bladder was measured using a second urethral catheter. To measure the pressure in the abdomen, a catheter was inserted in the rectum. In clinical practice, intrarectal pressure seemed to be a fair approximation of abdominal pressure. Bladder- and rectal-measuring catheters were connected to pressure transducers. All systems were zeroed at atmospheric pressure, and the reference point was the superior edge of the symphysis pubis. The intravesical pressure was the pressure within the bladder. The detrusor pressure was that component of intravesical pressure that was created by forces in the bladder wall. It was estimated by subtracting abdominal pressure (rectal pressure) from intravesical pressure. The urinary flow rate during voiding was defined as the volume of fluid expelled *via* the urethra per unit of time and was expressed in milliliters per second. Urinary flow rate was measured using a rotating disc uroflowmeter (standard equipment in general urologic practice). Flow rate was registered simultaneously with the pressures. The maximum flow rate was the maximum measured value of the flow rate during voiding.

In this study, bladder pressure was measured using a 5-French urethral catheter, rectal pressure was measured using a 14-French catheter, and both were expressed as centimeters of water. After emptying *via* the catheter, the bladder was filled with saline at 37°C, through a second 5-French urethral catheter, at a constant rate of 50 ml/min with the patient in the supine position. Filling was stopped when the patient had a strong desire to void. The volume in the bladder at this point was defined as the cystometric capacity and was recorded. Voiding with simultaneous recording of pressures and flow was then performed in the standing position. The patient urinated around the catheters in the uroflowmeter. From the recordings, maximum urinary flow rate and detrusor pressure at maximum flow rate were estimated.

When baseline evaluation was successfully completed and within normal limits, a peripheral intravenous catheter was placed, and monitoring with pulse oximetry, noninvasive blood pressure measurement, and continuous electrocardiography were initiated. The investigator counted respiratory frequency every hour.

Spinal puncture was performed at the L3–L4 interspace, with the patient in an upright sitting position, using a 25-gauge pencil-point needle. In a randomized, double-blind manner, participants received 10 or 30 μg sufentanil or 0.1 or 0.3 mg morphine intrathecally, dissolved in 1 ml normal saline.

Twenty minutes after the intrathecal administration of the test drugs, a new pressure–flow study was performed. The bladder was filled to its cystometric capacity. The presence or absence of urge was recorded. Participants were then allowed to urinate. After voiding, the bladder was emptied *via* the catheter to determine the residual volume.

Heart rate, respiratory rate, blood pressure, and oxygen saturation were recorded. The presence or absence of itching, nausea, and vomiting were separately recorded.

Thereafter, urodynamic measurements were repeated every hour until full recovery of normal lower urinary tract function, defined as a residual volume less than 10% of bladder capacity and maximum flow and voiding time within 10% of their initial value, up to a maximum of 24 h.

After completion of the study protocol, a urodynamic engineer, blinded to the randomized study drug allocation, evaluated the recordings to determine at what time lower urinary tract function had returned to normal.

Based on urodynamic data, we calculated detrusor contraction strength and urethral resistance factor when urinary flow was present and artifact-free tracings were available using the urethral resistance factor algorithm of Griffiths *et al.*[9]

After completion of the last urodynamic measurement, participants were asked to fill out a questionnaire about the level of discomfort experienced during the study. They were contacted the day after the study to detect any possible late adverse outcomes, in particular the occurrence of symptoms suggestive of lower urinary tract infection.

The methods, definitions, and units used in the urodynamic studies were those proposed by the International Continence Society (Bristol, United Kingdom), except when specifically noted.[10]

Statistical Analysis

Results are presented as mean ± SD or as median and 25th/75th percentiles. Comparison was performed using one-way analysis of variance, followed by Kruskal–Wallis and Mann–Whitney U tests. Categorical variables were compared using the Fisher exact test.

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Table 1. Demographic Data and Baseline Urodynamic Characteristics

	Sufentanil		Morphine	
	10 μg	30 μg	0.1 mg	0.3 mg
Variable				
n	10	10	10	10
Height, cm	180 ± 7	179 ± 7	180 ± 10	179 ± 7
Weight, kg	80 ± 15	78 ± 13	83 ± 15	74 ± 12
Age, yr	33 ± 8	40 ± 14	36 ± 13	39 ± 13
Heart rate, beats/min	68 ± 9	66 ± 11	64 ± 10	62 ± 10
Mean blood pressure, mmHg	93 ± 9	97 ± 11	100 ± 12	99 ± 10
Respiratory rate/min	14 ± 1	13 ± 1	14 ± 1	14 ± 2
Urodynamic variables				
Cystometric capacity, ml	467 ± 207	478 ± 104	480 ± 74	527 ± 159
Maximum flow, ml/s	18 ± 7	13 ± 4	22 ± 9	14 ± 5
Bladder pressure at maximum flow, cm H_2O	38 ± 14	30 ± 9	35 ± 11	32 ± 15

Data are presented as mean ± SD.

Results

A total of 40 participants completed the study. Baseline characteristics and urodynamic parameters are listed in table 1. The groups were well matched with respect to demographic and urodynamic variables, although subjects in the 30-μg sufentanil group were somewhat older and had slightly lower maximum urine flow.

The typical response of lower urinary tract function to the intrathecally administered opioids consisted of a decrease in urinary flow rate with an increased voiding time and residual volume; both drugs induced a complete block of micturition in some volunteers. Urge was often decreased, and some participants used abdominal strain to compensate for decreased detrusor contractility. There was recovery of urge and micturition over time with gradual increase of urinary flow rate and a decrease of both voiding time and residual volume to baseline values.

Figure 1 shows the time needed for complete recovery of lower urinary tract function for both drugs. In the groups receiving sufentanil and the group receiving 0.1 mg morphine, all participants had complete recovery of bladder function within 24 h, which was the maximum duration of the study. Two participants receiving 0.3 mg morphine did not have full recovery of their bladder function after 24 h. They were allowed to go home after careful instruction. Both patients reported normal voiding on follow-up the day after the study.

Figure 2 shows the number of participants who were

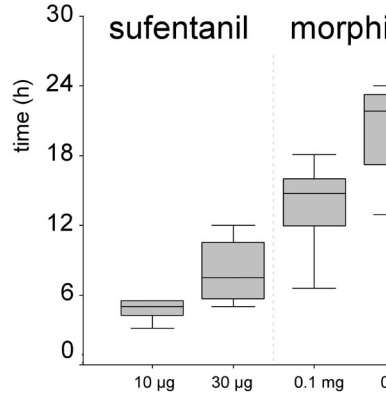

Fig. 1. Time to complete recovery of lower urinary tract function *versus* opioid and dosage used. *Box plots* show median and 25th and 75th percentiles. *Whiskers* denote 10th and 90th percentiles.

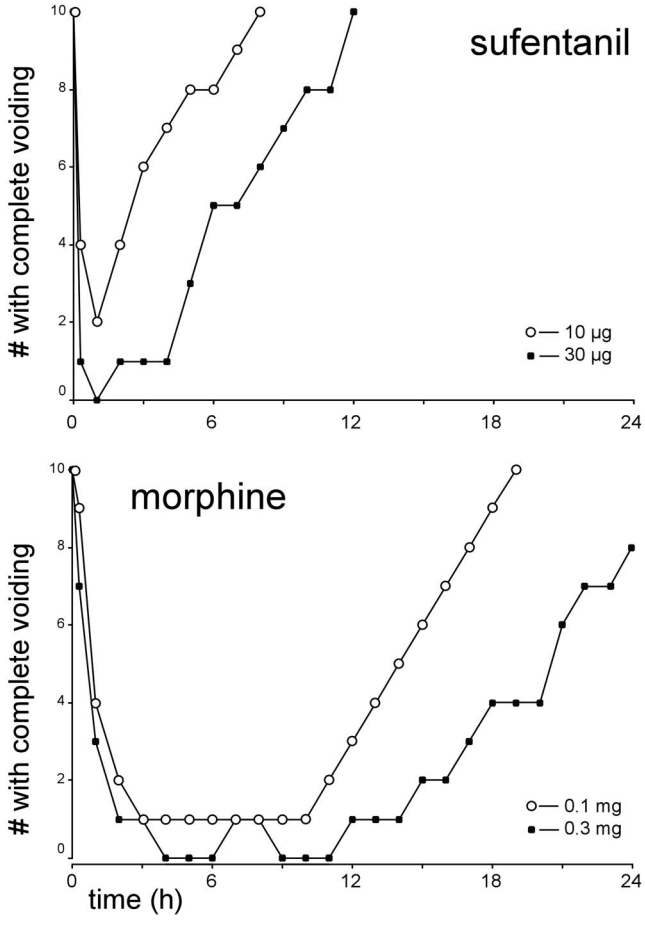

Fig. 2. Number of participants able to completely empty their bladder *versus* time after intrathecal injection of sufentanil (10 or 30 μg) or morphine (0.1 or 0.3 mg).

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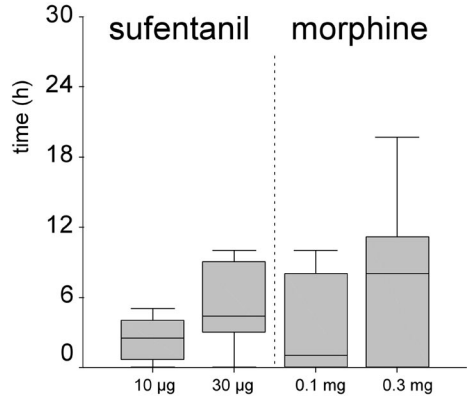

Fig. 3. Time to recovery of a normal sensation of urge after bladder filling *versus* opioid and dosage used. *Box plots* show median and 25th and 75th percentiles. *Whiskers* denote 10th and 90th percentiles.

able to completely empty their bladder *versus* time after intrathecal injection of the study drug.

Figure 3 shows the recovery of urge. Not all participants experienced a change in the sensation of urge. Low-dose sufentanil decreased urge in six subjects, and

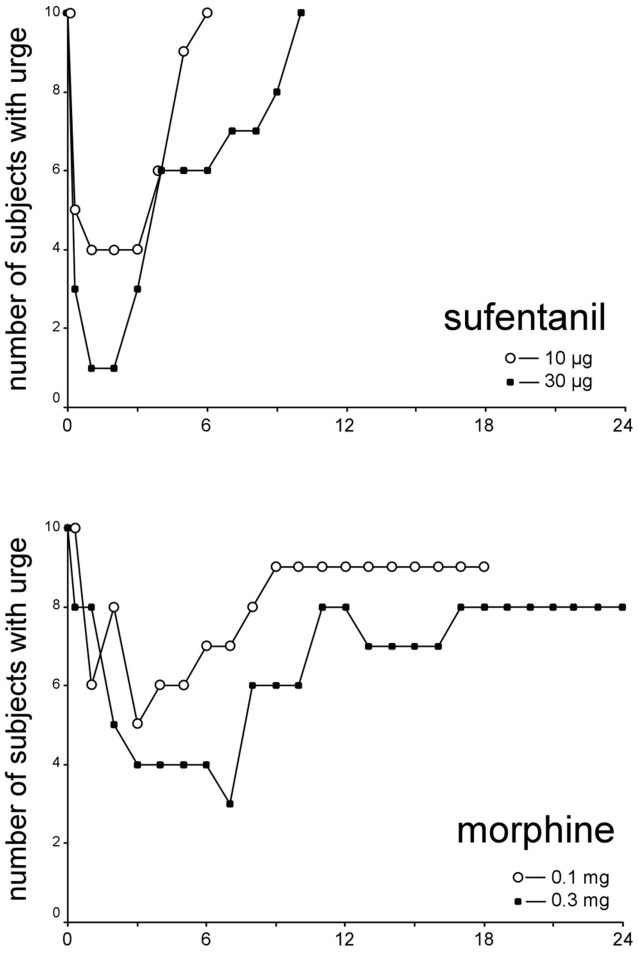

Fig. 4. Number of participants experiencing a normal sensation of urge after bladder filling *versus* time after intrathecal injection of sufentanil (10 or 30 µg) or morphine (0.1 or 0.3 mg).

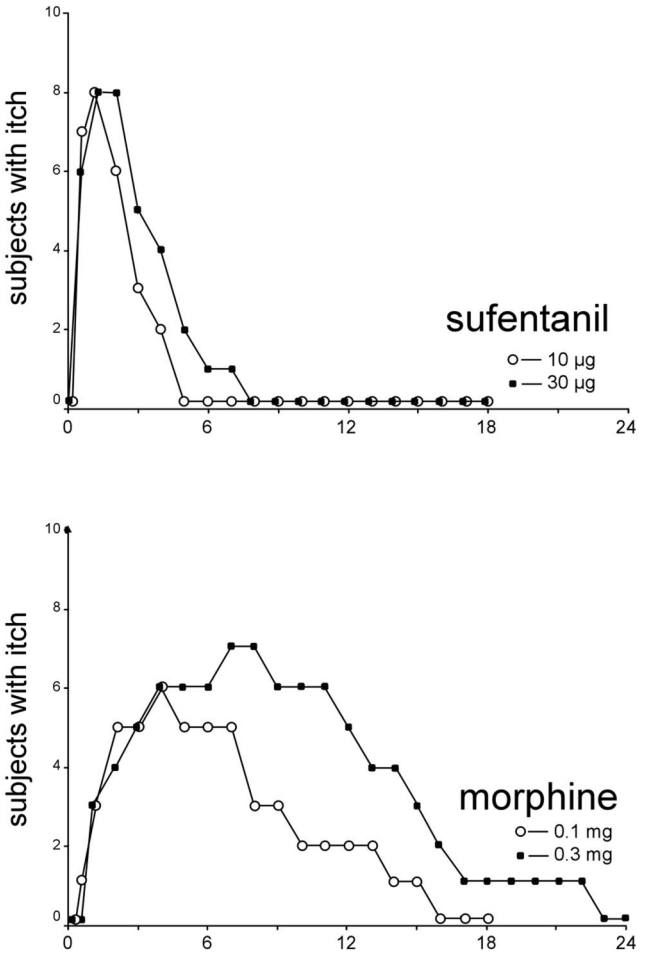

Fig. 5. Number of participants experiencing itch *versus* time after intrathecal injection of sufentanil (10 or 30 µg) or morphine (0.1 or 0.3 mg).

the higher dose of sufentanil decreased urge in nine subjects. Morphine decreased urge less than sufentanil did. Figure 4 shows the number of participants with a normal sensation of urge during the observation period. Urge is a subjective observation. Three participants continued to report a slight decrease in the sensation of urge throughout the study.

Based on the pressure–flow studies, we calculated urethral resistance and detrusor contraction strength in subjects who were able to void and had satisfactory tracings. Because of extensive use of abdominal strain, not all calculations were possible. There was no consistent pattern in change of urethral resistance with either drug. None of the calculated urethral resistance factor values were in the range indicating severe bladder outlet obstruction. Most of the detrusor contraction strength measurements showed an initial decrease with gradual recovery.

Itching occurred frequently. Figure 5 shows the number of participants experiencing itching *versus* time for both drugs. Nausea and vomiting were less common. In the group receiving 10 µg sufentanil, two subjects ex-

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perienced nausea, and one vomited. After 30 μg sufentanil, these numbers were three and one, respectively. After 0.1 mg morphine, there were also three subjects with nausea, and one of them also vomited. In the 0.3-mg morphine group, three subjects had nausea, and all three vomited.

During the investigation, no changes in heart rate, blood pressure, or respiratory rate were observed at any time. An oxygen saturation measured by pulse oximetry less than 95% was not observed at any time during the study protocol with both study drugs.

One participant experienced post–dural puncture headache that was managed with conservative treatment. He completely recovered within 1 week. Analysis of the questionnaire revealed that none of the other participants had experienced the protocol as unpleasant.

Discussion

The data from the current study indicate that intrathecal opioids cause marked lower urinary tract dysfunction. This is the first study in which the effects of intrathecal opioids were investigated in nonsurgical volunteers in the absence of concomitant administration of local anesthetics. The data indicate that recovery to normal lower urinary tract function is significantly faster after intrathecal sufentanil than morphine. Recovery time was clearly dose dependent with both drugs.

Urinary retention is a major side effect of opioid administration. The mechanism responsible for urinary retention is not completely clear. Voiding is a reflex, controlled from the brain stem, the periaquaductal gray, and the medial preoptic area. Therefore, opioids may exert their effects on either the supraspinal or the spinal level. Thus, opioids can interfere with the urge sensation, the detrusor and sphincter function, and the coordination between detrusor and sphincter function.

Only a few studies report on the sensation of urge after neuraxial opioid administration. Rawal *et al.*[8] administered morphine both systemically and epidurally and evaluated urinary tract function using carbon dioxide cystometry in human volunteers. They filled the bladder up to the point at which urge was noted and reported an increase in maximum bladder capacity. We scored the presence or absence of urge at maximum cystometric capacity. Changes in urge were often observed, but the subjects experienced a normal urge sensation long before all urodynamic parameters had returned to baseline. In our study, there was no clear correlation between the presence or absence of urge and the ability to void.

Most animal studies regarding opioids and bladder dysfunction were performed in unanesthetized rats using the model developed by Yaksh *et al.*[11] In this model, the animal is instrumented with a bladder catheter externalized percutaneously and an implanted intrathecal catheter. Bladder pressure and urinary output can be recorded. Using this model, Dray and Metsch[3] showed that systemic morphine affects bladder motility and that this effect could be reversed by intrathecal naloxone. They also showed that intrathecal morphine injections suppressed bladder contractions and that this effect occurred most rapidly when injection occurred at the lumbosacral level. Increasing the intravesical pressure could overcome the decreased bladder motility at lower doses of intrathecal morphine. The authors suggested that the major effect of morphine on bladder motility occurred through the lumbosacral spinal region.

Rawal *et al.*[8] observed a marked decrease of detrusor contractility in humans after 2, 4, and 10 mg epidural morphine, lasting approximately 15 h, independent of dosage used. No changes in bladder function after 10 mg morphine intravenously or intramuscularly were found. The authors also reported increased maximal bladder capacity. These effects on the bladder could be antagonized with intravenous naloxone. The authors concluded that urinary retention is not a systemic effect of opioids and argued that the rapid onset of loss of detrusor contractility after epidural injection suggests a spinal site of action.

The findings in the current study suggest that intrathecally administered sufentanil and morphine interfere with voiding in a similar way. Apart from duration and intensity of the effect, there was no difference between the two opioids. Detrusor contraction strength is always affected. In our study, effects on bladder function occurred within 1 h after intrathecal drug administration. This favors the theory that bladder dysfunction, as in the study of Dray and Metsch,[7] is caused by a spinal effect of the drugs administered, because rostral spread takes at least several hours. Onset time and duration of the urodynamic effects are determined by the particular opioid and dosage used, with a large interindividual variability in recovery time. Whether the effects of intrathecal opioids on the bladder can be antagonized with naloxone was not part of the current study and may need further evaluation in humans.

If opioids were to inhibit sphincter relaxation, the effect would be increased intravesical pressure without voiding. The data from Rawal *et al.*[8] and Durant and Yaksh[5] suggested that failure of sphincter relaxation contributed to the urine retention. We were unable to detect this pattern in any volunteer. In contrast, if opioids were to cause sphincter relaxation, incontinence, decreased urethral resistance, or both might be expected. In the current study, sphincter relaxation was not affected because no consistent changes in urethral resistance during voiding at successive times could be detected. None of our volunteers were incontinent when they had a full bladder, and in some volunteers, we saw detrusor contractions without actual voiding. Sphincter relaxation therefore seems unlikely. Our cal-

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culations consistently indicate a decrease in detrusor contraction strength, suggesting that this is the main effect of intrathecal opioids.

Several pharmacokinetic studies on intrathecal opioids have been performed since the introduction of the technique in 1979. Sufentanil, being more lipophilic than morphine, has an earlier onset because it penetrates easier in nervous tissue. Hansdottir *et al.*[12] calculated the clearance of sufentanil in cerebrospinal fluid as $27 \pm 5\ \mu l \cdot kg^{-1} \cdot min^{-1}$. Nordberg *et al.*[13] reported clearances for morphine of $2.81 \pm 0.41\ \mu l \cdot kg^{-1} \cdot min^{-1}$ and $3.41 \pm 0.55\ \mu l \cdot kg^{-1} \cdot min^{-1}$ after administration of 0.5 and 0.25 mg intrathecal morphine, respectively. The terminal half-life of sufentanil is reported as 0.6–1.4 h, depending on the model used.[12] For morphine, this is 3.1 h.[13] These kinetic data may explain the shorter duration of effects of intrathecal sufentanil *versus* morphine on micturition.

Intrathecal administration of morphine can cause late respiratory depression due to rostral spread. Bailey *et al.*[14] were able to demonstrate that maximum respiratory depression occurred 3.5–7.5 h after drug administration, which is consistent with spinal cerebrospinal fluid passive flow characteristics that determine the spread of intrathecal opioids to rostral areas in the brain. Nordberg *et al.*[13] also reported on the slow onset of effects of intrathecal morphine, consistent with a slow penetration of the drug into the nervous tissue and also dependent on the rostral spread of the substance. Effects on bladder function were seen within 1 h after intrathecal drug administration in our study. This indicates that bladder dysfunction is caused by a spinal effect of the drugs administered. Our study clearly indicates that duration and intensity of lower urinary tract dysfunction is dose dependent. This result is different from the study of Rawal *et al.*,[8] in which different epidural dosages of morphine caused similar effects on lower urinary tract function. Most likely, this difference is a result of the different routes of administration. According to Yaksh, spinal opioids suppress polysynaptic reflex activity at the spinal level in a dose-dependent way.[15]

The current study indicates that intrathecal opioids inhibit the micturition reflex by affecting the afferent and efferent limbs of the reflex arc, which results in long-lasting impairment of detrusor contractility. In the recovery phase of the micturition reflex, the sensory input recovered before the detrusor contraction strength had returned to baseline values.

Although the urge sensation is determined in a subjective manner, it is likely that spinal opioids affect the bladder sensation. The impairment of the detrusor contraction strength can be explained by the studies of Glazer and Basbaum[16] and de Groat *et al.*[17,18] They demonstrated in cats that parasympathetic preganglionic neurons contain enkephalins, which are transported intraaxonally, *via* the S2 ventral roots to the parasympathetic bladder ganglia. de Groat *et al.*[17,18] and Dray and Metsch[3] proved that intrathecal administration of enkephalins produced inhibition of micturition and that naloxone injected intrathecally blocked the inhibitory effects of the opiate peptides. In addition, in untreated animals, naloxone increased the frequency of bladder contractions, and large doses produced tonic contractions of the bladder. de Groat *et al.*[17] suggested that the enkephalin system normally exerts an inhibitory modulating effect on the release of acetylcholine.

In theory, the presence of two urethral catheters might influence the sensation of urge, the measurement of flow rates, and the calculation of resistance. In most urodynamic centers, pressure–flow studies are performed with urethral catheters for bladder filling and intravesical pressure measurements. An alternative technique is to use a suprapubic catheter. Clearly, such a technique would avoid any influence of urethral instrumentation and catheterization on detrusor pressure and flow rate. However, it would obviously make the investigation of the pressure–flow relation more invasive. Besides, even in the majority of men who present with lower urinary tract symptoms secondary to benign prostatic hyperplasia, an 8-French urethral catheter has no significant effect on flow rate or the urethral resistance factor.[19] Because the total area of two 5-French catheters is smaller than that of a single 8-French catheter, we assume that the results of our pressure–flow studies will be minimally affected by the presence of the urethral catheters. In addition, even if there is some influence of the catheter, this effect will be similar during repeated measurements, and if changes in urethral resistance are observed, these cannot be attributed to the presence of the catheters.

The definition of functional bladder capacity may need clarification. Conforming to the recommendation of the International Continence Society, cystometric capacity during filling cystometry is defined as the bladder volume at strong desire to void. From filling cystometric investigations *via* the transurethral route in 160 men, it seemed that effective bladder capacity (cystometric capacity minus residual volume) corresponded significantly with the maximum voided volume reported on their voiding diaries.[20] The latter represents the "strong desire to void" volume. Because there is significant agreement between effective capacity, estimated by filling cystometry through a urethral catheter, and maximum voided volume reported on voiding diaries, the sensation of strong urge to void is apparently not affected by the presence of a transurethral catheter during cystometry.

The effects of intrathecal opioids on bladder function are different from those of intrathecal local anesthetics. In a previous study, we demonstrated a complete absence of urge and detrusor contractility up to recovery of sensation of pinprick in the S2–S3 dermatome.[21] At that time, both urge and detrusor contractility were

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normal again. There was no gradual recovery of urge or detrusor contraction.

The observed effects of intrathecal opioids on lower urinary tract function may have clinical implications. Even when patients are able to void, there may be abnormal bladder function and a large residual volume. Patients indicating urge or a full bladder who are unable to void should be catheterized without delay, because they have certainly reached their functional bladder capacity. Absence of urge does not exclude the possibility that the bladder has reached its functional capacity. However, to discover whether urge develops with overdistension was not part of the current study. Bladder distension is a possible consequence that, when extensive, may result in permanent damage to the lower urinary tract and various degrees of chronic dysfunction, including incontinence. Because overdistension should be prevented at all times, routine clinical monitoring of the filling condition of the urinary bladder seems justified. Voluntary abdominal strain can be applied in case a full bladder is suspected or diagnosed by ultrasound, and ultimately, single bladder catheterization is indicated if voiding is not achieved before the bladder becomes excessively distended.

In conclusion, intrathecally administered opioids interfere with bladder function in healthy volunteers by causing dose-dependent suppression of detrusor contractility and decreased sensation of urge. Recovery of normal lower urinary tract function is significantly faster after intrathecal sufentanil than morphine, and the recovery time is clearly dose dependent. In the recovery phase of the micturition reflex, impaired voiding is mainly the result of reduced contractility.

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