The Effect of a Low Dose of Intrathecal Morphine on Impaired Micturition Reflexes in Human Subjects with Spinal Cord Lesions

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The potential therapeutic value of a low dose (200–250 μg) of intrathecal (i.t.) morphine on bladder capacity was tested in six subjects with chronic suprasacral spinal cord lesions. Micturition reflexes were examined by saline fill cystometry accompanied by EMG recordings from the external anal and urethral sphincters and selected lower limb muscles. Hyperactive detrusor reflexes were associated with a low capacity bladder in five of the six subjects. All subjects revealed vesicoexternal sphincter dyssynergia, and vesical-induced and spontaneous contractions of the abdominal and lower limb musculature. The result was incontinence and frequent catheterizations. Within 5–15 min of the bolus morphine injection into the L1–2 i.t. space, bladder capacity increased to near-maximal values in all subjects. Soon thereafter, uninhibited detrusor contractions, spontaneous motor discharges, and vesicosomatic (limb) reactions were abolished. A peak effect was observed within 2–4 h. Alterations of bladder capacity persisted for 18–22 h. Side effects included pruritus and nausea. Intrathecal morphine acts at sacral spinal cord sites, e.g., primary afferents and/or dorsal horn neurons, mediating vesicocecal and vesicosomatic (sphincter, limb) reflexes, and spontaneous motor discharges. Clinically, i.t. morphine may be an effective therapy for individuals with suprasacral spinal cord lesions when a low capacity bladder interferes with their quality of life. (Key words: Analgesie, intrathecal: morphine. Reflex: micturition. Spinal cord: injury.)

WHEN ADMINISTERED intraspinally, e.g., intrathecal (i.t.) or epidural, to normal animals and humans, morphine suppresses vesicosomatic reflexes, causing naloxone-sensitive enhancement of bladder capacity.1–6 This action purportedly occurs at sacral spinal cord sites. Moreover, in normal humans i.t. morphine may alter vesicourethral function, creating vesicoexternal sphincter dyssynergia.7 Vesicoexternal sphincter dys-

synergia implies inappropriate contractions or failure of relaxation of the external urethral sphincter during vesical (detrusor) contraction.7,8 Clinically, these behaviors are frequently associated with retention of urine.2,5,9

Such observations are in accordance with evidence that morphine binds to opioid receptors within the spinal micturition pathway,10,11 and high densities of opioid receptors are distributed at dorsal horn locations of vesical and pudendal afferent projections and vesicosomatic neurons (e.g., lamina I).12–15 As dorsal rhizotomy leads to partial depletion of opioid receptors in the dorsal horn,16,18 it may be assumed that morphine acts at these presynaptic and/or postsynaptic sites.4,18

In subjects with suprasacral spinal cord lesions, the presence of hyperactive micturition reflexes, associated with low threshold and uninhibited detrusor contractions and vesicoexternal sphincter dyssynergia, often lead to a small capacity bladder with frequent incontinence and predisposition to urinary tract infections. These vesical reflexes are further exaggerated by spontaneous flexor-extensor motor contractions of proximal (including trunk) and distal muscle groups of the lower limbs (e.g., the mass reflex, often referred to as flexor spasms, or spasticity). Such an intersegmental motor discharge pattern frequently induces a strong phasic rise in intravesical pressure and consequently represents a form of somatovesical interaction.9

This investigation was conducted to determine whether low dose morphine injections into the lumbar i.t. space suppress micturition reflexes and, thus, increase bladder capacity in two groups of subjects, designated as complete and incomplete suprasacral spinal cord lesions. The experimental protocol was also designed to elucidate the mechanisms underlying the anticipated changes in bladder capacity in the two groups of subjects.

Materials and Methods

SUBJECTS

The criteria for selection of two subjects with complete and four subjects with incomplete suprasacral spi-

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nal cord lesion were: 1) failure of systemic drug therapy to attenuate hyperactive micturition reflexes (enhanced detrusor contractions, and/or vesicoexternal sphincter dysynergia, and augmented vesicosomatic and somatosacral reflexes) associated with incontinence and a frequent intermittent catheterization schedule; 2) a stable neurologic, urologic, and functional status; 3) absence of factors (infection, anatomic disturbance of the upper and/or lower urinary tract, decubitus ulcers, etc.), which may alter sensitivity of the vesical and/or somatic reflexes; and 4) discontinuation of medication used to modify spasticity and vesical and/or somatic contractility at least 3 or 4 days prior to testing. Informed consent was obtained in all cases. The procedures and informed consents were approved by the Institutional Review Board of the Catholic Medical Center.

**Cystometry**

Pressure–volume relationship of the bladder was determined by filling the bladder with saline at rates of 12 ml/min and 60 ml/min. The test was performed with the subject lying at a 30° trunk-flexed position. A Foley® catheter and a bladder pressure (Life-Tech #BPC-4A) catheter were introduced transurethrally into the bladder; the former was used for retrograde bladder filling and the latter to measure intravesical pressure. Intrarectal pressure was measured through a Foley® catheter placed in the rectal canal. Both intravesical and intrarectal pressures were determined (Life Tech Pressure Transducer #1880 and Pressure Transducer Amplifier #1870T), and detrusor pressure was calculated by electronic subtraction of intrarectal pressure from intravesical pressure.

The cystometry fill phase was curtailed concurrently with an urgent desire to void, the first indication of leakage per urethra or a bladder volume of 700 ml, whichever occurred first. The volume at the termination of the fill phase was designated as the maximum bladder capacity, a value approximating the volume threshold of the micturition reflex in pretreatment trials (control response in fig. 1A). The voiding phase through the catheter followed a short relative isometric phase (fig. 1). The cystometry trials were repeated on four to six occasions with a minimal interval of 10 min between each trial.

Electromyographic (EMG) recordings were obtained by means of wire electrode pairs inserted into the external striated urethral and anal sphincters, and into selected lower limb muscles (e.g., tibialis anterior, biceps femoris-short head). The EMG signal was processed by differential amplifiers (Coulbourn High Gain Bioamplifier/Coupler #S75-01) utilizing a bandpass of 10–1,000 Hz. In addition, the EMG signal was integrated for 10 s before and after peak detrusor pressure (table 1). Both EMG and pressure signals were simultaneously recorded on FM magnetic tape (Vetter Model G) and further amplified and displayed on an ink writing polygraph (Gould 2800) throughout the three cystometry phases.

**Drug Administration**

With the subject in a lateral decubitus position, a single bolus of preservative-free morphine sulfate (200–250 μg Duramorph®) in a volume of 1 ml preservative-free normal saline was injected into the i.t. space between L1 and L2. Immediately following this procedure, the subject was repositioned supine with 30° of trunk flexion. Cystometric tests continued from 5 min to a minimum of 27 h following the i.t. morphine injection.
TABLE 1. The Effect of Bolus Injections of Intrathecal Morphone on Bladder Capacity, and on Detrusor and Striated Sphincter Responses to Bladder Filling

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/ Sex</th>
<th>Etiology Site/ Extent</th>
<th>Duration (min)</th>
<th>Dose (µg)</th>
<th>Maximum Bladder Capacity* (ml)</th>
<th>Peak DP† (cmH₂O)</th>
<th>DP Threshold (mmH₂O)</th>
<th>EMG @ Peak DP‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45/F</td>
<td>VAS-T2/I</td>
<td>28</td>
<td>250</td>
<td>111</td>
<td>79</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>21/M</td>
<td>TR-T9/I</td>
<td>16</td>
<td>250</td>
<td>478</td>
<td>13§</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>37/F</td>
<td>MS-Cer/I</td>
<td>60</td>
<td>200</td>
<td>38</td>
<td>61</td>
<td>30</td>
<td>---</td>
</tr>
<tr>
<td>4</td>
<td>44/F</td>
<td>MS-Cer/I</td>
<td>144</td>
<td>200</td>
<td>128</td>
<td>9§</td>
<td>110§</td>
<td>278§</td>
</tr>
<tr>
<td>5</td>
<td>28/F</td>
<td>TR-T8/C</td>
<td>11</td>
<td>200</td>
<td>79</td>
<td>80</td>
<td>63</td>
<td>110</td>
</tr>
<tr>
<td>6</td>
<td>30/M</td>
<td>TR-C5/C</td>
<td>21</td>
<td>250</td>
<td>67</td>
<td>76</td>
<td>50</td>
<td>110</td>
</tr>
</tbody>
</table>

Subjects were administered i.t. morphine (200–250 µg). Etiology: VAS = vascular; MS = multiple sclerosis; TR = trauma. Site: Cer = identifiable level in cervical region. Extent: C = complete; I = incomplete lesion; EUS = external urethral sphincter; EAS = external anal sphincter.

Maximum bladder capacity and other pretreatment control (CO) and post-treatment morphine (MO) values obtained during 60 ml/min fill cystometry.

† Detrusor pressure.

DATA ANALYSIS

To express a measure of central tendency and dispersion of obtained dependent values, the arithmetic mean (X) and SD were estimated. Premorphone bladder capacity and urethral and anal sphincter EMG values were compared to corresponding peak postmorphone values by the paired t test.

Results

In five of the six subjects, cystometry revealed volume-induced hyperactive micrurition reflexes as manifested by: 1) an augmented vesicoesovesical reflex with a low threshold and uninhibited detrusor contractions; 2) vesicoexternal sphincter dyssynergia; and 3) vesicosomatic (limb) reactions (e.g., flexor spasms), frequently inducing a phasic rise in intravesical pressure during the contraction phase (figs. 1A and 2A). The result was an incontinent voiding pattern with a forceful stream and a low capacity bladder (58–128 ml). In the sixth subject (table 1; patient 2), the pretreatment bladder capacity was 478 ml; this response was accompanied by a weak detrusor contraction, vesicoexternal sphincter dyssynergia, and a strong vesicosomatic response. Subjects with both incomplete and complete lesions demonstrated spontaneous mass reflexes (spasticity) with and without vesical filling. These reactions were frequently associated with a rise in intravesical pressure and a somatovesical reaction, and they were capable of initiating detrusor contractions during the filling phase (fig. 1). In the other three subjects with an incomplete lesion, i.t. morphine caused an increase in the threshold of the detrusor contraction and/or the perception of urgency. Nevertheless, the magnitude of reflex contraction (patient 5) or of the perceived intensity in the desire to void (patient 4) was virtually unchanged.

Subsequently, the character and intensity of the vesicoexternal sphincter reflexes were modified as evidenced by a pronounced increase in tonic EMG activity of the striated anal and urethral muscles during the fill and relative isometric periods of the cystometry measurements (figs. 1B and 2B). Whereas table 1 reflects significantly raised EMG values for both muscles at peak detrusor pressures (X = 277 ± 160%; P < 0.02, and 330 ± 233%; P < 0.05, for the urethral and anal muscles, respectively; n = 5), intensified values (X = 278 ± 67%) were also observed at equivalent pretreatment and post-treatment bladder volumes. The latter observation was particularly striking in three subjects when a slow rate of filling elicited a reflex threshold sufficient to permit an appropriate assessment of the relationship
between volume and EMG discharge (fig. 2). In contrast, EMG activity of both muscles was not altered during resting (empty bladder) conditions.

Concurrently, uninhibited contractions and limb-motor discharges or flexor spasms (occurring spontaneously or during vesical filling and contraction) were abolished following i.t. morphine (figs. 1 and 2). The elimination or weakening of the profound flexor spasms or the mass reflex reduced somatosensory and vesicosomatovesical reactions (fig. 1B). Voiding patterns disclosed a dribbling rather than forceful flow. These modifications in the various elements comprising the micturition reflex reached a peak within 2–4 h (figs. 1B and 2B). Recovery was characterized by the restoration of bladder capacity within 18–24 h (fig. 1C). Reappearance of phasic vesicosphincter activity and of uninhibited detrusor contractions usually occurred with a further delay of 1–4 h (fig. 1D). Strong somatosensory reactions (i.e., mass reflexes) did not reemerge for 35–60 h.

Morphine i.t. caused pruritus (distributed about the face, arms, and trunk of three subjects), nausea (described by two subjects) and piloerection (observed on the limbs and trunks of four subjects). Naloxone iv (Narcan®; 400–800 µg) suppressed pruritus but failed to reduce nausea. However, droperidol iv (Inapsine®; 600 µg) was effective in the management of nausea. Pruritus and piloerection, as well as morphine-induced physiologic changes, i.e., inhibition of vesicovesical and enhancement of vesicosphincter reflexes, can be reversed by naloxone iv when the dose is ≥10 µg/kg.

**Discussion**

The notion that i.t. morphine acts at segmental sacral cord sites is supported by: 1) observations of enhanced bladder capacity in subjects with complete suprasacral spinal cord lesions; 2) kinetic characteristics (e.g., relatively rapid penetration and action accompanied by a slow rate of clearance) favoring localized action; and 3) reports regarding suppression of bladder contractility at doses that are ineffective when administered systemically.

Intrathecal morphine has a profound effect on bladder capacity in subjects with complete and incomplete suprasacral spinal cord lesions, transforming a low capacity bladder to a moderate capacity bladder. Among the six subjects studied, bladder capacity appears to be modified by the following: suppression of the vesicovesical reflex as evidenced by an attenuated rate of rise of detrusor pressure (three subjects), or by an increased threshold of reflex contraction (or of urgency to void, three subjects); suppression of uninhibited detrusor contractions; modification of the character and degree of urethral sphincter motor activity; and reduction of somatosensory and vesicosomatovesical reactions.

Augmented urethral sphincter EMG activity during bladder filling (i.e., enhanced vesicourethral sphincter dysynergia) connotes raised urethral tonus and pressure, leading to increased detrusor voiding pressures. However, our observations suggest that increased sphincter EMG activity is not associated with a rise in detrusor pressure during bladder filling, implying a lack of correspondence between EMG activity and urethral pressure. This has been confirmed by measurement of urethral pressure in both normal subjects and subjects with spinal cord lesion exposed to i.t. morphine.

The apparent difference in the mechanisms of the vesicovesical reflex inhibition may be ascribed to the differential effects of i.t. morphine on the afferent limb of the spinal and supraspinal micturition reflex systems. The role of vesical primary afferents in reflex micturition has been demonstrated by capsaicin-in-

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**†† Unpublished observations.**

duced degeneration studies in normal animals. Appar-ently, reduction of the bladder afferent fiber contribu-
tion to the supraspinal micturition reflex circuit causes
an increased threshold to the initiation of micturition
during filling, a behavior also observed following ad-
ministration of intraspinal morphine in normal animals
and humans, and among three of the subjects in this
study (patients 2–4; table 1). In contrast, three subjects
(two complete suprasacral spinal cord lesions) reveal a
different reflex pattern to filling following i.t. morphine
treatment, namely, a change in rate of increase of
micturition pressure with little alteration in reflex threshold;
apparently, this response is not observed in normal sub-
jects. We speculate that this observation represents
suppression, rather than extinction, of transmission of
bladder afferent signals through spinal pathways, per-
mitting both mechanical (e.g., viscoelastic) and reflex
mechanisms to participate in the slow rate of rise of
detrusor pressure. The magnitude of vesicle reflex ac-
tivity is independent of the dose of i.t. morphine within
a range of 50–400 μg.***

The opposing effects between vesicle-evoked vesical
and striated sphincter reflex contractions following an
i.t. morphine injection also implies ample central pro-
cessing of vesical information in the spinal cord. The
present study reveals that i.t. morphine produces an
increase in sphincter activity during vesical stimulation
but does not cause a change in resting EMG discharges.
This result suggests that i.t. morphine releases or disin-
hibits vesicosomatic (sphincter, pudendal) reflexes
rather than somatic reflexes. Such behavior may be
ascribed to action at presynaptic and nonsynaptic pri-
mary vesical afferent sites, however, postsynap-
tic effects on neurons capable of integrating vesical
and pudendal afferent data must be considered. It is
likely that integration occurs at a sacral cord location
where there is evidence of substantial overlap of both
afferent groups, dendrites from the sacral parasympa-
thetic nucleus (which can be modulated by pudendal
afferent stimulation), neurons projecting to higher cor-
tical centers (which convey signals for perceptual anal-
ysis), and correspondence between the distribution of en-
kephalins and opiate receptors, e.g., lamina I. Further,
the time course of the spinal drug action on vesico-
vesical and vesicospincter reflexes, and on sup-
pression of spontaneous and vesical-induced limb motor
discharges (flexor spasms or spasticity) leading to exci-
table somatovesical reactions (e.g., figs. 1 and 2) is appar-
tently sufficient to attainpostsynaptic effects.***

In conclusion, i.t. morphine treatment reveals a strik-
ing modulatory action on hyperactive micturition re-
exes, comprised of enhanced vesicoavesical and somato-
vesical reflexes, and on limb (vesical induced and
spontaneous) reactions in subjects with supraspinal sa-
cral cord lesions. Consequently, we propose that i.t.
morphine might be therapeutically advantageous to this
subject population, given 1) the presence of disabling
low capacity bladder associated with frequent incon-
tinence, and/or phasic intersegmental type of spasticity
(3); 2) the lack of clinical effectiveness of commonly
utilized, systemically administered, pharmacologic
agents; and 3) a method of continual delivery of mor-
phine, e.g., implantable infusion pump.31

Continuous i.t. infusion of morphine by an implanted
pump has been used widely for the treatment of chronic
pain.32,33 This technique has also been used to suppress
spasticity in subjects with spinal cord lesions.34 For
many of these subjects, this form of treatment is a pref-
erable alternative to destructive, surgical, and/or
chemical procedures. On the other hand, in populations
treated for pain or spasticity, complications and side
effects from continuous infusion of i.t. morphine are
serious and include respiratory depression, nausea-
emesis, blocking of the spinal catheter, infection, and
mechanical pump failure. Other disadvantages of the
pump system are the cost of the pump, surgery, and
medication, and the need for frequent reservoir refills.
In a group of 16 subjects with spasticity, Erickson
observed one pump failure and one infection during an
interval of 1–5 yr. Although sustained reduction of
spasticity was observed at doses of 2–6 mg/day, time-
dependent increases in dose schedule were noted in two
subjects. In another study of five subjects with spasticity
and hyperactive micturition reflexes, chronic i.t. infu-
sion of morphine (0.5–0.9 mg/day) for a 5-mo period
did not cause side effects, i.e., nausea, pruritus, which
were observed with i.t. bolus injections of morphine
(200 μg).*** Moreover, side effects were not encoun-
tered when the dose was increased to 1.5 mg/day as a
result of drug tolerance. To obviate the magnitude
and rate of development of tolerance to morphine, the
administration of a drug such as an α2-adrenergic
agonist, which acts at a different receptor site, may be
contemplated.17,85,86,***

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†††† Personal communication.

*** Unpublished observations.

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trathecal infusion of morphine in human subjects with spinal cord lesions

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