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 vesicounversal sphincter dysynergia, 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 vesicoskeletal 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: Analgesia, intrathecal: morphine. Reflex: micturition. Spinal cord: injury.)

When administered intraspinaly, e.g., intrathecal (i.t.) or epidural, to normal animals and humans, morphine suppresses vesicoskeletal 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 vesicouexternal sphincter dysynergia.7 Vesicouexternal 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,10,11,14 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).12-17 As dorsal rhizotomy leads to partial depletion of opioid receptors in the dorsal horn,10,13 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 vesicouexternal sphincter dysynergia, 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 vesicoureteral sphincter dysynergia, and augmented vesicoureteral and somato- vesical 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 Injection of Intrathecal Morphine on Bladder Capacity, and on Detrusor and Striated Sphincter Responses to Bladder Filling

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (y)</th>
<th>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 (cmH₂O)</th>
<th>EMG @ Peak DP</th>
<th>% Post MO</th>
<th>CO</th>
<th>MO</th>
<th>EUS</th>
<th>EAS</th>
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<tbody>
<tr>
<td>1</td>
<td>45/F</td>
<td></td>
<td>VAS-T2/I</td>
<td>28</td>
<td>250</td>
<td>111</td>
<td>79</td>
<td>90</td>
<td>228</td>
<td>250</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>21/M</td>
<td></td>
<td>TR-T9/I</td>
<td>16</td>
<td>250</td>
<td>478</td>
<td>135</td>
<td>95</td>
<td>420‡</td>
<td>680</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>3</td>
<td>37/F</td>
<td></td>
<td>MS-Cer/I</td>
<td>60</td>
<td>200</td>
<td>38</td>
<td>61</td>
<td>30</td>
<td>119</td>
<td>100</td>
<td></td>
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<td></td>
<td>TR-T8/C</td>
<td>11</td>
<td>200</td>
<td>59</td>
<td>76</td>
<td>50</td>
<td>450</td>
<td>175</td>
<td></td>
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</tbody>
</table>

Subjects were administered i.t. morphine (200–250 μg). Etiology: VAS = vascular; MS = multiple sclerosis; TR = trauma. Site: Cer = unidentifiable 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. Premorphine bladder capacity and urethral and anal sphincter EMG values were compared to corresponding peak postmorphine values by the paired t test.

Results

In five of the six subjects, cystometry revealed volume-induced hyperactive micturition reflexes as manifested by: 1) an augmented vesicovesical reflex with a low threshold and uninhibited detrusor contractions; 2) vesicoexternal sphincter dysynergia; and 3) vesicosomatic (limb) reactions (e.g., flexor spasm), 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 dysynergia, 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 somatosensory reaction, and they were capable of initiating detrusor contractions during the filling phase (fig. 1). Within 5–15 min of i.t. morphine injection, the vesicovesical reflex was substantially altered. Bladder capacity was significantly increased (X = 291 ± 113%; P < 0.01; n = 6; table 1) despite persistent vesicoexternal sphincter dysynergia, uninhibited detrusor contractions, and vesicosomatovesical reactions. In the two subjects with complete spinal cord lesions (patients 5 and 6) and one subject with an incomplete spinal cord lesion (patient 1), the rate of rise of detrusor pressure during the contraction phase was markedly attenuated and the peak rate of rise of detrusor pressure for the three subjects was reduced by 93% from a mean 340 ± 35 cmH₂O/min to 25 ± 13 cmH₂O/min. Low post-treatment rates of rise of detrusor pressure in these three subjects were associated with little alteration in the detrusor reflex threshold and with a small reduction in peak detrusor pressure (X = 11 ± 5%; figs. 1B and 2B, table 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 = 273 ± 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...
physiologic changes, i.e., inhibition of vesicovesical and enhancement of vesicospincter 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 somatovesical and vesicosomatovesical reactions.

Augmented urethral sphincter EMG activity during bladder filling (i.e., enhanced vesicovesical sphincter dysynergia) connotes raised urethral tonic muscle activity, 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-
duced degeneration studies in normal animals. Apparent-ly, reduction of the bladder afferent fiber contribution to the supraspinal micturition reflex circuit causes an increased threshold to the initiation of micturition during filling, a behavior also observed following administration 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 detrusor pressure with little alteration in reflex threshold; apparently, this response is not observed in normal subjects. We speculate that this observation represents suppression, rather than extinction, of transmission of bladder afferent signals through spinal pathways, permitting both mechanical (e.g., viscoelastic) and reflex mechanisms to participate in the slow rate of rise of detrusor pressure. The magnitude of vesical reflex activity is independent of the dose of i.t. morphine within a range of 50–400 μg.**

The opposing effects between vesical-evoked vesical and striated sphincter reflex contractions following an i.t. morphine injection also implies ample central processing 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 disinhibits viscosomatic (sphincter, pubendal) reflexes rather than somatic reflexes. Such behavior may be ascribed to action at presynaptic and nonsynaptic primary vesical afferent sites; however, postsynaptic 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 parasympathetic nucleus (which can be modulated by pudendal afferent stimulation), neurons projecting to higher cortical centers (which convey signals for perceptual analysis), and correspondence between the distribution of enkephalins and opiate receptors, e.g., lamina I. Further, the time course of the spinal drug action on vesico- and vesicospincter reflexes, and on suppression of spontaneous and vesical-induced limb motor discharges (flexor spasms or spasticity) leading to excitable somatovesical reactions (e.g., Figs. 1 and 2) is apparently sufficient to attain postsynaptic effects.

In conclusion, i.t. morphine treatment reveals a striking modulatory action on hyperactive micturition reflexes, comprised of enhanced vesicourethral and somato-vesical reflexes, and on limb (vesical induced and spontaneous) reactions in subjects with supraspinal sacral 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 incontinence, and/or phasic intersegmental type of spasticity; 2) the lack of clinical effectiveness of commonly utilized, systemically administered, pharmacologic agents; and 3) a method of continual delivery of morphine, e.g., implantable infusion pump.

Continuous i.t. infusion of morphine by an implanted pump has been used widely for the treatment of chronic pain. This technique has also been used to suppress spasticity in subjects with spinal cord lesions. For many of these subjects, this form of treatment is a preferable 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, timedependent increases in dose schedule were noted in two subjects. In another study of five subjects with spasticity and hyperactive micturition reflexes, chronic i.t. infusion 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 encountered 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 alpha-2-adrenergic agonist, which acts at a different receptor site, may be contemplated.

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