Response to P. Storey

To the Editor:

Thank you for the opportunity to respond to Dr. Storey's letter. We are somewhat confused by it because it is not at all clear what he is suggesting. If he is suggesting that *starting doses* of transdermal fentanyl should be twice what we recommend, we believe this would result in widespread overdosing with this drug. This seems to be the gist of his point 1 and the table. In point 2, however, he appears to be agreeing with our dosage recommendations and actually describes the reasons behind them.

Dr. Storey provides no data to substantiate the figures in his table. Our figures were based on our own published clinical experience[1] and other documented evidence.[2] We agree that our recommendations are conservative and will mean that patients may need top-up analgesia during early treatment with transdermal fentanyl, and that a significant proportion will need to titrate the dose upward. However, roughly 50% will not (a figure with which Dr. Storey seems to agree). The converse of this is that if Dr. Storey's conversion ratio is used to calculate *starting doses*, 50% of patients will receive excessive doses of transdermal fentanyl to start with.

We do not use transdermal fentanyl as our standard strong opioid, but only in carefully selected patients, whose opioid analgesic requirements are stable. Top-up doses of immediate-release morphine are used freely during the early days of treatment and, in our experience, this allows patients to have perfectly adequate pain control without excessive adverse effects and to achieve steady state rapidly with transdermal fentanyl and a stable dose. It is easy enough to titrate up the dose as necessary, but more complicated to backtrack in the event of excessive adverse effects.

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Amenorrhea Associated With Intraspinal Morphine

To the Editor:

Intraspinal opioids have been shown to produce decreased plasma testosterone levels and sexual dysfunction in males.[1] Recently, we have seen the effect of intrathecal morphine on menstrual function in a women whose spinal therapy was interrupted by catheter malfunction. The patient developed severe back pain with radiation to the left leg after a full-term pregnancy, during which she carried twin boys. She underwent a laminectomy and diskectomy without relief, followed several months later by a posterior spinal fusion, which provided mild improvement of the back pain.

The parathesias of the left leg continued and progressed to include involvement of the posterior lateral calf radiating to the lateral aspect of the left foot. After several years, the patient also developed right leg pain. A myelogram revealed mild bulging at the L3–L4 disc and clumping of the nerve roots of the cauda equina, consistent with arachnoiditis. Epidural injections were ineffective, as was conservative treatment consisting of physical therapy and oral analgesics (including nonsteroidal antiinflammatory drugs, antidepressants, anticonvulsants, and weak opioids). After developing increased motor weakness, a third surgery involving take down of the old fusion and neuroforaminal enlargement at L4–L5 and L5–S1 was performed.

After 3 years of treatment with various oral therapies, the patient was referred for implantation of a drug pump. At presentation, she was unemployed due to the pain, overweight, and hypertensive. She had experienced sedation and persistent nausea with less than 100 mg oral morphine equivalents per day. A SynchroMed® pump was implanted. Intrathecal morphine was begun at 0.5 mg/day and gradually titrated to 3 mg/day to afford relief. At this dose, the patient took no oral supplementation, no longer required antihypertensive medication, and returned to work after several years of unemployment.

Five years later, at age 53, the patient began to complain of increasing pain, which she attributed to increasing activity at work and the addition of an active grandchild to her household. Aggressive, periodic dose increases were ineffective. After 4 months, the patient reported that she resumed menses, inquiring whether this was related to intrathecal drug therapy. Apparently, she had ceased menstruating within 1 month after initial pump implantation. She had failed to report this initial cessation, as the change was perceived to be beneficial. Endometrial biopsies were normal, as were serum estradiol, FSH, and LH levels, indicating that she was not menopausal. Radiographs of the pump and catheter system were normal; however, small cracks or holes are generally not seen with these studies.[2] The drug delivery system was surgically explored, revealing a small hole in the catheter proximal to its entrance into the spinal canal. A new catheter was placed and the intrathecal morphine dose was decreased to the previously effective 3 mg/day. Since this revision, the patient has again developed amenorrhea.

Although disruption of menstruation and infertility have been reported in those using heroin,[3] this case illustrates the effect of intrathecal morphine on menstruation during a period when neither patient nor investigator knew whether the drug was being administered. The prevalence of amenorrhea in women receiving systemic or intraspinal opioids is unknown and is difficult to determine, as most of our female patients are postmenopausal, have undergone hysterectomy, or have concomitant endocrine disorders. It is also unclear whether hormonal therapy may overcome these effects, particularly because this patient was unwilling to seek such treatment for the amenorrhea. Male patients experiencing decreased libido and difficulties with performance are given testosterone by intramuscular injection or patch. Based on this patient's experience and the anecdotal reports of others working with spinal opioids, we now routinely alert both male and female candidates to the possible effects of intraspinal morphine on sexual function and fertility. Several women have declined therapy due to this potential effect.

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