Epidural Opiates and Urinary Retention: New Models Provide New Insights

Urinary retention occurs following acute systemic opiate therapy, and is due to complex effects on peripheral and central neurogenic mechanisms controlling the micturition reflex. In recent years, opiates have been administered with greater frequency by the epidural route to produce segmental analgesia, particularly for the postoperative relief of pain in obstetrical and surgical procedures. With this route of opiate administration, bladder dysfunction has been widely noted. For the most part, urinary retention has not been regarded as a serious medical complication. For the patient, however, micturition difficulties are a source of severe and often prolonged discomfort, sometimes warranting repeated bladder catheterization, a procedure which may lead to potentially serious urinary tract infections. Other bladder problems may also arise since epidural opiates produce detrusor hypotonicity but do not appear to impaire urine production. Thus, bladder overdistension due to continuous filling may occur and, if not alleviated, may produce some permanent impairment of urethral vesicle function. From these observations, it would seem contradictory to advocate the use of epidural morphine in the symptomatic treatment of urinary tract dysfunction, but, clearly, there are circumstances such as bladder spasm and ureteral colic where morphine is beneficial. In these situations, the centrally mediated reduction of detrusor smooth muscle tone, together with powerful analgesia, would be desirable.

The spinal actions of opiates on visceral reflexes are clearly of clinical and scientific importance. Knowing how these effects are mediated would help rationalize the management of the clinical problem of urinary retention, but could also be exploited to provide alternative methods to treat a variety of vesicle dysfunctions. Mechanistic studies have been made in laboratory animals under general anesthesia. These studies have shown that intrathecal opiates inhibit the micturition reflex as expected. This is likely due to depression of preganglionic neurons in the sacral parasympathetic nucleus, resulting in a reduced activity in the pelvic nerve and insufficient cholinergic activation of bladder smooth muscle. Transmission of afferent activity from the bladder is also believed to be impaired. This, however, is due to the activation of opioid receptors on primary afferent nerve terminals with the consequent inhibition of transmitter release in the spinal cord. These mechanistic studies have now been extended in several important ways, and are reported in the present issue of Anesthesiology. Thus, Durant and Yaksh have developed a novel experimental model in which cystometric measurements were made in unanesthetized rats via a chronically implanted bladder cannula. At the same time, the effects produced by the administration of analgesic doses of morphine via an indwelling intrathecal cannula were evaluated. Analgesia was assessed using the tail-flick method. A further technical advantage was that the urethra was unobstructed and, therefore, voiding of urine could be measured. Comparison of fluid voiding rate with intravesicular pressure gave an indirect index of urethral sphincter tone. The data obtained showed that morphine analgesia and inhibition of the micturition reflex occurred in parallel. Moreover, inhibition of voiding was accompanied by an increase in intravesicular pressure caused by the contin-
uous filling of the bladder during the course of the experiment. Dribbling of fluid from the bladder occurred only when intravesicular pressure exceeded the resistance of the urethral sphincter. This observation suggested that a significant contribution to urinary retention was likely to be caused by detrusor-urethral sphincter dyssynergia due to a failure of sphincter relaxation.

Recent clinical experience mentioned earlier suggests that bladder dysfunction is likely to remain a problem when opiates are injected epidurally. Is bladder catheterization, therefore, the only reliable method by which urinary retention can be relieved? Clearly, normal function may be restored by naloxone administration, but also with the loss of the desired analgesia. An alternative has been the use of cholinergic agonists, which directly stimulate detrusor smooth muscle, or adrenergic antagonists, which reduce muscle tone in the sphincter. These and other agents have been used with varying success. Durant and Yaksh have further pursued the question of alternative pharmacological strategies. They have evaluated a number of prototype agonists and antagonists in an attempt to reverse the urinary retention and, thus, to guide future clinical practice. Interestingly, apomorphine, a dopamine receptor stimulant, appeared to provide the most promising profile of activity. It did not impair morphine analgesia, but induced almost complete bladder emptying. Although relaxation of the urethral sphincter was discussed as a possible mechanism, further study regarding this seems necessary.

Clinically, apomorphine has a number of serious drawbacks, including its brief action, powerful emetic properties, and central stimulant/depressant effects; the latter a clear contraindication for use with other central depressants like morphine. Other dopamine receptor stimulants, such as bromocriptine, may be better tolerated. But it is uncertain whether this agent might be beneficial for opiate-induced urinary retention when it is efficacious in the treatment of hyperreflexive and unstable urethral conditions.

Perhaps it might be easier to pursue a strategy which would avoid or minimize urinary retention by using epidural opiates with fewer side effects; e.g., methadone or pentazocine.21,12 It is now certain that opiates exert their effects by interactions with receptor subtypes. These have been designated as mu, delta, or kappa on the basis of differential sensitivity of opiates in various peripheral smooth muscle bioassay systems and in studies of ligand binding to fragments of synaptic membranes. Studies with spinal intrathecal injection of receptor selective opiates have shown that inhibition of the micturition reflex is produced only by mu and delta, but not kappa, ligands.7,8 Such experiments indicate that opiate analgesics with relatively more kappa receptor properties would likely cause a lower incidence of, and less severe, urinary retention. Indeed, clinical experience appears to support this.12 The experimental approach of Durant et al. and their initial findings reported here9 certainly hold the promise that the many outstanding issues concerning the control of bladder function may soon be resolved.

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References