

## Epidural Narcotic Infusion Reservoir: Implantation Technique and Efficacy

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Several authors have reported prolonged relief of pain with epidural narcotic analgesia (ENA).<sup>1,2</sup> Specifically, Zenz *et al.*<sup>3</sup> described administration of ENA in 40 cancer patients for up to 118 days. The implementation of chronic ENA therapy has been delayed due to occasional reports of insidious and delayed respiratory depression following intraspinal administration of narcotics (predominantly intrathecal).<sup>4</sup> Furthermore, a safe system did not exist to limit the hazards of intrathecal or epidural catheter borne infection. We recently implanted a completely self-contained system allowing continuous ENA without an exposed catheter or frequent percutaneous injections. Since the first implantation (February 6, 1981), seven patients have received implants. Concurrently, Onofrio *et al.* implanted a similar system for continuous intrathecal morphine administration in one patient with cancer pain.<sup>5</sup> This patient was followed for three months with good pain relief and no evidence of narcotic tolerance. In this report we present a brief description of this implanted continuous epidural infusion system and the resultant analgesic outcome among seven patients who had received implants.

## MATERIALS AND METHODS

An implantable continuous epidural infusion system was devised by joining a "non-reactive" Silastic epidural

catheter<sup>6</sup> with an implantable drug delivery system, the Infusaid®. This system was tested successfully up to nine months in the Dorset ram with saline and variable morphine concentrations with no evidence of respiratory depression (up to 12 mg/day, unpublished data). The Infusaid® weighs 180 g empty and has a drug reservoir capacity of 50 ml (fig. 1). This device is percutaneously refillable through the inlet septum. We have chosen to use devices with a 2-3 ml/day flow rate to allow a refill cycle of around 15-20 days. Other investigators have used up to 10 ml of saline vehicle for acute epidural narcotic injections, implying that these volumes are required to achieve optimum analgesic duration and intensity.<sup>7,8</sup> Our studies with sheep implanted with the continuous epidural infusion system indicated that a narcotic equilibrium concentration is reached in the lumbar and cisternal cerebral spinal fluid such that the volume infused is less critical (unpublished data). As a consequence, the flow rate is chosen primarily for patient convenience (*i.e.*, to limit the frequency of refills). Figure 2 shows a roentgenograph of patient seven with an Infusaid model 400 implanted for continuous ENA therapy.

These studies were initiated following approval of our institution's Committee for the Protection of Human Subjects and informed consent from each patient. All patients have intractable pain that failed to be controlled or relieved by conventional analgesic approaches, a "predicted" life expectancy of greater than four months, and elect this therapy over neurosurgical intervention at the time of evaluation. Further suitability is defined by the presence of at least a 50 per cent sustained reduction (>8 hours) of visual pain analogue scale scores (VPASS),<sup>9</sup> compared to a baseline profile VPASS, following single epidural narcotic injections (preservative-free morphine [0.06-0.08 mg/kg]). The presence of significant mental depression (demonstrated by a Zung Self-Rating Depression Score of >0.65<sup>10</sup>) which is likely to influence accurate pain reporting is considered an exclusion factor until the patient can be treated for this depression.

The implantation was performed in the operating room using a regional epidural anesthetic, with the patients awake and in the lateral position. The implantation procedure takes place in two stages. The first stage consists of placing the Silastic catheter (1.65 mm OD) and a cardiovascular guide wire (0.63 mm OD) through a

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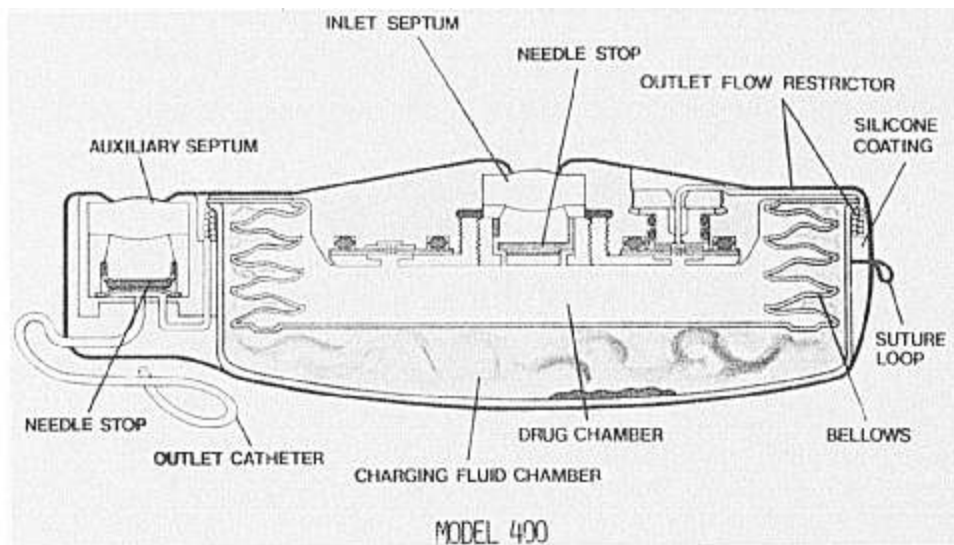


FIG. 1. Cross-sectional view of the Infusaid® Model 400 demonstrating the two-chambered system and separate side port for bolus injection. Model 100 has the same internal construction without the side port. (Permission given by Metal Bellows Corporation, Sharon, Massachusetts)

modified 9-gauge Tuohy needle passed into the epidural space (usually T12-L1). A 5-cm midline vertical incision was made over the appropriate spinous process to allow lateral subcutaneous tunneling of the catheter prior to introduction of the Tuohy needle. The catheter and guide

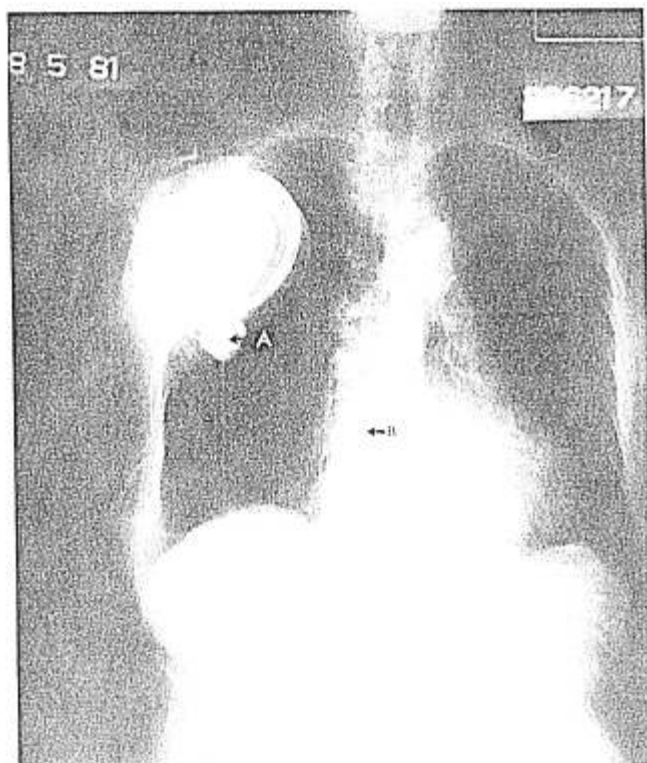


FIG. 2. Anterior posterior chest roentgenogram of patient seven implanted with an Infusaid® Model 400 in the right subclavian position on the anterior chest wall. Arrow A indicates the side port septum for bolus injection. Arrow B indicates the metal connector at the junction of the radiopaque Infusaid catheter with a non-radiopaque silastic epidural catheter just prior to entry into the thoracic epidural space.

wire were guided by fluoroscopy and correct placement of the catheter was confirmed by metrizamide (3–5 ml) epidurogram. The epidural catheter was secured to the superficial dorsal lumbar fascia with nonabsorbable ligature and patency was documented by saline injection. Permanent catheter position was chosen to effect antinociception in the affected segmental sensory afferent distribution. The second stage involves the implantation of the Infusaid® pump. Prior to implantation, the Infusaid® was filled with the morphine solution (1 mg/ml) and then prewarmed to 37°C. The Infusaid® was then placed into a subcutaneous pocket, created by blunt and sharp dissection, either on the abdomen or subclavian area. The Silastic Infusaid® catheter was then subcutaneously tunneled from the pump pocket to the back incision where it was connected to the Silastic epidural catheter with a straight metal connector. The incisions were closed, a sterile dressing applied and the patient observed in the postanesthesia recovery room until regression of the thoracic epidural anesthetic occurred (stable blood pressure, pulse, and return of motor function). All patients received routine postoperative monitoring with vital signs (blood pressure, pulse, and respirations) every four hours during the first 24 hours. In no instance was it necessary to monitor more frequently than tid after the first 24 hours (all patients were alert and no cognitive impairment was noted with repeated observation).

Following the surgical procedure the patients were evaluated in the hospital for three to five days to assess analgesic response, to observe the surgical incisions and to observe each patient for any signs of adverse reactions (respiratory depression, mental depression, pruritis, urinary retention, etc.). Prior to discharge, the patients and their families were educated as to the systems function, possible side effects, and steps to take in the event

TABLE 1. Descriptive Characteristics and Analgesic Outcome of Epidural Reservoir Implant Recipients

Patient	Sex	Age (Years)	Diagnosis	Pain Site	Duration of Pain	Catheter Site	VPASS (10-Day Means)		
							Baseline	6 Weeks	12 Weeks
1	M	60	Adenocarcinoma of the rectum	Hips, back, and legs	1 Year	T12-L1	4.7	2.3	3.3
2	F	58	Adenocarcinoma of the rectum	Back and legs	6 Months	T9-10	4.8	0.2	1.4
3	F	48	Intractible low back pain	Back and legs	10 Years	T9-10	6.9	1.0	2.6
4	M	75	Adenocarcinoma of the rectum	Back and legs	8 Months	T9-10	3.4	1.3	1.2
5	M	52	Intractible low back pain	Back and legs	10 Years	T9-10	6.3	5.1	6.7
6	F	83	Adenocarcinoma of the rectum	Hips and legs	2 Months	T8-9	6.2	0	0
7	F	74	Adenocarcinoma of the rectum	Back, hips, and legs	18 Months	T9-10	4.8	2.0	2.0

a problem should occur. (Note: a criterion for patient selection was the residence, in the patient's home, of a family member trained to observe the patient for any signs of complications.) In addition, their local Visiting Nurses Association and physician were contacted and also informed about the system. When the patients were discharged from the hospital, all care and refilling of the implanted system was performed at their home by the local visiting nurse.

Analgesic outcome was evaluated by comparing baseline and serial postimplantation VPASS. Prior to starting treatment, patients maintained one week of daily VPASS to establish a baseline pain level. Following implantation, the patients continued to fill out daily VPASS in order to assess their response to therapy. Preimplantation scores were then compared with postimplantation scores utilizing a mean ten-day score.

### RESULTS

Table 1 shows the descriptive characteristics of the implanted patient population and analgesic outcome. Technically, all pumps have performed within the 15 per cent variation in flows claimed by the manufacturer with two exceptions. Patient one's flow rate fell to 25 per cent of its predicted flow rate between five and six months of operation. This alteration could be explained by the slight increase in viscosity associated with the infusion of an increased concentration of morphine (7-10 mg/ml) (This has been previously verified in our laboratory, unpublished data) and a slight hypothermia. In contrast, patient number two developed an increased flow rate >15 per cent which was associated with repeated febrile urinary tract infections.

Table 1 also demonstrates the analgesic outcome over the first three months of therapy. At six weeks postimplantation, six of seven patients (including all patients

with cancer related pain) reported that their pain (VPASS) was reduced to less than 50 per cent of preimplantation levels. Further, all seven patients received no other narcotics, excluding their epidural narcotic. The mean VPASS at six weeks postimplantation was 1.7, vs. 5.3 prior to intraspinal narcotic therapy. When evaluated following three months of therapy, five of seven demonstrated sustained maintenance analgesia as judged by a VPASS of less than 50 per cent (mean 2.4) of pre-intraspinal narcotic therapy. However, patient number one had developed lumbo-sacral involvement which subsequently responded to an increased epidural dose of 30 mg/day. Patients 1 and 2 have subsequently died, but their analgesia was sustained for six months by epidural morphine doses up to 30 mg/day. The mean VPASS at three months was slightly greater than at six weeks, perhaps indicating a general trend toward tolerance. However, at this time analgesia was quite obtainable by modest increases in dosage (mean epidural morphine dose delivery required for this group at six weeks was 4.0 mg ± 4.3 mg/day, while at twelve weeks the mean narcotic delivery was 8.9 mg ± 10.8 mg/day). Patient 5 demonstrated a slight reduction in mean VPASS at six weeks having concomitantly stopping all oral analgesics (four years of 600 mg/day codeine and additional 200 mg/day thioridazine and 100 mg/day amitriptyline). Though his subsequent VPASS actually exceeds the pretreatment level, his functional status improved. This was supported by increased activity levels and social involvement documented by a nurse observer during biweekly home visits.

With morphine dosages of 2-30 mg/day via this implanted system, no evidence of respiratory depression, pruritis, nausea, vomiting, or urinary retention have occurred. All implantation site incisions have healed well with no evidence of either localized skin irritation or most importantly infection.

All patients were weaned off all other narcotics over

3–5 days following initiation of continuous ENA. However, some of the patients have occasionally had moderate pain which spontaneously occurs with suspected increases in size of the primary tumor mass or after unusual physical activity. The duration of discomfort usually exists for 1–2 days but then subsides. Characteristically, all patients have reported increased appetite and an improved ability to sleep through the night. These subjective observations were verified independently by either the spouse or residing family member and by body weights obtained in follow-up clinic visits.

#### DISCUSSION

This study demonstrates the versatility and reliability of this implanted system for sustaining continuous drug delivery to the epidural space. The intention of this approach was to provide patients with a system requiring infrequent injections, mobility, and freedom from a percutaneously exiting catheter. Though the true incidence of complications (*i.e.*, infection, epidural abscess, etc.) and system failure will require a larger patient series, clearly the feasibility of this system seems established.

Because of the number of reported instances of respiratory depression following intraspinal narcotics, a significant concern has existed that chronic intraspinal narcotics would result in respiratory depression. Our data, the reports of chronic ENA therapy by Zenz *et al.*<sup>3</sup> and Onofrio *et al.*<sup>5</sup> do not support this fear. Further, it is our experience that these patients sleep and eat well while total systemic narcotic requirements are reduced. That no respiratory depression occurred might be explained by tolerance due to prior narcotic analgesic exposure in our patients. Also perhaps, continuous ENA, in contrast to bolus injection, does not result in a sudden rise in cerebral spinal fluid (CSF) narcotic levels but rather leads to a low equilibrium concentration between CSF and plasma. This is supported by our findings of low cisternal levels of narcotic during chronic lumbar epidural morphine administration to sheep (unpublished data). Bolus injections in contrast would result in sudden rises in CSF narcotic levels which may reach the brain stem respiratory centers with a mass effect. In our study continuous epidural morphine doses up to 30 mg/day did not lead to respiratory problems. Little chronic ENA experience has been reported, however Zenz *et al.*<sup>3</sup> used bolus epidural injections of up to 20 mg of morphine four times a day in one patient without respiratory difficulties. Nevertheless, this latter practice (repeated bolus ENA) would be expected to lead to respiratory difficulties.

Though the chronic administration of intraspinal narcotics may offer an alternative to neuroablative proce-

dures for the relief of intractable pain, at least two major obstacles will demand satisfactory solutions prior to widespread dissemination of this technique; tolerance and neurotoxicity. First, an increase in dose is necessary to sustain analgesia, suggesting narcotic tolerance has occurred. Interestingly, not every patient requires an increase in dose and the dose escalation rate and ultimate ceiling have been quite variable between patients. To some extent, this could reflect dural thickening or a gradual increase in the diffusion pathway which the relatively lipid insoluble agents, such as morphine, must traverse. Histopathologic studies currently underway tend to support that this indeed may be a partial factor. With respect to cancer pain, an increase in dose in these patients might be expected to occur with the extension of disease to involve sympathetic pain fibers which are perhaps more resistant to the spinal action of narcotics, or by extension of disease into a segmental field extrinsic to the area primarily affected by the intraspinal infusion.<sup>11</sup> Nevertheless, progressive spinal narcotic tolerance is most likely the reason for this increasing dose requirement. Progressive dose increases may compensate for such tolerance in some terminal cancer patients where relief of suffering is the only legitimate concern. Such an approach in other instances invites progressive increases in cisternal CSF narcotic levels and eventual respiratory depression. As a consequence, methods to prevent, forestall, or reverse spinal narcotic tolerance and monitoring techniques for CSF narcotic concentrations (thus demonstrating adequacy or excessiveness of intraspinal narcotic delivery) are currently the object of active research at this center.

It is not known whether chronic intraspinal narcotic infusions and/or indwelling intraspinal catheters will cause neurotoxicity. Thus, prior to significant application of chronic intraspinal narcotics to chronic pain patients (pain not associated with malignancy), neuropathologic studies should be performed as frequently as possible to assess any effects due either to chronic intraspinal agents or implanted materials.

In summary, based on our encouraging initial results, we believe this approach should be studied judiciously in controlled, perhaps multicentered investigations.

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## Relationship of Alveolar-Arterial Oxygen Tension Difference in Diaphragmatic Hernia of the Newborn

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In congenital diaphragmatic hernia of the newborn, pulmonary hypoplasia and persistent fetal circulation cause acidosis, hypercapnia, and hypoxemia.<sup>1-5</sup> The magnitude of the cardiopulmonary shunt, as indicated by the alveolar-arterial oxygen tension difference (A-aD<sub>O<sub>2</sub></sub>) at an inspired oxygen concentration of 100 per cent (FI<sub>O<sub>2</sub></sub> 1.00), usually decreases immediately following reduction of the hernia. Preliminary data suggested that the A-aD<sub>O<sub>2</sub></sub> at that time may be an accurate predictor of ultimate outcome.<sup>5</sup> If this is true, the A-aD<sub>O<sub>2</sub></sub> then may identify those infants at greatest risk of respiratory failure following anesthesia and operation.

### METHODS

To delineate the relationship of the A-aD<sub>O<sub>2</sub></sub> to survival, we prospectively studied 39 newborns with diaphragmatic hernia. Prior to and during anesthesia and oper-

ation we treated the infant's acidemia and hypoxemia with: (1) tracheal intubation, (2) manually controlled hyperventilation at frequencies of 40 to 60 breaths per min and peak inspiratory pressures of 25 to 40 cmH<sub>2</sub>O in an effort to achieve a PaCO<sub>2</sub> of 25 to 30 mmHg, and (3) intermittent intravenous sodium bicarbonate in doses estimated to restore arterial pH to 7.40. In an effort to minimize barotrauma, we limited peak inspiratory pressures to 40 cmH<sub>2</sub>O. Despite these efforts, asphyxia of varying degrees persisted prior to hernia reduction. Under general anesthesia with neuromuscular blockade, at an FI<sub>O<sub>2</sub></sub> of 1.00, blood samples were obtained immediately before and after reduction of the hernia. The A-aD<sub>O<sub>2</sub></sub> was derived in the conventional manner.<sup>6</sup> Samples were collected from indwelling arterial catheters into heparinized syringes, iced, and analyzed within minutes for pH and blood-gas tensions on an Instrumentation Laboratories 113 or 213 System. All values were corrected for temperature, and pH values were converted to hydrogen ion concentrations (cH) for statistical analysis. Mean values were compared using the conventional student *t* test for differences.

We were concerned with the influence of the arterial sampling site on the A-aD<sub>O<sub>2</sub></sub>. Shunting through the ductus arteriosus could contaminate systemic arterial blood with pulmonary arterial blood, and has been observed in infants with diaphragmatic hernia.<sup>7</sup> Therefore, we analyzed the effect of the sampling site on gas tensions after reduction of the hernia by comparing values obtained from infants whose right radial or temporal artery were sampled with those infants whose umbilical artery was sampled.

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