Subarachnoid Adrenal Medullary Transplants for Terminal Cancer Pain

A Report of Preliminary Studies

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Background: The prolonged use of opioids to treat intractable pain with currently available therapeutic modalities is often unsatisfactory, usually because of tolerance or complications. Extensive studies carried out in the authors' laboratories have indicated that the transplantation of adrenal medullary tissue into the spinal subarachnoid space can significantly reduce pain in animal pain models, most likely via release of opioid peptides and catecholamines. The current study was undertaken to assess the feasibility and efficacy of subarachnoid adrenal medullary transplantation in alleviating terminal cancer pain in humans.

Methods: Two milliliters of human adrenal medullary tissue were prepared in the laboratory and then transplanted via lumbar puncture into the subarachnoid space in five patients suffering from terminal cancer pain. Pain scores (VAS), functional activity, and opioid intake were assessed and recorded before and after the transplantation procedure. In addition, CSF samples were collected before and (when possible) at fixed intervals after transplantation for biochemical and cytologic analysis.

Results: Four of the five patients demonstrated progressive decreases in pain scores after the transplant procedure, with concomitant reductions in opioid intake. Three of these four patients remained pain free, two for over 10 months, while the other had a recurrence of her pain after surgery for spinal cord compression secondary to metastases 10 weeks after transplant. The fifth patient had no pain reduction by 1 month after the procedure, and refused further followup. After the transplants, spinal CSF samples revealed increased concentrations of met-encephalin in three of the five patients, and increased concentrations of catecholamines in the four patients in whom they were determined.

Conclusions: The results obtained in this study indicate that subarachnoid adrenal medullary transplantation may provide a unique and effective approach to the management of intractable chronic pain in humans. (Key words: Transplant, adrenal, medulla, subarachnoid, pain, enkephalins, catecholamines.)

PHARMACOLOGIC treatment of intractable cancer pain is often unsatisfactory. Some patients rapidly develop tolerance to parenteral opioids, resulting in progressively increasing dosages that often produce unpleasant and/or undesirable side effects. The use of epidural and subarachnoid opioids offers many advantages, but introduces the problem of mechanical malfunction of tunneled catheters, injection ports, and pumps, as well as the possibility of infection that can occur with any invasive technique. During the past 7 yr, studies carried out in our laboratories have indicated that the transplantation of adrenal medullary tissue into the spinal subarachnoid space can significantly reduce pain in several rodent pain models without the development of tolerance.1–4 Adrenal medullary chromaffin cells were selected, because they secrete both catecholamines and opioid peptides, agents that independently,
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and possibly synergistically, reduce pain when injected locally into the spinal subarachnoid space. A significant advantage of this transplant approach to the alleviation of pain is that it acts as a living "biologic pump" that can serve as a local endogenous source of pain-reducing, neuroactive substances on a long-term or permanent basis, reducing, or even eliminating, the need for repetitive exogenous opioid administration. The current report presents the first application of this approach in humans.

Materials and Methods

Before the initiation of this pilot study in humans, approval was obtained from the University's Institutional Review Board to carry out subarachnoid adrenal medullary transplantation in five patients suffering from intractable pain secondary to clearly established, non-resectable, carcinomatous lesions. It was agreed that the procedure would be carried out only in patients who had already developed a need for high or progressively increasing doses of opioids with progressively decreasing analgesia, and whose life expectancy was 6 months or less.

Once identified, suitable candidates were referred to the University of Illinois Pain Control Center, while adrenal glands were transported from the Regional Organ Bank of Illinois to the University in a sterile tissue-transport solution. All donors were otherwise healthy adults, ranging in age from 20 to 53 yr, who died from either gunshot wounds or wounds sustained in motor vehicle accidents. Within 3 h of the harvesting of the glands, the medullary tissue was separated from the rest of the gland, sectioned, and cultured. Every effort was made to exclude cortical tissue, but, undoubtedly, some cortical cells were included in the culture. (Most likely the cultures were "contaminated" by other cells, such as endothelial cells, fibroblasts, etc.) After 5–7 days in culture, the functional integrity of the cells was assessed by high-pressure liquid chromatography (HPLC) determination of catecholamine production, and by radioimmunoassay (RIA) for met-enkephalin production in representative tissue fragments. In addition, the viability of the cultured fragments was assessed immunocytochemically by labeling the tissue with tyrosine hydroxylase antibody and then microscopically determining the morphologic integrity of the cells. Only after functional integrity and viability of the tissue had been established was the recipient admitted to the hospital. At this time, the procedure and the possible benefits and risks were explained to the patient one final time, and written consent was obtained. Then, after a baseline physical examination and determination of baseline visual analog pain scores (VAS), activity levels, and levels of opioid consumption, the patient was given 500 mg cyclosporine orally. This dose was repeated the following morning, the day of the transplant procedure.

On the morning of the procedure, the adrenal medullary tissue was removed from culture, and a suspension of 1–2-mm fragments was prepared under sterile conditions. Within 30–45 min of this preparation, the adrenal medullary tissue fragments (representing two human adrenal medullas) were centrifuged for transplantation. After removal of the supernatant, approximately 2 ml of adrenal medullary tissue was available for injection. In the meantime, an intravenous infusion was started in the recipient, and a course of prophylactic antibiotics was begun. Then, under aseptic conditions, lumbar puncture was accomplished with a 14-G Tuohy needle; a sample of cerebrospinal fluid (CSF) was withdrawn for baseline laboratory studies; and the adrenal medullary tissue was injected into the subarachnoid space. After this, 3 ml of the patient's CSF was injected to flush any residual cells through the spinal needle. After the needle was removed, the patient received several liters of intravenous fluids before discontinuing the infusion.

The patients were discharged from the hospital on the day after the transplant procedure with a prescription for 10 mg·kg⁻¹·d⁻¹ cyclosporine for the first 2 weeks after discharge. They were also given preprinted "pain evaluation diaries" to allow them to assess, on an ongoing basis, the effects of the transplant by recording pain scores (VAS), activity patterns (time out of bed), and analgesic consumption. Finally, the patients were asked to return 1 week and 1, 2, 4, and 6 months after the transplant procedure for CSF sampling and analysis, and for determination of their level of pain scores, activity patterns, and opioid analgesic intake.

Results

Case 1

This patient was a 61-yr-old woman with a 6-yr history of carcinoma of the colon that had been treated with
multiple, sequential surgical procedures, including colostomy and ureteral diversion, and also with radiation therapy and chemotherapy. As her disease progressed, she developed back and lower extremity pain that became increasingly more severe in spite of escalating doses of opioids. An adrenal medullary transplant was carried out using tissue from a 53-yr-old man. As seen in figure 1, her pain scores decreased progressively over the first 8 weeks after the transplant (fig. 1A), and her opioid intake decreased concomitantly. By the end of the tenth week (fig. 1B) she required no further opioid analgesics. During this time, the met-enkephalin levels in her CSF increased threefold in the first week and sixfold in the subsequent 3 weeks. Catecholamine determinations were not carried out on this first patient (fig. 1C). For the last 2 months of her life, the patient stated that “pain was no longer a problem.”

Case 2

This patient was a 69-yr-old man with a 4-yr history of carcinoma of the colon, initially treated by surgical resection, and subsequently by 45 radiation treatments for metastases. His pain, predominantly sacral, was highly “position dependent,” in that he was in mild to moderate pain even in bed, but when he attempted to sit up, the pain became unbearable. When he no longer obtained relief from parenteral opioids, an epidural catheter had been implanted for opioid delivery, and, although this temporarily provided improved pain relief, after several weeks the catheter became infected and had to be removed, at which time the patient was referred for adrenal transplantation. The procedure was carried out using the tissue obtained from a 21-yr-old man. After this, the patient’s pain decreased rapidly (fig. 2), and he was able to discontinue all of the opioid analgesics except for occasional oxycodone (Percocet, DuPont, Wilmington, DE) tablets (fig. 2B). The onset of pain relief was accompanied by a remarkable increase in daily activity (fig. 2C); by the end of 2 months after transplant, the patient was up and about for 12 h a day, and when attempts were made to contact him concerning his 2-month CSF sample, he was on vacation in another state. Serial studies carried out on his CSF (fig. 2D) indicated a moderate elevation of the norepinephrine levels before the transplant and a slight decrease after the procedure. On the other hand, there was a marked increase in the dopamine level at 12 weeks, but there was no increase in his met-enkephalin level. Nonetheless, the patient continued to be pain

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Fig. 1. Pain scores (A), daily narcotic intake (B), and CSF met-enkephalin levels (C) after adrenal medullary transplantation in patient 1 (see text).
free until his death almost a full year after his adrenal transplant.

**Case 3**

This patient was a 49-yr-old woman with a 3-yr history of carcinoma of the left breast treated by mastectomy followed by chemotherapy. Two years after mastectomy, she began to complain of pain in her lower back, right hip, and buttocks, at which time computerized tomographic (CT) scan of the thoracic spine revealed metastatic lesions in the second and third thoracic vertebrae with evidence of cord compression. She underwent a successful course of radiation therapy applied to this area, but, later that year, magnetic resonance imaging (MRI) of the lumbosacral spine showed metastases to the second and third lumbar vertebrae, as well. Surgical intervention was not recommended; therefore, the patient received further radiation therapy. Nonetheless, she continued to complain of severe low back pain that radiated to her right hip and that was becoming unresponsive to opioid analgesics.

At the time of adrenal transplantation, only about two-thirds of the usual volume of CSF required for analysis was collected; it then became very difficult to obtain additional fluid, and what was obtained was blood tinged. Nonetheless, the adrenal medullary tissue from a 20-yr-old man was transplanted as planned, after it had been ascertained that the needle was still within the subarachnoid space. Figure 3A shows that, the first month after the transplant, the patient's pain decreased, as did her opioid intake, although her opioid intake had increased transiently between 20 and 30 days before.

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Case 4

This patient was a 52-yr-old man with a 3-yr history of colon cancer, initially treated by abdominoperineal resection, followed by both chemotherapy and radiation therapy. X-rays and CT scans revealed pulmonary metastases and diffuse abdominal lymph node enlargement, and, in addition, left ureteral obstruction, for which a left ureteral stent was placed. He did well until he developed pain in the sacral area with radiation to the suprapubic region, and, when the pain became unresponsive to increasing doses of opioid analgesics, he was referred to the Pain Control Center, where he received a subarachnoid adrenal medullary transplant using tissue from a 21-yr-old man. As seen in figure 4A, this patient’s pain abruptly decreased, and, by the end of 3 weeks, the patient had decreased his opioid intake to zero (fig. 4B). The serial CSF analyses (fig. 4C) indicated that norepinephrine levels increased almost threefold by the end of the first week after transplant, and sixfold by the end of the eighth week. Both dopamine and met-enkephalin levels were also increased after the procedure.

Case 5

This patient was a 41-yr-old man who had undergone 22 abdominal procedures for Gardner’s syndrome, a syndrome of multiple desmoid tumors that, in this case, caused repeated episodes of gastrointestinal obstruction. Although the precise nature and origin of the patient’s pain were unclear, because the pain was unresponsive to high doses of opioids, he was recommended for an adrenal medullary implant, which was carried out using tissue from a 31-yr-old donor. During the first month after the procedure, the patient did not report significant pain relief, in spite of large increases in CSF levels of catecholamines and met-enkephalin (fig. 5). However, he subsequently refused to return to the hospital for evaluation and insisted that he be maintained
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**Discussion**

In the animal studies that are the basis of the current study, Sagen and Pappas assessed the effects of adrenal medullary transplants on noiception in rats using models of both acute and chronic pain. Results of the studies using an acute pain model indicate that transplants of solid tissue pieces of adrenal medulla into the spinal subarachnoid space increase tail-flick latencies, paw-pinch thresholds, and hot-plate latencies when stimulated by injection of low doses of nicotine. This effect was not seen with control transplants. Chronic pain was originally assessed using the arthritic rat model. It has been suggested that the initial weight loss and subsequent retardation of weight gain in these animals is indicative of a chronic state of pain. Transplants of adrenal medullary tissue (but not control tissue) significantly attenuated this normally seen weight loss in arthritic rats. More recently, in a rodent neuropathic pain model, adrenal medullary transplants in the spinal subarachnoid space have been found to reduce pain resulting from nerve damage. This recently developed animal model shows many parallels to chronic pain as experienced in humans, including hyperalgesia, allodynia, and dysesthesia. Again, using this model, transplants of adrenal medullary tissue, but not control tissue, significantly reduced the typical signs of chronic pain behavior in these animals.

The analgesia produced by adrenal medullary transplants appears to be mediated by both the opioid peptides and the catecholamines released by the trans-

Fig. 4. Pain scores (A), daily narcotic intake (B), and CSF catecholamine and met-enkephalin levels (C) after adrenal medullary transplantation in patient 4 (see text). DA = dopamine; EPI = epinephrine; MET = met-enkephalin; NE = norepinephrine.

on meperidine (Demerol, Sanofi Winthrop, New York, NY); therefore, further details and followup are unavailable.

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Fig. 5. Cerebrospinal fluid catecholamine and met-enkephalin levels after adrenal medullary transplantation in patient 5 (see text). DA = dopamine; EPI = epinephrine; MET = met-enkephalin; NE = norepinephrine.
planted chromaffin cells, because the effect can be blocked by the opioid antagonist naloxone and attenuated by the adrenergic antagonist phentolamine. In addition, increased levels of both opioid peptides and catecholamines were found to be present in the CSF of rats with adrenal medullary (but not control) transplants. 

Interestingly, in rats, both allografts of rat adrenal glands and xenografts of bovine or human adrenal glands survived well and reduced pain sensitivity for at least 1 yr after transplantation. Throughout that time, morphologic studies showed that the transplanted chromaffin cells still appeared healthy, with little evidence of immunologic reaction in the central nervous system of the host rat.

The issue of tolerance to the antinociceptive effects of adrenal medullary transplants is important, because opioid peptides are released continuously from the transplanted cells. This was addressed by generating dose-response curves to morphine before and after adrenal medullary transplantation. Surprisingly, not only was there no apparent tolerance to morphine in adrenal medullary transplanted animals, but the morphine dose-response curve was shifted to the left, indicating that the analgesic response to morphine was potentiated by the transplants. It is certainly possible that the combination of the endogenous opioids and the catecholamines released by the transplanted cells produces effects that are additive (and even synergistic) to those of the exogenous opioids. In addition, there was no apparent tolerance to the transplants during the 10-week course of the arthritic pain or the neuropathic pain in the chronic pain models. These results, taken together, indicate that the combined release of low levels of neuroactive substances from the transplanted cells may reduce pain sensitivity without the development of significant tolerance.

In short, the results obtained in all of these laboratory studies indicate that a unique analgesic effect is produced by adrenal medullary transplantation in animals, and this led us to undertake the current investigation to assess the efficacy of subarachnoid adrenal medullary transplantation in alleviating chronic pain in humans.

However, an important consideration and potential limiting factor in the transplantation of adrenal medullary tissue in humans is the limited availability of donor tissue and the difficulty of coordinating donor availability and recipient readiness. Therefore, as a preliminary step, it was necessary to determine whether, and for how long, donor adrenal medullary tissue can be maintained in tissue culture after removal from a donor and before transplantation into a recipient. Again, studies by Sagen and Pappas indicate that human adrenal medullary tissue can be maintained for at least 30 days in culture. Furthermore, using a tyrosine hydroxylase antibody, they found that human adrenal medullary explants contain numerous healthy chromaffin cells after 5–7 days in culture, a finding supported by biochemical studies. Therefore, in these initial clinical trials, adrenal medullary transplantation was always carried out after maintenance in culture for a minimum of 5–7 days. Preliminary accounts of the results of these studies have been reported previously.

The results of this preliminary study indicate that subarachnoid adrenal medullary transplantation shows real promise as a means of alleviating chronic pain in humans, as it did in our animal studies. Of the first five patients, three obtained significant and long-lasting pain relief after the transplant procedure; one obtained similar relief early, followed by a recurrence of her pain with the development of a serious neurologic problem; and the other claimed no relief whatsoever. The sustained relief in patients 1, 2, and 4 is similar to the relief of acute postoperative pain (and increased CSF met-enkephalin levels) observed by several investigators after surgical adrenal medullary autografts in patients with Parkinson's disease.

Why patient 3 had a recurrence of her pain after an initial period of relief is not clear, although pain treatments do have variable results in patients, including placebo benefit. It may be that the spinal block, with the reduced volume of CSF secondary thereto, and ultimate spinal cord compression may have inhibited the transplanted tissue viability, limited its perfusion with CSF, or, perhaps, limited the diffusion of the neuroactive substances released by the transplanted cells to spinal cord sites above the level of the block. It is also possible that the subsequent surgical procedure in some way caused the demise of the transplanted cells, resulting in recurrence of the patient's pain.

Finally, the failure of patient 5 to obtain any relief whatsoever, particularly in view of the marked elevations in both norepinephrine and met-enkephalin, is difficult to explain. The referring physician felt that the patient's need for exogenous opioids may have precluded cooperation or an admission of pain.
relief, which might have terminated his supply of meperidine.

Obviously, while the results of the current study are encouraging, they must be interpreted with a certain degree of caution because of the lack of a parallel control group of patients.

As is not infrequently the case with first studies of any new pharmacologic agent or therapeutic agency in humans, this pilot study has raised as many questions and challenges as it has answered. Perhaps the most puzzling feature is the variability in the response to the transplant and, more specifically, the lack of correlation between the response of the CSF levels of catecholamines and met-enkephalin and the patient's subjective response in terms of analgesia. Possible factors that could contribute to this variability include patient selection, handling and preparation of the adrenal medullary tissue before transplantation, and immunologic responses to the tissue after transplantation.

It would appear logical, for example, that a patient who has become totally unresponsive to opioids is likely to be a poor candidate for this procedure if the mechanism by which the transplant produces analgesia is, in fact, the release of opioid peptides from the transplanted chromaffin cells. Thus, in those patients in whom the initial level of met-enkephalin (or catecholamines) is low, perhaps suppressed by the exogenous administration of opioids, the transplanted chromaffin cells responded to these low levels (or were not suppressed by high levels) and produced levels of met-enkephalin and catecholamines that would have been produced endogenously in the absence of exogenous suppression. On the other hand, in those patients whose met-enkephalin (and/or catecholamine) levels were already high, perhaps because of a lower intake of exogenous narcotics, the transplanted chromaffin cells were stimulated less (or even suppressed) by the already elevated levels of these peptides (and amines).

Furthermore, the preparation of the adrenal medullary tissues for transplantation may be important in terms of transplant viability. As stated earlier, results in the laboratory have indicated that the short-term maintenance of adrenal medullary tissue in culture significantly improves tissue viability and increases both catecholamines and opioid peptide production, perhaps because of the time required for the tissues to recover from the dissection and transportation procedures. In addition, maintenance in explant culture may allow for the migration of passenger leukocytes out of the explanted tissue, reducing the potential immunologic response when transplanted to an allogenic host. Again, studies carried out in the laboratory would seem to support this hypothesis in that the survival of adrenal medullary allografts in rats was shown to improve after short-term maintenance in explant culture.27

One may postulate that the age of the donor may explain some of the inconsistencies in the expected production of catecholamines or met-enkephalins. However, Carmichael et al. have indicated that, while the catecholamine content of the adrenals in elderly patients with Parkinsonism may be reduced, it has not been established that there is a normal age-related decline in adrenal medullary catecholamines.28 Furthermore, the donors in all of our patients were relatively young, with four of the five being 20–31 yr of age and the other being 53 yr of age; and the recipient of the 53-yr-old donor's adrenal medullary cells did as well as (or better than) all of the others.

And finally, as with any transplantation, the efficacy of the immunosuppressive drugs can have an enormous impact on the success or failure of the procedure. Although our transplant patients were instructed to continue cyclosporine A therapy for 2 weeks after their adrenal medullary transplant procedure, the necessity for this therapy for the long-term survival of the adrenal medullary transplant has not been demonstrated. Although it has been said that the central nervous system may be "immunologically privileged" to some extent, recent studies have indicated that this "privilege" is limited.29 Nonetheless, a short-term period of immunosuppressive therapy was used in our patients, because previous studies in the laboratory demonstrated that this improves the long-term survival of even xenografts of bovine chromaffin cells in the central nervous system of the rat.11 Furthermore, long-term treatment with cyclosporin A can be toxic, with potentially serious complications, including hepatotoxicity and nephrotoxicity.31,32

Of course, there is another possible explanation for the variable correlation between the levels of met-enkephalin and catecholamines and the resultant degree of pain relief. Although animal studies have indicated that pain-reducing adrenal medullary transplants produce significant levels of both met-enkephalin17 and catecholamines16 in the CSF, adrenal medullary chromaffin cells also produce and release several other neurotransmitter substances that have been implicated in pain modulation, particularly vasoactive intestinal poly-
peptide (VIP), encrypted enkephalin-containing peptides, neuropeptide Y, and somatostatin. Therefore, it is possible that, to date, we have not assessed the appropriate peptides. Other possible explanations include failure of the neuroactive substances to reach receptor sites, concentration gradients between the sampling site and the site of action, and even local inflammatory responses. Nonetheless, these biochemical assays do, at the very least, provide some indication of chromafin cell survival in the spinal subarachnoid space of the patients studied.

In summary, four of the patients in this preliminary clinical study obtained dramatic pain relief, three of them long lasting, after subarachnoid adrenal medullary transplantation. Although the mechanism by which this transplant procedure produces pain relief may be via increases in CSF opioid peptides and catecholamines, the pattern of these increases was not consistent, and did not always correlate with the degree of pain relief. The encouraging results achieved in this initial, preliminary study indicate that subarachnoid adrenal medullary transplantation may provide a unique and effective approach to the management of pain in humans. However, the preliminary nature of these observations should be emphasized. In particular, the lack of placebo controls and lack of autopsy findings leave the precise mechanism of the observed effects unclear at this point. Certainly, further controlled studies are warranted before full-scale clinical trials are undertaken.

References


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