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Animal Study

Tissue Distribution of Clonidine Following Intraforaminal Implantation of Biodegradable Pellets: Potential Alternative to Epidural Steroid for Radiculopathy

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Background: Epidural steroid injections have shown efficacy in short-term pain relief, but often require repeated injections in order to provide continued pain relief. It has been suggested that a continuous, locally administered dose of an anti-inflammatory compound may provide sustained pain relief at doses lower than those needed with injections.

Objective: To evaluate the distribution of clonidine after transforaminal placement of a biodegradable drug delivery depot system.

Study Design: A preclinical animal study.

Methods: A biodegradable polymer drug depot designed to provide sustained delivery of clonidine was placed in or near a single lumbar neural foramen in 12 farm pigs. Clonidine tissue concentrations were measured at the implant site and at incremental distances from the implant over a time period of 12 weeks. Plasma clonidine levels were measured at 4 hours postimplantation on days 1, 2, 3, 5, and 7, and then weekly until the termination of the study.

Results: Clonidine was detectable up to 6 cm away from the drug depot. The highest concentrations of clonidine were present within the targeted spinal nerve; the concentration decreased with increasing distance from the depot. Clonidine was undetectable in plasma from all animals at all time points.

Limitations: While clonidine was detected up to 6 cm from the drug depot, it is unknown if the drug concentration has clinical relevance.

Conclusions: The results indicate that a biodegradable depot designed to be placed in a specific location to provide local sustained release of an anti-inflammatory and analgesic drug may be a feasible new approach to treat radicular pain associated with intervertebral disc pathology and other spinal conditions.

Key Words: clonidine, radiculopathy, pain, intraforaminal, injection, spine, sciatica

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In 1934, Mixter and Barr (1) linked sciatic pain to the mechanical compression of lumbar nerve roots by an intervertebral disc. Mechanical compression of a nerve root by the protruding disc was considered the sole pathophysiological mechanism for inducing radiculopathy, but more recent experimental evidence (2-6) suggests that nerve inflammation is another, and possibly more important, mechanism

for inducing lumbar radiculopathy. Evidence from animal (7-12) and human (13-15) studies suggest that material from the nucleus pulposus triggers an autoimmune response if this portion of the intervertebral disc leaks from the annulus and is exposed to the immune system. Supporting evidence includes the observation that a number of pro-inflammatory mediators, including tumor necrosis factor-alpha (TNFα), phospholipase A2, Substance P, interleukin-1β (IL-1), IL-6, and IL-8 have been derived from the human nucleus pulposus (16).

The recognition of a second mechanism for inducing pain has not greatly changed the standard treatment of sciatica which is designed to relieve the patient's symptoms during the period of natural healing and/or resorption of the disc fragment, but it did provide theoretical support for the procedure of injecting an anti-inflammatory medication into the epidural space as a way of treating discomfort from acute disc herniations. It is believed that most patients could be treated successfully without surgery if there was adequate time for healing of the annular tear and resorption of the disc fragment (1,17-19). Current nonsurgical treatments include: physical therapy (PT), nonsteroidal anti-inflammatory drugs (NSAIDs), oral steroid medications, and the injection of corticosteroids into the epidural space of the spine adjacent to the herniated intervertebral disc.

The use of epidural steroid injections (ESIs) has become the standard of care, although unresolved questions remain concerning acute and long-term efficacy. Some recent studies suggest ESIs offer a transient benefit to the patient but no sustained benefit in terms of pain reduction, functional recovery, or a reduced need for surgery (20). There are several studies that suggest ESIs may offer a benefit only in short-term pain relief, typically ranging in duration from 7 days to one month (21-24). Other studies, however, show that ESIs neither improve pain relief nor reduce the number of patients undergoing surgical decompression (25) as compared to patients treated with placebo saline injections (24,26-28). The number of conflicting studies evaluating ESIs show that the efficacy of the therapy remains under question, and the number of references demonstrating equivalent outcomes between ESI and placebo support the position that the ESI may not be the optimal standard of care should a viable alterative treatment mechanism arise.

The TNF-α inhibitors and clonidine, a compound used to treat hypertension (29-33), neuropathic pain (34-37), opioid detoxification (38-40), and attention deficit hyperactivity disorder (41-43), have been reported to have anti-inflammatory activity (44-51), and injection into the epidural space was evaluated as a possible replacement for ESIs (52-59). Epidural injections often require frequently repeated interventions, and may lead to increased costs and transient cycles of efficacy due to the intermittent bursts of drug concentration in the vicinity of the nerve. It is possible that a continuous, locally administered dose of an anti-inflammatory compound may provide sustained pain relief at lower doses than those traditionally needed with epidural injections that bathe the targeted portions of the central nervous system and result in some peripheral circulation of the active drug. This concept was substantiated in the rat chronic constriction injury model when etanercept was delivered by means of a locally targeted biodegradable polymeric formulation which resulted in reduced pain-associated behaviors for approximately 2 months (60). A clonidine drug depot also showed a sustained 2 month reduction of pain-associated behaviors in the same animal model (unpublished data).

One of the shortcomings of chronic constriction injury studies is that the drug depot is placed within the same intramuscular pocket as the nerve injury, possibly even in direct contact with the nerve injury. One of the issues with administration of a medication that is designed to stay in the initial location is that it is uncertain how close to the irritated nerve root the drug depot would need to be placed in order to reduce pain and inflammation.

In the present study, the biodistribution of clonidine resulting from implanting a clonidine hydrochloride formulation in a solid, biodegradable pellet carrier (pellets) was assessed in farm pigs, an animal that is large enough to allow for a clinically relevant evaluation. The evaluation in this large animal model will be helpful to predict the tissue distribution of the medication in humans, and to assess whether a neural foraminal placement of the pellets would have the potential to treat the target area of concern when conducting future human studies.

Methods

Surgical procedures

Twelve female Yorkshire mix pigs (Genetiporc, Alexandria, MN) weighing 43.0 kg to 51.6 kg on the day of the procedure were used in this study. All experiments were conducted in accordance with the Animal Welfare

Act of 1966 and approved by the Institutional Animal Care and Use Committee at Medtronic Physiological Research Laboratories (Minneapolis, MN). Anesthesia was induced by intramuscular injections of 4 mg/kg Telazol with one mg acepromazine and 0.01 mg/kg buprenorphine, and maintained using isoflurane.

A total dose of approximately 300 µg of clonidine HCl encapsulated in a total of 3 pellets made of biodegradable polylactic acid polymer and formulated to deliver the drug for 3 months was placed in the lateral lumbar foramen at the L4-5 level with an 18 gauge Tuohy needle and stylet. The pellets were injected adjacent to the exiting spinal nerve using a posterolateral transforaminal approach with fluoroscopic guidance. The needle was advanced into position and a small amount of myelographic-compatible, nonionic iodinated contrast medium was injected to ensure an appropriate needle tip location prior to the transforaminal implantation. The pellets were inserted into the hub of the Tuohy needle and driven though the end of the needle by replacing the stylet. This was repeated until all of the pellets had been placed.

Following each pellet placement procedure, the respective animal was placed in left or right posterior oblique recumbent position, and the jugular vein was isolated. A vascular access port was then placed, and the line was advanced to the atriocaval junction. It was secured in place with TICRON stitching, and subcutaneously tunneled to the retroauricular location. The incision was closed, the vascular access port was heparinlocked, and the animal was allowed to recover.

Tissue Collection

Three animals were scheduled for sacrifice at 2, 4, 8, and 12 weeks by inhalation of isoflurane and an intravenous injection of pentobarbital sodium and phenytoin sodium (1 mL/4.5 kg body weight). The dorsal section of the pig containing the lumbar and sacral spine was excised en bloc. The injection site was identified by surveying the postplacement fluoroscopic image and the procedural notes. On the dorsal surface of the caudal section of the torso, including the lumbar and sacral spine, transverse lines were drawn using tissue dye to mark the sections to cut. Seven transverse sections, each one cm thick, were cut. The section containing the pellets was designated as A (Fig. 1). The second, third, and fourth sections immediately cephalad to section A were designated B, C, and D, respectively. The fifth, sixth, and seventh sections were designated E, F, and G, from cranial to caudal, respectively, immediately caudal to A. The caudal surfaces of every axial section were marked with tissue dye in order to maintain the appropriate orientation.

The implanted pellets were visually located and

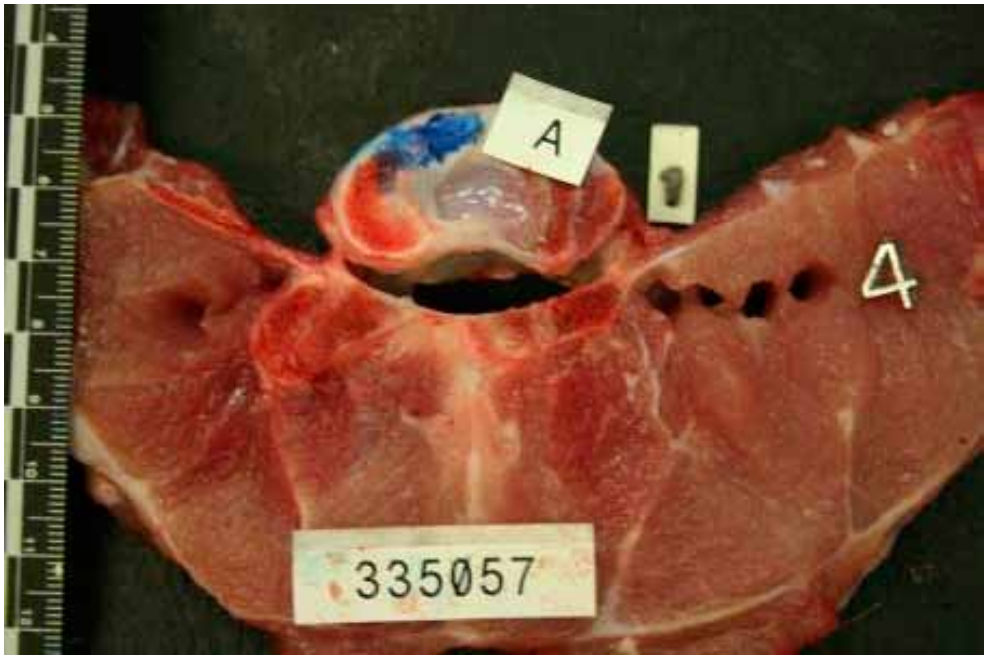

Fig. 1. Area for tissue sampling from transverse sections with black arrows indicating the location of the 8 mm punch biopsies.

removed from the tissue sections. Each axial section was then sub-sampled using 8 mm biopsy punches. The first punch in each section (designated Punch 1) buttressed the lateral position of the bony superior articular process as close as the bony elements would allow. Additional sections were taken one cm (Punch 2), 2 cm (Punch 3), and 3 cm (Punch 4) just lateral to the center of the first punch (Fig. 1). A total of four 8 mm punches were removed from each of the 7 transverse sections (samples 1-4, from medial to lateral, respectively). The spinal cord and epidural tissue within the spinal canal were collected from each of the 7 transverse sections for clonidine extraction (sample 5). When the neural (intervertebral) foramen was present in the section, the tissue within the neural foramen on the same side of the implants was collected (sample 6). Two control muscle samples from the forelimb and 2 control fat samples from the cheek, each weighing approximately one g, were also collected from each animal.

Systemic and Local Tissue Drug Levels

The clonidine tissue concentration analysis was performed by Bioanalytical Systems, Inc. (West Lafayette, IN). Clonidine was cold (4˚C) extracted from tissue (0.41 ± 0.02 g sections) overnight following homogenization in 2.0 mL of 100 mM ammonium acetate buffer. Samples were spun in a centrifuge and 300 µL of clear supernatant was mixed with 50 µL of isotope-labeled internal standard solution (5 ng/mL in acetonitrile) and 600 µL of acetonitrile for protein precipitation. The deproteinized supernatant was collected and dried under nitrogen at 40˚C. The samples were reconstituted with 5% acetonitrile in water with 0.1% formic acid and injected into an LC/MS/MS system using a Restek PFP analytical column (Restek, Bellefonte, PA) with a 10 mM ammonium acetate / 80% acetonitrile / 0.2% acetic acid / 20% water mobile phase. The samples were analyzed using a Sciex API 4000 LC/MS/MS system (Applied Biosystems/MDS SCIEX, Foster City, CA). Data acquisition was performed using Sciex API 4000 Analyst software.

The drug concentration data were plotted as a function of distance from the targeted foramen, with animals separated into groups by their common termination weeks (Fig. 2). The distances are expressed as the straight line distance from the center of each 8 mm punch to the approximate exiting point of the nerve leaving the neural foramen. The intraforaminal nerve material is designated as distance "0." The Pythagorean Theorem was used to estimate the distances for punches taken from axial slices caudal and cephalad from the slice containing the target (i.e., sections/slides B, C, D, E, F, and G as described in the tissue collection methods).

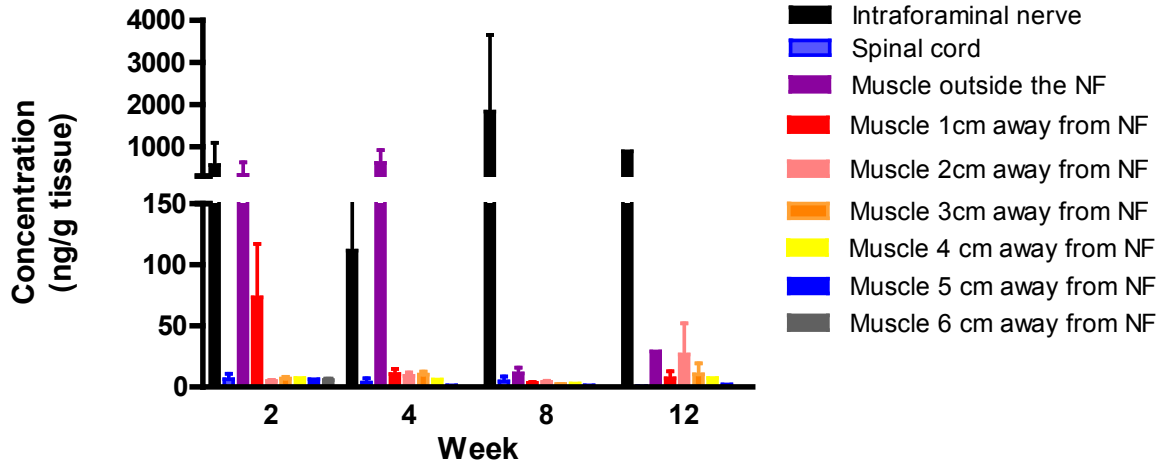

Fig. 2. *Clonidine tissue levels over a 12-week period following transforaminal epidural clonidine pellet administration.*

Blood samples were collected concurrently at 4 hours (± 30 minutes), one day, 2 days, 3 days, 5 days, 7 days, and then weekly until termination. At each time-point, 5 mL of blood was collected in EDTA K2 coated tubes. Each sample was spun in a centrifuge at 3000 rpm for 10 minutes. The plasma was separated, frozen, and stored at -70°C. Samples were shipped to Anapharm, Inc. (Quebec, Canada) for analysis. Clonidine was extracted from an aliquot of porcine EDTA K2 plasma using a liquid-liquid extraction procedure, then injected into a liquid chromatograph equipped with a tandem mass spectrometry detector. The quantitation method is by peak area ratio. A weighted (1/C2) linear regression was performed to properly determine the concentration of clonidine in porcine plasma. All regressions were generated by MDS Sciex Analyst version 1.4.1 and Thermo Electron Corporation Watson LIMS software version 7.0.0.01b (Thermo Scientific, Waltham, MA). Even though this study was performed using an unvalidated assay, in-study performance data demonstrated that it is suitable for the determination of clonidine in porcine EDTA K2 plasma over an analytical range of 20.0 to 2000 pg/mL. The percent CV (precision) and the percent bias (accuracy) ranged from 2.59 to 9.91 and from -2.06 to 1.66, respectively, for the calibrators. The percent CV and the percent bias ranged from 2.83 to 7.81 and from -4.92 to -6.30, respectively, for the quality control samples.

In Vitro Elution

Elution was carried out in triplicate at 37°C in phosphate-buffered saline (pH 7.4) with slight agitation. Three pellets of the clonidine HCl formulation were placed in 2 mL of phosphate-buffered saline. At specified time points, the elution medium was removed and the elution volume was replenished to 2 mL. The removed elution medium was then analyzed for clonidine content using high performance liquid chromatography. Cumulative drug elution was plotted as a function of time and presented in Fig. 3.

Results

All plasma samples submitted for analysis were below the 20.0 pg/mL detection limit for clonidine.

Although there was a significant amount of variation among the levels found within the same groups,

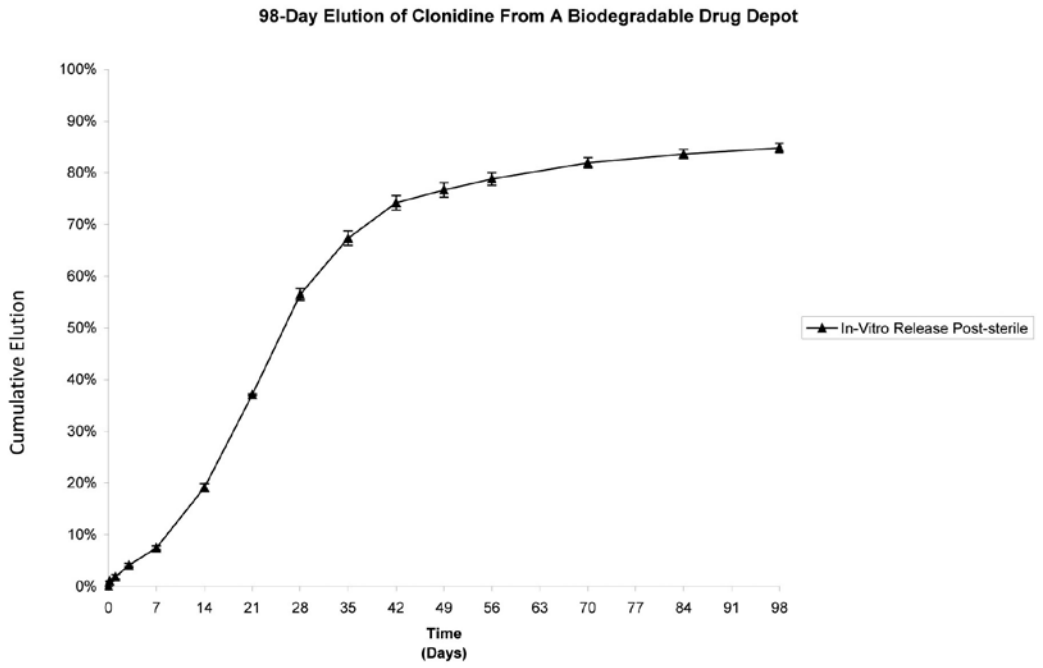

Fig. 3. *In vitro elution of clonidine from a biodegradable drug depot.*

the data presented in Fig. 2 suggests that at 2 and 4 weeks after administration of the pellets within the foraminal space, clonidine tissue levels of approximately 1,000 ng/g of tissue were found in the intraforaminal nerve and in muscle samples just outside the foramen. Clonidine levels within the intraforaminal nerve remained high at the 8 and 12 week postadministration time points, while levels in the muscle just outside the foramen dropped to approximately 10-30 ng/g of tissue. In the muscle section one cm away from the foramen, clonidine levels above 50 ng/g were observed at week 2 postadministration, but decreased to below 10 ng/g of tissue at weeks 4, 8, and 12. Clonidine levels in the spinal cord, as well as in the muscle samples taken 2 and 3 cm away from the foramen, remained at approximately 10-30 ng/g of tissue throughout the study. Clonidine remained above detection limits out to at least 6 cm in all animals. Time (i.e., week of termination) did not have a significant effect on tissue concentrations.

In vitro elution of clonidine from the pellets showed sustained elution of clonidine through 98 days (Fig. 3). The elution rate was most rapid over the first 28 days, during which 56% of the total drug was released. After day 28, the elution rate of the formulation slowed considerably, eluting an additional 29% of the loaded clonidine through day 98.

Discussion

Lumbar ESIs are a common treatment of neuropathic limb pain in those who have failed conservative treatments such as PT and oral NSAIDs, and in those who are neurologically stable. The efficacy of ESI remains a controversial topic for several reasons. One of the controversial points is the method of needle placement. Overall, there is only modest evidence that ESIs using different needle approaches are superior to placebo or no treatment, and relief, when achieved, is often transient (61-63). A recent Cochrane systematic review concluded that there is good evidence that a transforaminal approach is superior to both caudal and interlaminar approaches (64). This suggests that targeting the specific spinal nerve or nerve root may result in better efficacy. It is theorized that a medication providing anti-inflammatory activity in the form of a slow-eluting depot adjacent to the irritated neurological structure may provide a more controlled and sustained relief of symptoms in patients with disc herniations and/or radiculopathy.

Clonidine HCl is an imidazoline derivative and exists as a mesomeric compound. It was first approved in the United States in 1974 to treat hypertension in an oral tablet form, and then in 1996 as a solution for epidural administration indicated for the treatment of severe pain in cancer patients. The antihypertensive and central analgesic effects of clonidine appear to be mediated by stimulation of α2-adrenergic receptors in the brainstem or the spinal cord, (65-66). In rodent models of thermal hyperalgesia induced by sciatic nerve ligation, clonidine has superior efficacy when compared to morphine (67). It is generally believed that clonidine interferes with pain signal transmission in the central nervous system, and evidence suggests that it does so by inhibiting voltage-gated sodium and potassium channels (68). Since clonidine does not rely on opioid receptors (69), cross tolerance does not appear to develop between clonidine and opioids; thus, clonidine is an effective adjunct to morphine in the treatment of severe pain, even in opioid-tolerant patients (67,70).

Within the last 15 years, a number of publications have reported promising reductions in postoperative pain following the local administration of clonidine within the surgical incision (71-74). Most recently, transforaminal injections of a clonidine solution were evaluated in a small number of sciatica patients (59). Clonidine treatment was associated with a significant improvement in pain scores at 2 and 4 weeks relative to baseline without serious adverse events or signs of hypotension (59).

Increasing evidence derived from animal and clinical studies suggest that clonidine may have peripheral anti-inflammatory effects. In a study of colorectal surgery patients, pretreatment with clonidine and postoperative patient controlled epidural analgesia including clonidine resulted in a significant reduction in circulating IL-1 receptor antagonist, IL-6, and IL-8 versus patients not given clonidine (48). In a model of inflammatory sciatic nerve neuritis, peripheral clonidine injected at the site of nerve injury elevated transforming growth factor -β1, which is known to reduce the secretion of TNF-α and multiple inflammatory interleukins (75). In a similar study of peripheral sciatic nerve ligation, clonidine reduced both IL-6 and IL-1β in the injured nerve (51). In a model of zymosan-induced sciatic nerve injury, clonidine caused a dose-dependent decrease in hypersensitivity and reduced leukocyte count and leukocyte content of IL-1α, IL-1β, and IL-6 (50). In this study, clonidine also prevented the zymosan-induced macrophage recruitment and expression of TNF–α. Macrophages express α2-adrenergic

receptors, and nerve injury is associated with a robust macrophage-driven inflammatory response (47). Clonidine appears to blunt this response in models of nerve injury, reducing the tissue concentrations of pro-inflammatory cytokines (47). Clonidine has been shown to have a suppressive effect on TNF-α (51, 76) and Interferon-γ (IFN-γ) (77).

In another peripheral sciatic nerve ligation study, clonidine increased withdrawal thresholds while reducing phosphorylation of p38 mitogen-activated protein kinase, an enzyme involved in the development of neuropathic pain, inflammatory pain, and apoptosis (78). Clonidine suppresses endotoxin-induced accumulation of IL-8 and MCP-1 in models of endothelial cell inflammatory states (79), demonstrating that the anti-inflammatory effect of clonidine is not specific to nerve injury. The anti-inflammatory effects of clonidine are blocked by co-administration of an α2-adrenergic receptor antagonist (50). The analgesic effect of a peripheral clonidine injection in nerve injury models has a slower onset and a longer duration of action than a single spinal injection (80-81). This provides further evidence suggesting that clonidine has distinct peripheral and central effects on pain and inflammation.

One observation from the present study was the apparent lack of relationship between in vitro clonidine release from the drug depot and tissue drug concentration. The in vitro release data show a fairly linear percentage of release through 5 weeks, then the release slows down and plateaus through the end of the analysis period at 14 weeks. At 4 weeks in vitro, approximately 56% of the clonidine had been released, at 8 weeks another 22% had been released, and at 12 weeks another 7% had been released. In contrast, in the target nerve tissue there were much higher clonidine concentrations in the 8 and 12 week samples versus the 4 week samples. This would suggest that clonidine may accumulate in the tissue, creating a secondary depot that maintains more constant tissue drug levels than might be predicted based on drug elution data that were obtained by measuring the amount of drug eluted into a liquid at body temperature.

Despite the relatively high concentration of medication in the soft tissue which would be considered optimal for inducing local anti-inflammatory activity and analgesia, plasma levels of clonidine obtained from the central venous system were undetectable. Preferential distribution in the targeted tissue was achieved with clonidine levels being approximately 10 times higher within the intraforaminal nerve and in the muscle sections just outside the foramen relative to levels found in the spinal cord and 1-6 cm away from the foramen. These data are promising for achieving the goal of a long-lasting analgesic/anti-inflammatory response in vivo without having to place the medication precisely in the exact targeted position. An approximate placement with high surrounding soft tissue concentrations would make it possible to perform effective placements reproducibly over a number of patients, and, although it may be most effective to place the depot immediately adjacent to the irritated nerve tissue, some margin of placement error would be acceptable.

Conclusions

In this study, we demonstrated that clonidine-containing biodegradable pellets can be placed effectively in a perineural location in swine using a transforaminal injection technique, and that sustained drug concentrations could be achieved in the targeted intraforaminal nerve and surrounding tissues up to 6 cm away without any detectable plasma levels of the medication.

Additional investigation will be necessary in both animals and humans to determine whether a biodegradable depot that provides a sustained release of clonidine can be used as a new approach to treat sciatica with or without an associated disc herniation. Human studies should be considered using depot pellets delivering varying doses of clonidine as compared to comprehensive medical management. Future comparative studies could also involve comparing medical management with ESI's or with a sham pellet group. We believe this new mode of delivery could open a major pathway for future treatment of patients with sciatica by expanding medication choice, and by a creating the potential for a longer acting therapy.

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