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Chronic, Constant-Rate, Gastric Drug Infusion in Nontethered Rhesus Macaques (*Macaca mulatta*)

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As part of a study of antipsychotic drug treatment in monkeys, we developed a technique to provide chronic, constant-rate, gastric drug infusion in nontethered rhesus macaques. This method allowed us to mimic the osmotic release oral delivery system currently used in humans for continuous enteral drug delivery. Rhesus macaques (n = 5) underwent gastric catheter placement by laparotomy. After the catheters were secured to the stomach, the remaining catheter length was exited through the lateral abdomen, tunneled subcutaneously along the back, and connected to a 2-mL osmotic pump enclosed in a subcutaneous pocket. Osmotic pumps were changed every 2 to 4 wk for 1 y and remained patent for the duration of the study. Four complications (including cutting of the catheter, incisional dehiscence at the pump site, and loss of 1 catheter into the abdominal cavity requiring catheter replacement) occurred among the 80 pump changes performed during the yearlong study. At necropsy, histopathologic examination of the catheter implant sites revealed mild changes consistent with a foreign-body reaction. Our results indicate that the gastric catheter and osmotic pump system was well tolerated in rhesus macaques for as long as 12 mo after placement and suggest that this system will be an attractive option for use in studies that require chronic, constant-rate, gastric drug infusion in nontethered monkeys.

Abbreviations: PET, positron emission tomography; OROS, osmotic release oral system; PEG, percutaneous endoscopic gastrostomy.

Nonhuman primates are important model systems for a variety of pharmacologic studies. In particular, the primate brain is significantly larger and more complex than that of other animals,[15] making the rhesus macaque an important tool for the study of psychoactive medications.[2,6,9] Many of these medicines, such as antidepressants and antipsychotics, develop their therapeutic actions over several weeks,[4,7,17] and chronic dosing is required to study the phenomenon of interest. In developing chronic dosing strategies in the macaque model, several key considerations are route of administration and the timing and frequency of administration. Parenteral administration frequently is chosen because of its reliability; however, administration through the gastrointestinal tract better mimics the absorption and first-pass hepatic metabolism to which most drugs are subject when taken orally by humans. In many animal models, drugs are administered in a pulsitile fashion, typically once or twice daily, analogous to how most medication is administered in human patients. However, a potential confound when using this method is that drug half-lives may differ substantially in laboratory animals and humans,[13] and unless such differences are accounted for, drug levels may vary excessively in the animal. For example, the antiinflammatory drug phenylbutazone has an elimination half-life of 96 h in humans but 3 to 5 h in rats.[12] Clearly, the timing of blood levels or assays relative to the last dose of drug must be tailored to the model being used. Alternately, drugs can be administered by constant infusion, which achieves consistent drug levels so that behavioral testing or brain imaging results are not affected by timing of dosing and testing.

Chronic drug dosing is a particular challenge for studies in nonhuman primates because of the difficulty in handling these animals compared with laboratory rats or mice. Repeated parenteral injections offer an easy, reliable approach to chronic dosing; however, they require either training the animal to accept injections or repeated restraint, which is stressful. Exposure to repeated stressors can itself confound some studies of the brain because of the substantial and long-lasting effects stress can have on neurotransmitter systems and circuitry.[10,14,16] In some cases, administration through the gastrointestinal tract is desired to better mimic the metabolism that most medications undergo when given orally to humans. The simplest method for enterally dosing nonhuman primates is to give drugs in preferred food treats. However, some medicines have unpalatable tastes that are difficult to disguise, or nonhuman primates may not reliably eat these treats when offered and may store these treats in cheek pouches for extended periods and later spit them out. This behavior may be problematic for studies in which precise control of drug levels is required, such as studies involving positron emission tomography (PET) scans of drug binding. Alternately, drugs can be administered by using orogastric tubes, but this methodology requires restraint and sedation of animals for each dose. Clearly, the route and means of drug delivery in a chronic macaque study must be matched carefully to the needs of the study.

As part of a study of the relationship between antipsychotic drug dose, drug levels in serum and cerebrospinal fluid, and brain receptor occupancy, we evaluated a surgical technique to provide constant-rate gastric drug infusion in rhesus monkeys by using a subcutaneous osmotic minipump connected to a gastric catheter. In addition to providing reliable drug dosing that avoided daily manipulation of the animals, this method

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allowed us to mimic the osmotic release oral system (OROS) that currently is used in humans to deliver various drugs, including paliperidone, methylphenidate, hydromorphone, and nifedipine.[3] The OROS delivery system consists of a miniature osmotic pump in pill form that, when swallowed, releases medication at a constant rate as it travels through the gastrointestinal tract and achieves steady drug levels (without peaks and valleys) with once-daily dosing, regardless of drug half-life.[3] Over the course of the yearlong study, we found that monkeys tolerated repeated pump changes to accommodate drug washout through saline administration and changes in drug or dosage with few complications. This method will be useful in future studies for reliable chronic dosing of nonhuman primates in which drug administration through the gastrointestinal tract is preferable.

Materials and Methods

Animals. Male, Indian-origin, nonspecific pathogen-free, rhesus macaques (n = 5) were assigned to a study to evaluate dose and brain receptor uptake of 2 antipsychotic drugs. Animal weights ranged from 8.12 to 12.18 kg at the start of the study, and ages ranged from 5.25 to 7.5 y. All experimental procedures were approved by the Institutional Care and Use Committee of Emory University. Animal housing rooms were maintained in accordance with the *Guide for the Care and Use of Laboratory Animals*.[11] All animals were fed a standard commercially formulated nonhuman primate diet (Monkey Diet Jumbo 5037, PMI Nutrition International, St Louis, MO) and supplemented with daily produce as part of the environmental enrichment program.

As part of the experimental protocol, all animals underwent initial brain imaging, which included an MRI scan to identify anatomical landmarks and a PET scan to determine the baseline D2 dopamine receptor binding potential. After waiting at least 24 h to allow degradation of the radioligand used for PET scans, each animal was implanted with a gastric catheter connected to a subcutaneous osmotic pump.

Catheters and pumps. Custom radioopaque polyurethane catheters (length, 30 in.; with a tapered diameter of 0.055 to 0.039 in.; Strategic Applications, Libertyville, IL) were used in this study. The inner diameter of the catheter was narrow and tapered to minimize the volume that the pump had to fill before the compound reached the stomach. The catheters included a 1.5-cm-diameter polyethylene terephthalate (Dacron, DuPont, Wilmington, DE) suture patch 1 cm from the tapered end. The total catheter volume was 120 µL. Osmotic minipumps (Alzet, Durect, Cupertino, CA) had a 2-mL capacity, and both 2-wk (model 2ML2, infusion rate = 4.68 µL/h) and 4-wk (model 2ML4, infusion rate = 2.34µL/h) pumps were used.

Pump preparation. Prior to placement in macaques, pumps were prepared as recommended by the manufacturer. Sterile saline or drug solution that had been filtered through a 0.2-µm syringe filter was loaded into the pumps by using a blunt needle. The regulator then was inserted, the pump was placed in a sealed container of sterile saline, and the container was incubated overnight in a 37 °C oven to prime the osmotic mechanism. The following day, the pump was implanted. Because we made no attempt to prime the catheter with the drug solution, there was an approximately 24-h lag between connecting a pump to the catheter and delivery of the drug to the stomach. For our study, this delay was considered useful because it allowed some recovery time after surgery before pump placement before the animal began to receive a potentially sedating antipsychotic medication.

Gastric catheter placement. After an overnight fast, animals were anesthetized with an intramuscular injection of tiletamine hydrochloride and zolazepam hydrochloride (3 to 5 mg/kg; Telazol, Fort Dodge Laboratories, Fort Dodge, IA). Animals were intubated and maintained on a mixture of isoflurane gas (concentration, 1% to 3%) and 100% oxygen. The heart rate, respiratory rate, indirect blood pressure, end-tidal CO_2, O_2 partial pressure, and body temperature were monitored throughout the surgical procedures. The abdomen, left side, and upper back were clipped and aseptically prepared for surgery with povidone–iodine scrub, and the animal was placed in dorsal recumbancy on a sterile sheet. Before an incision was made, the catheter was checked for patency with a sterile saline flush. A back-up catheter was kept on hand in case of problems with the initial catheter.

A 6- to 8-cm ventral midline incision was made in the upper abdomen. The stomach was identified, grasped with Babcock forceps, and exteriorized onto saline-moistened laparotomy pads. A pursestring suture of 4-0 Vicryl (Ethicon, Johnson and Johnson Medical, Somerville, NJ) was preplaced in the gastric serosa of a less-vascular portion of the fundus, just above the greater curvature. A stab incision was made through the stomach wall in the center of the pursestring suture by using a #11 blade or large-bore needle. The catheter then was inserted into the stomach, with the tip extending into the lumen. Before completing the suturing, we used concurrent gastroscopy to confirm that the catheter tip was in the gastric lumen and not within the wall of the stomach. The pursestring suture was tightened to prevent gastric leakage, and the attached disc was sutured to the serosa of the stomach by using 8 simple, interrupted sutures of 4-0 or 5-0 nylon (Ethilon, Ethicon, Johnson and Johnson Medical) evenly spaced around the disc (Figure 1 A). Saline then was flushed through the catheter to confirm patency.

After the catheter was secured to the stomach, a 1-cm incision was made in the skin on the left lateral abdomen just below the last rib. A mosquito hemostat was pushed through the abdominal wall to grasp the end of the catheter, which was pulled through the abdominal wall, leaving a small amount of slack in the abdominal portion of the catheter. The catheter was secured to the abdominal wall with a single ligature of 5-0 nylon. The midline incision was closed in 3 layers, with 3-0 Vicryl sutures for the muscle and subcutaneous tissues and 4-0 PDS (Ethicon, Johnson and Johnson Medical) for the skin.

The animal was rolled onto its right side, and a rigid, hollow trocar was used to create a tunnel from the catheter exit site on the left side to a small incision in the upper midback (Figure 1 B). The catheter was passed through the trocar and the trocar then removed, leaving the catheter buried subcutaneously and exiting the incision on the back. A large hemostat was used to bluntly dissect the subcutaneous space distal to the incision to create a large pocket. The pump, prefilled with either drug or saline, was placed in the pocket. To ensure that the catheters would be sufficiently long after implantation, they were manufactured a generous 30 in. in length. After a small amount of extra catheter was left to allow for movement of the pumps during changes, the excess catheter was removed, and the catheter was attached to the outlet of the osmotic pump (Figure 1 C). The skin over the pocket and the small incision on the left side used for the trocar access were closed with simple, interrupted sutures of 4-0 PDS (Figure 1 D). After surgery, the macaques received 0.1 to 0.2 mg/kg meloxicam once daily and 0.01 mg/kg buprenorphine hydrochloride every 6 h for 5 d and then as needed.

Osmotic pump replacement. During the course of the yearlong study, pumps were changed every 2 to 4 wk to allow washout

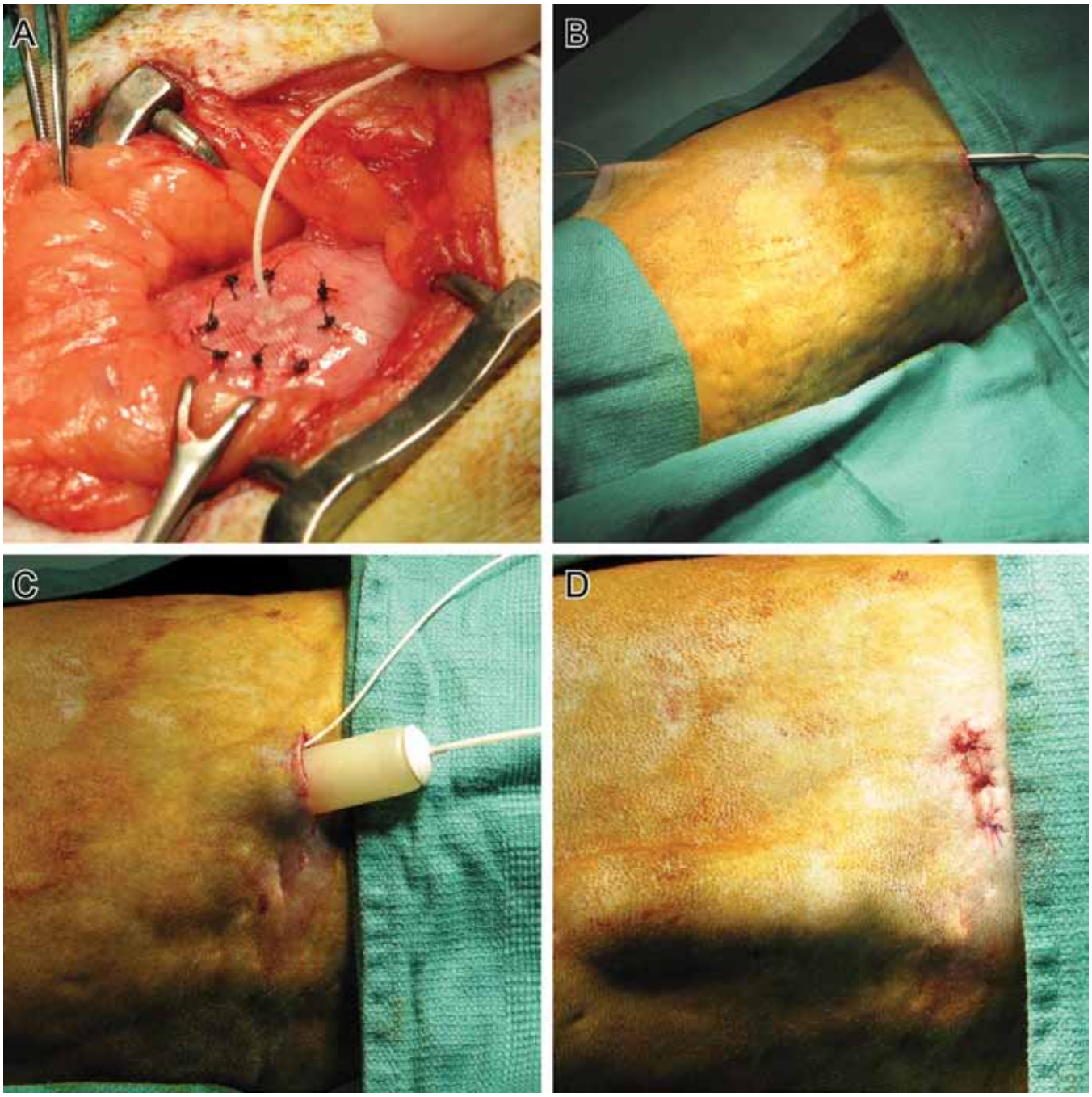

Figure 1. Implanting the gastric catheter and osmotic pump. (A) The catheter disc is secured to the stomach. (B) Tunneling the trocar and catheter under the skin. (C) Placement of the osmotic pump with attached catheter into the pocket. (D) The pump secured in the pocket. Note that the pocket is sufficiently large so that the pump will not put tension on the incision.

from drug or to initiate treatment with a different drug or dose. For pump replacement, the animals were fasted overnight and anesthetized with an intramuscular injection of Telazol (Fort Dodge Animal Health) or ketamine hydrochloride (10 mg/kg; Ketaset, Fort Dodge Laboratories). The area around the pump was clipped and aseptically prepped with povidone–iodine or chlorhexidine surgical scrub. For the first few pump changes, an incision was made proximal to the pump, the pump was removed, and a new subcutaneous pocket on the opposite side of the back was created with large hemostats for the replacement pump. This method, however, necessitated tunneling the catheter subcutaneously to the new incision. The amount of fibrous tissue that formed around the catheter made this procedure increasingly difficult. For subsequent pump changes, an incision was made over the top of the osmotic pump just large enough to remove it. Small hemostats were used to break down fibrous tissue surrounding the pump, and it was expressed out of the pocket. A large hemostat was inserted through the incision but redirected to create a new pocket. The new pump was inserted into the pocket, the catheter attached, and the incision closed with a single layer of simple interrupted sutures of 4-0 PDS. Animals received a single dose of meloxicam (0.2 mg/kg) at the time of pump changes.

Catheter monitoring. Gastric catheter tips were examined periodically by endoscopy for changes to the gastric mucosa and to confirm patency. This procedure was performed during

scheduled osmotic pump changes. To confirm patency of the catheter, a saline-filled 3-mL syringe with a 25-gauge needle was inserted into the catheter end after removal of the osmotic pump, and the catheter was flushed. Visualization of saline from the catheter tip within the gastric lumen confirmed patency.

Study procedures. As part of the study protocol, animals underwent cranial PET scans 24 h before all osmotic pump changes to determine brain receptor occupancy. Samples of cerebrospinal fluid and blood also were collected at this time. Osmotic pumps were replaced on alternating 2- or 4-wk schedules, depending on whether the pump contained drug or saline. The study drug was administered for 2 wk, followed by a washout period with saline for 4 wk. Drug concentrations in the prefilled osmotic pumps varied over the course of the study. In addition, the principal investigator conducted behavioral testing at specific time points identified in the study protocol.

Euthanasia and necropsy procedures. Approximately 12 mo after catheter placement, the monkeys were anesthetized with ketamine or Telazol, given 5000 IU heparin intravenously, euthanized with 100 mg/kg IV pentobarbital, and transcardially perfused with fixative solutions to allow study of brain tissue responses to drug treatment. The abdominal cavity, stomach, catheter track, and pump site were examined to determine any negative consequences of chronic gastrostomy tube placement and repeated pump changes. A complete gross necropsy examination was done, with selected tissues obtained for microscopic evaluation. Tissues were processed routinely, embedded in paraffin, sectioned at 5 µm, and stained with hematoxylin and eosin for histologic evaluation, with selected tissues stained by the Masson trichome method.

Results

All 5 macaques tolerated placement of the gastric catheter and pump changes well. The animals maintained good condition throughout the course of the yearlong study, during which they increased in body weight by 0.82 to 1.58 kg, an increase of 6.7% to 15.8% compared with their beginning body weight. The catheters remained patent, as demonstrated by dose-dependent increases in serum drug levels and brain receptor occupancy on PET scans. At selected pump changes, animals underwent gastroscopy to inspect the catheter tip in the stomach (Figure 2). Examination revealed images that varied from distinct, tubular catheter tips, with normal-appearing gastric mucosa, to obscured tips with apparent mounding, or hypertrophy, of surrounding mucosa. Portions of some of the catheter tips were darkly discolored, an effect we attribute to prolonged contact with stomach acid. At necropsy, patency of all catheters was verified by injecting dye into the catheters.

Complications during pump changes. A total of 4 complications occurred during the course of 80 pump changes for this study. On 2 occasions, the catheter accidentally was cut close to its connection to the osmotic pump during routine pump changes. In both cases, we were able to repair the catheter intraoperatively by the use of a hypodermic needle, sized to fit in the catheter. The needle was scored with a #20 scalpel blade and snapped at the scored line, forming a connector that was inserted into each end of the cut catheter (Figure 3). As a result we modified our techniques for all subsequent pump changes. First, several connectors were prepared and kept available at all pump changes. Second, the incision for pump changes was moved to directly over the end of the pump, giving us a firm surface for incision and preventing cutting of the catheter. No further inadvertent catheter cuts were made after this procedural change.

In addition, dehiscence of an incision site occurred once during the study, likely due to local infection. To repair the breakdown, the opposite side of the macaque's back was prepped and a new pocket made on that side. The catheter was cut and attached to a replacement pump, which was placed in the new, clean pocket. The skin of the new pocket was closed with 4-0 PDS. The area over the old pump was cleaned and an incision was made over the distal portion of the pump, through which the pump and the remaining short piece of catheter were removed. The area was irrigated with saline and left open. The macaque was treated with 300 mg ceftriaxone daily for 7 d and 2.4 mg meloxicam daily on day 1, followed by 1.2 mg daily for 2 d. No problem developed with the new pocket, and the old pocket healed without complication.

Finally, at one pump change, the end of the catheter was found to be disconnected from the pump and could not be located, even though radiographs appeared to show the catheter in the area of the pump. Laparoscopy, done to locate the exit site, revealed that the end of the catheter actually was in the peritoneal cavity. The catheter was not patent, and an obturator was placed briefly in the catheter before its replacement. After careful removal of the initial gastric disc implant, a new catheter was placed approximately 3 cm from the site of the old one, by using the procedure described previously. This additional surgery occurred approximately 5 mo following the initial catheter placement and was approved by the IACUC to reduce the number of animals used for the study.

Pathologic evaluation. On conclusion of the study, the macaques were euthanized by pentobarbital overdose for tissue collection. In addition, the stomach and pump sites were examined to assess associated tissue changes. All animals were in good physical condition. Gross examination revealed minimal localized fibrous adhesions that extended between the catheter peritoneal entrance or catheter implant sites and omental fat or the liver. The outer portion of the implant site was smooth (Figure 4 A). Several macaques had localized scarring on the diaphragm or the liver where they came into direct contact with the catheter or suture disc on the stomach. Microscopic examination of the implant site revealed that the suture disc was well-encapsulated within a fibrous connective tissue capsule (Figure 5 D), with the disc tightly adherent to the gastric serosa. In the first animal examined, the fibrous capsule surrounded a central core, which consisted of a prominent fibrous reaction intermixed with numerous disc fibers. Small numbers of foreign body giant cells (Figure 5 A) within the core contained disc fibers (Figure 5 B). Trichrome staining of the implant site as well as of sites of localized scarring of the liver or the diaphragm showed that changes at these sites were limited to fibrosis. In addition, minimal acute inflammation and fibrosis was present in the subcutis at the osmotic pump and catheter tunnel sites in this animal. Examination of gastric implant sites of the 4 other animals in the study similarly revealed that the disc material was well encapsulated, with inflammatory infiltrates contained almost entirely within the suture disc adherent to the stomach, occasionally extending along the catheter in the stomach wall. In no case did this inflammation involve the gastric mucosa. The inflammation present in all 5 animals was qualitatively similar, ranging from the fibrous reaction with few giant cells in the initial animal to a mixed inflammatory reaction in several animals that contained both foreign-body giant cells and varying numbers of neutrophils, which often occurred in dense sheets (Figure 5 C). Other changes included lymphocytic aggregates in the submucosa bordering the catheter tract in 3 of the macaques.

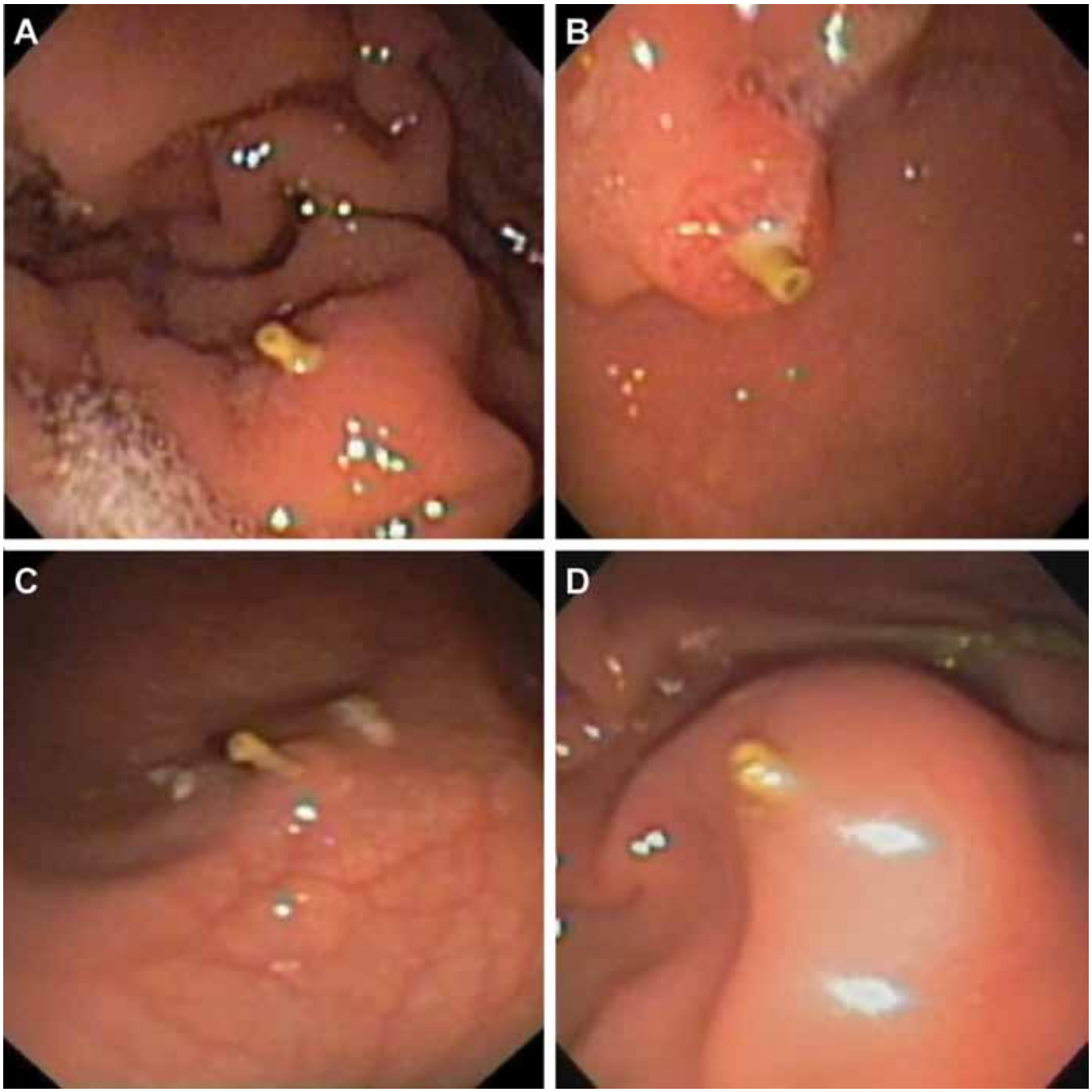

Figure 2. Gastroscopy images from 4 different animals showing the catheter tip in the stomach lumen.

Discussion

Our results indicate that the gastric catheter and osmotic pump system is well tolerated in rhesus macaques for at least 12 mo after placement. All gastric catheters remained patent, with minimal complications. Subcutaneously placed osmotic pumps have been used widely at our facility for decades with few problems and minimal evidence of animal discomfort. That pattern compares well with our observations in the current study.

In the system we describe here, the duration of use appears to be limited only by the number of osmotic pump changes possible. Monkeys developed fibrosis at the site of pump placement, making osmotic pump changes increasingly difficult over time. Monkeys underwent an average of 16 pump changes over the course of the year. Based on the extent of scarring present at the study conclusion, we suggest that 16 changes approach the maximum that can be expected without complication.

Alternative approaches that we considered included a percutaneous endoscopic gastrotomy (PEG) tube, an OROS delivery system, and a tether system. PEG tubes are primarily used to provide enteral access in patients that require nutritional support.[8] Because PEG tubes are designed to allow food administration, the diameter of the tube is typically much larger than the catheter used in the current study. Our study protocol required administration of only 4.68 µL drug/h, and the large amount of dead space in the PEG tube would not support reliable continuous infusion of the small quantity of drug into the gastric lumen. In addition, a device would need to be created to connect the end of the PEG tube to the much smaller opening on the osmotic pump.

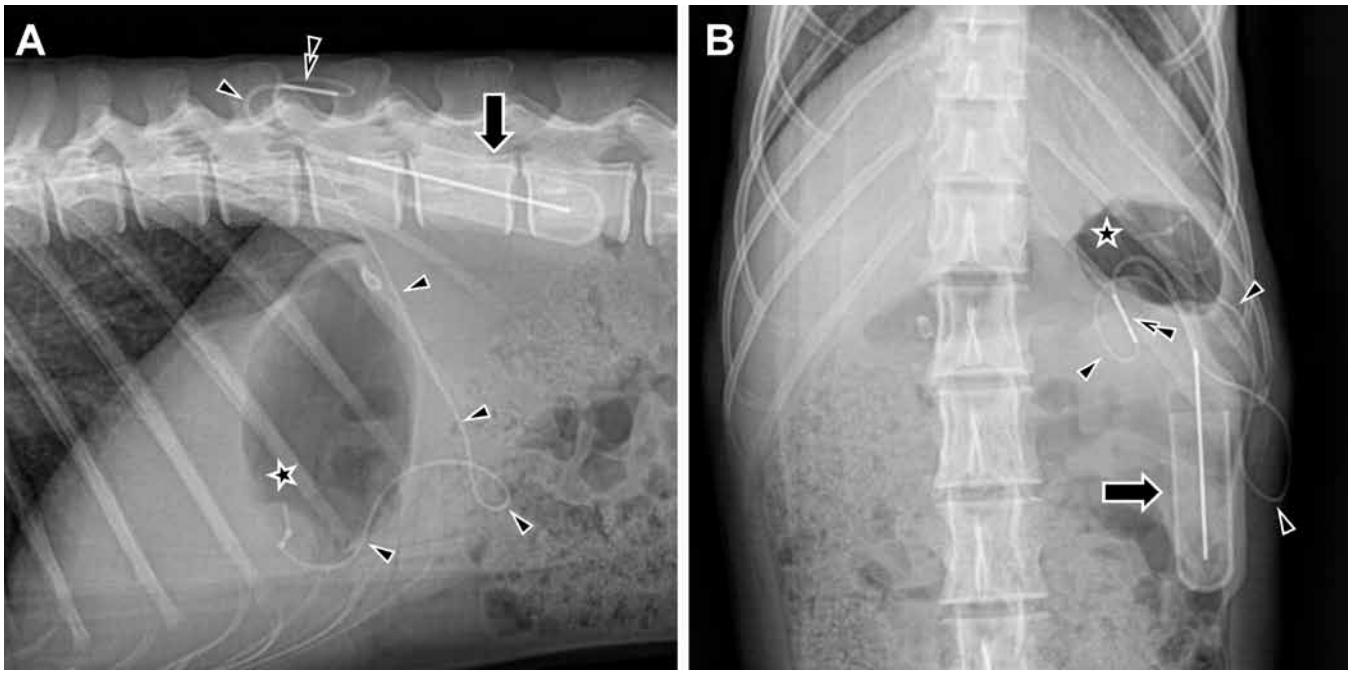

Figure 3. (A) Lateral and (B) ventrodorsal radiographs showing the osmotic pump (large arrow), catheter (single arrowheads), catheter repair connector (double arrowhead), and tip of the catheter in the stomach lumen (star).

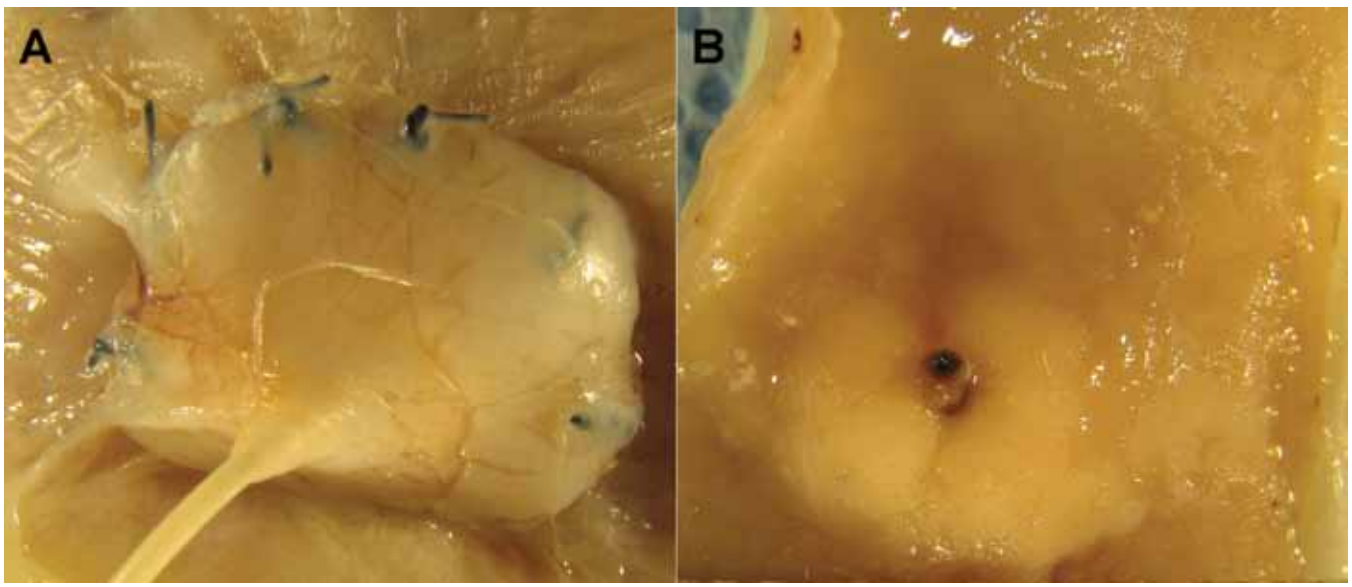

Figure 4. An example of a gastric catheter insertion site from the (A) serosal and (B) luminal surface of the stomach at necropsy. (A) The catheter and suture disc are visible from the serosal side of the stomach. Note that the suture disc is well-encapsulated. (B) From the gastric lumen, the tip of the catheter within the stomach can be seen. Some darkening of the catheter tip is present.

The OROS delivery system is an ingestible osmotic pump for continuous, controlled drug release. Although OROS pills are available for paliperidone, they are designed for human use and contain much larger quantities of drug than was required in this study. Because of the unique design of these pills, we could not obtain them in the drug concentrations required for this study. As an additional obstacle, reliable administration of these pills would require daily gavage.

We also considered using a recently described tether system.[5] In this method, the gastric catheter was tunneled through the subcutaneous tissue to an exit site on the monkey's back and connected to a syringe pump through a tether attached to a swivel at the top of a custom-designed cage. This system was undesirable for our study because our facility does not currently use this type of caging, and our personnel lack expertise in working with tethered animals. In addition, part of the current study protocol required frequent transfer of monkeys from their home cage for imaging or cognitive testing. Use of a tether complicates the transfer of animals out of the home cage and requires anesthesia. Our gastric catheter and osmotic pump system, in contrast, allowed easy and frequent transfer of monkeys for imaging or cognitive testing.

For studies that require chronic gastric infusion of a single drug, use of a refillable osmotic minipump constitutes a potential further refinement. Recently, a refillable, programmable, microinfusion pump was described for use in rats.[1] These pumps are designed to be refilled percutaneously and might minimize or eliminate the number of pump changes needed

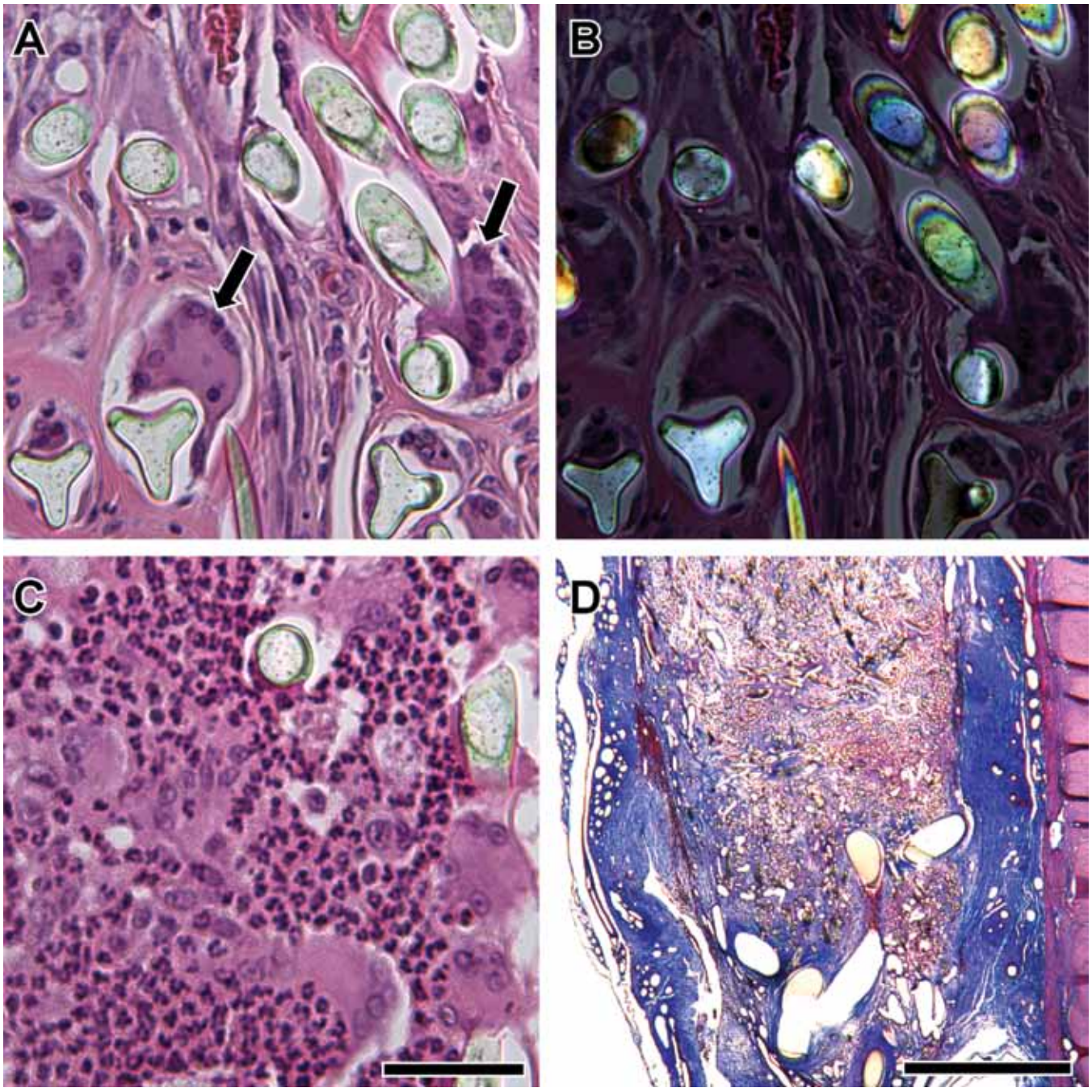

Figure 5. Histologic sections through the suture disc site. (A) Hematoxylin and eosin staining shows giant cell foreign body reaction (arrows), with giant cells typically apposed to suture disc fibers. (B) The same field as in panel A but under polarized light to better show the suture disc fibers. (C) A neutrophilic infiltrate was sometimes intermingled with the giant cell reaction. (D) Trichrome staining reveals fibrous encapsulation (dark blue) of the suture disc (center). The gastric wall is visible on the far right. Bars, 50 µm (A through C); 1 mm (D).

throughout the course of the study. We expect that with the use of a refillable pump, the duration of catheter viability could be extended significantly beyond 12 mo. One limitation, however, is that residual solution present in the pump chamber each time it is refilled makes this option less attractive for studies in which multiple drugs or doses are planned.

In one study,[5] invagination of the catheter disk within the gastric lumen occurred and was considered as a potential complication. As recommended by those authors,[5] we periodically examined the catheters endoscopically to assess disk invagination. Although apparent hyperplasia with mounding of the gastric mucosa around the catheter tip was present in several macaques on endoscopy at late time points in the study, this apparent hyperplasia was not evident grossly at necropsy. We hypothesize that the mounding may have been an artifact caused by insufflation of the gastric lumen during endoscopic examination. The mounds of gastric mucosa approximated the shape and size of the catheter disk. Because the disk developed a thick fibrous capsule over time, this area of the stomach may have been unable to expand under insufflation as readily as the surrounding tissue. With the tissue surrounding the disk pushed outward, the area under the disk may have appeared as a mound of gastric mucosa surrounding the catheter. None of our 5 macaques showed evidence of catheter invagination into the gastric lumen at necropsy.

A limitation of the gastric catheter–subcutaneous osmotic pump system is the limited volume of these pumps. For this study in macaques, we used pumps with a 2-mL volume, which is the largest available. If a high drug dose is required, the necessary drug concentration may be close to or exceed its maximal solubility. This situation might be accommodated by connecting 2 osmotic minipumps to the catheter via a Y connecter. Indeed, we did this for a single dose of study drug in one of the larger macaques. However, an important consideration for use of the gastric catheter-subcutaneous osmotic pump system is the number, concentration, and volume of planned drug doses and the maximum drug concentration that can be prepared.

Histopathologic changes were consistent with a foreign-body reaction and were not unexpected. Evidence of a localized inflammation at the osmotic pump site in one monkey was well contained and was not considered to be a significant problem. One possible explanation for this reaction is the inadvertent mild contamination that may have occurred during a pump change. Although this catheter design is a closed system, pump changes nonetheless create the risk of introducing infection. Therefore, use of aseptic technique is crucial.

In conclusion, the gastric catheter and osmotic pump system is an effective, well-tolerated method of chronic gastric drug administration in rhesus macaques. This method offers an attractive alternative for use in studies that require continuous, constant rate, enteral drug delivery in untethered monkeys.

Acknowledgments

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