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BRIEF COMMUNICATION

Esophageal Cannulation for Oral Drug Administration in the Sub-Human Primate

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HARLAND, E. C., M. C. WILSON AND J. A. BEDFORD. *Esophageal cannulation for oral drug administration in the sub-human primate.* PHARMAC. BIOCHEM. BEHAV. 7(4) 405–406, 1977. – A technique of esophageal cannulation used in rats was adapted for use in the sub-human primate. Cannulation of the esophagus requires general surgical skills and a very short postoperative recovery period. No interference in eating habits or tendency toward vomiting was noted following cannulation. This technique allows the investigator an effective method for oral dosing of drugs with minimal physical and emotional stress to the animals and is quite appropriate for oral drug self-administration studies.

Esophageal cannulation Sub-human primate Oral self-administration Chronic oral toxicity

SCHEDULED administration is a widely used technique in animal models to evaluate the toxicological, psychological, and pharmacological properties of chemicals and drugs. Techniques for drug administration should allow the investigator the ability to administer the test drug in specific doses at specific times by the desired route with minimal emotional and physical stress to the animal.

Oral administration techniques which are now used include incorporating the drug in the animal's food or water, naso-gastic intubation and gastic cannulation. Some drugs are not readily accepted orally by animals because of taste. Attempts to mask the taste of these drugs in food and drinking water have not been satisfactory and have inherent difficulties, especially when scheduled dosing is required.

Naso-gastic intubation requires physical restraint to hold the animal during the procedure. This produces excitement and emotional stress which may alter early behavior and/or pharmacological effects of the test drug.

To overcome these difficulties some investigators have developed a cannulation technique to bypass the mouth and deposit the substance directly into the stomach. This method allows an effective method of administering drugs orally with little restraint to the animal as well as possible self-administration of drugs. However, the intragastric cannulation technique requires well-developed surgical skills and considerable postsurgical care. If the cannula is not properly sutured to the stomach wall or is pulled loose, gastric juice will leak into the abdominal cavity producing peritonitis and probable death. The extensive abdominal adhesions, which develop with this procedure, involve in many cases the intestines, spleen, and liver [1].

Cannulation of the esophagus has the advantages of the intragastric technique but requires only general surgical skills and a minimum of postsurgical care [2].

METHOD

Eight male rhesus monkeys, *Macaca mulatta*, were used in this study. The animals were housed in a sound-proof chamber (91.5 cm × 91.5 cm × 124 cm) with an expanded metal floor for 1 week prior to surgery. The animals were fitted with restraining harnesses which were connected to the back of the chamber by a flexible arm. This equipment allows free movement within the chamber but prevents escape when the chamber is open. The animals were given free access to water and fed Purina monkey chow (8 chows twice a day). Food was withheld the morning of surgery. Animals were fed as usual following recovery from anesthesia.

Cannula Construction

The esophageal cannula was made from a 60 cm length of silicon rubber tubing (Siltube i.d. – 0.031 cm, o.d. 0.093 cm, Rodhelm Reiss, Inc.). A strand of 5–0 stainless steel monofilament wire was looped and tied 5 cm from the tip of the catheter with enough tension to indent the tubing

but not close the inside diameter of the tube. The cannula was then autoclaved and was ready for use.

Surgical Procedure

Anesthesia was induced by Ketamine HCl 10 mg/kg IM (Vetalar, Parke-Davis) and maintained with thiamylal sodium IV (Surital, Parke-Davis). The hair was removed from the neck and thoracic back using electric hair clippers (Model A5 Oster) equipped with a size 40 blade. A presurgical scrub using providone-iodine (ACU-dyne skin cleanser^{R}, ACME United Corporation) was given to the skin of the clipped area. A providone-iodine prep solution was then applied to the surgical area.

The anesthetized monkey was then placed on the surgery table which was covered by 4 layers of sterile muslim drape. The animal was positioned and draped for surgery.

The animal was positioned on its back with its head over the end of the table allowing the anterior surface of the neck to be extended. A 5 cm skin incision was made on the midline beginning approximately 1 cm anterior to the manubrium of the sternum. The bodies of the sternohyoideus muscles were separated by blunt dissection. The trachea lies medial to the sternohyoideus muscles and the esophagus immediately beneath it and to the animal's left. By moving the trachea to either side and bluntly separating the loose connective tissue the esophagus was grasped with Allis tissue forceps and raised to the surface of the incision. A small hole (1/2 cm) was made in the longitudinal muscles of the esophagus by placing the sharp points of Iris scissors into the muscle and spreading the points. Small rat-toothed forceps were placed in between the separated muscles to pick up the mucosal lining of the esophagus. The mucosa was identified by its yellowish-white color. A small hole was cut in the mucosa and the cannula passed into the esophagus until the stainless steel wire was flush with the muscles of the esophagus. A purse-string suture using this wire was made through the muscles of the esophagus. Two mattress sutures were made through the esophageal muscle around the cannula with 5–0 stainless steel wire, inverting the muscle around the cannula. Stainless steel wire was chosen over other available suture material because of its low tissue irritability and nonabsorption qualities.

The cannula was passed under the skin from the incision to the preferred exit point on the back. The cannula exited at a point along the midline of the back between the level of the shoulder blades, which allowed connection of the cannula to the infusion needle contained in the restraining harness. This was accomplished by bluntly dissecting the subcutaneous tissues with hemostatic forceps from the incision to a point just over the external jugular vein. The free end of the cannula was clamped in hemostates and pushed under the skin to the desired point on the back. A small incision was cut over the point of the hemostats through the skin and the cannula pulled through.

The sternohyoideus muscles were sutured back together and the cannula anchored with 5–0 stainless steel wire in the suture line of the muscle tissue. Care was taken to insure that no unusual tension was placed on the cannula as it was anchored in place as this would alter the normal positioning of the esophagus.

The skin was closed with 5–0 stainless steel wire. The cannula was then attached via the stainless steel harness and restraining arm to an infusion pump. An injection of 600,000 units of benzathine penicillin G and procaine penicillin G (Bicillin C-R, Wyeth Laboratories, Inc.) was given following surgery.

RESULTS

In the eight rhesus monkeys used in the experiment, two had functional cannulae after six weeks of daily dosing. Two died during the first week post surgery from drug overdose. On necropsies of these animals it was found that a very strong adhesion developed around the cannula as it enters the esophagus. The adhesions prevented food or other substances escaping the esophagus in this area. The mucosal lining of the esophagus was not grossly altered by the cannula, nor was inflammation or swelling apparent at the site where the cannula entered the esophagus. Two monkeys gained access to the distal end of the cannulae and the cannulae broke in situ. An attempt was made to remove the proximal portion of the cannula and replace it with a new cannula. It was found that the cannula was still securely in the esophagus, but due to the adhesions which developed between the esophagus and surrounding tissues recannulation was much more difficult. The cannulae were removed from these animals and uneventful recoveries followed. One other animal was able to remove his cannula intact and suffered no adverse effects. The last animal was removed from the experiment after 4 weeks of daily dosing due to sores developing on the shoulder under the harness shoulder strap; however, the cannula was still functional.

DISCUSSION

This experimental procedure for oral administration has several advantages. (1) Scheduled administration of drugs can be given without regard for taste, food consumption, or water intake. (2) Drugs can be given in solution. The dissolution time may be an important consideration in pharmacological or pharmacokinetic studies in which the latency of the drug effect is a prime factor. (3) It is possible to connect the cannula to tubing outside the chamber through the restraining arm, which allows dosing of the animals without experimenter-induced stress. This procedure provides a method for the chronic oral administration of substances without traumatizing the animal repeatedly as would occur if nasal intubation were used. The researcher is therefore better able to evaluate the acute and chronic effects of drugs on ongoing behavior. Furthermore, this procedure offers a method for developing self-administration studies for drugs with oral abuse potential.

The simplicity of the surgical procedure makes this technique available for use by most laboratories working with sub-human primates. If the subject manages to remove this cannula there is very little likelihood of infection or debilitating complications occurring.

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