Thomas M. Donnelly, DVM, Column Editor

## What's your diagnosis?

# Dyspnea and Porphyria in Rats

Submitted by Christine A. Bosgraaf, CVT, RLATG, Hans Suchy, Carrie Harrison, and Linda A. Toth, DVM, PhD

Our veterinary staff received a male 375-g Wistar rat in severe respiratory distress. On the previous day the rat had undergone surgery. An experienced research technologist, who had completed the identical procedure successfully in the past, did the surgery. He had anesthetized the rat with pentobarbital, 42 mg/kg intraperitoneally (i.p.) and did not require a second dose for adequate maintenance of anesthesia. Completion of the surgical procedure required approximately 60 minutes. Using aseptic technique, the research technologist placed a silicone implant subcutaneously in the right inguinal region and sutured it to the abdominal wall to prevent migration. After the surgery, he gave the rat a subcutaneous (s.c.) injection of buprenorphine (0.08 mg/kg) and returned him to his cage. When checked the next morning, the rat was salivating and had some bedding stuck to the area around his mouth. Approximately 36 hours after surgery, the rat was dyspneic and appeared to be choking. He was breathing heavily through his mouth and was salivating excessively, causing bedding to become matted around his mouth (**Fig. 1**). Porphyrin staining was present around the rat's eyes and on his front feet (**Fig. 1**).

Consequently, we decided to euthanize the rat. The research technician who euthanized the rat and removed the implant noted no obvious complications associated with the surgery. Veterinary staff did a necropsy immediately after euthanasia and found the esophagus to be grossly distended and strawlike in color (**Fig. 2**). The distension and discoloration extended from the cardiac orifice of the stomach to the cranial aspect of the thorax. The stomach was full and appeared larger than normal (**Fig. 2**), and the intestines were distended from gas with a small amount of fecal matter present. Esophageal and gastric contents were straw-colored, fibrous, compacted, dry, and crumbly upon manipulation (**Fig. 3**). Almost no food was present in the stomach. We did not see lesions in any other organs: the lungs were pink, the trachea was clear of any apparent obstruction or damage, the heart was unremarkable, and the thoracic cavity was free of fluid. We tested serum in-house for Sendai virus, mycoplasma, and coronavirus using the ImmunoComb system (Charles River Laboratories, Wilmington, MA), with negative results.

Several days later, another rat presented with history and clinical signs similar to those of the first rat. We also euthanized and necropsied this rat, and found similar lesions. We had maintained both rats on ad libitum food and water before and after surgery and housed them in polycarbonate cages with hardwood bedding.

Based on the surgical history of these rats, what could cause clinical and necropsy signs such as these?

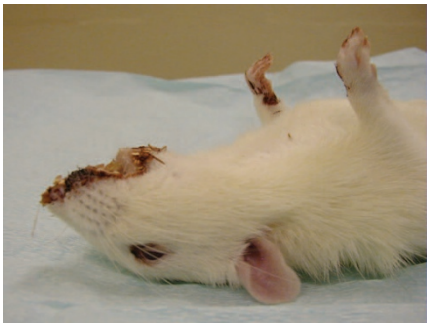

**FIGURE 1. Porphyria in a dyspneic rat.**

## What's your diagnosis?

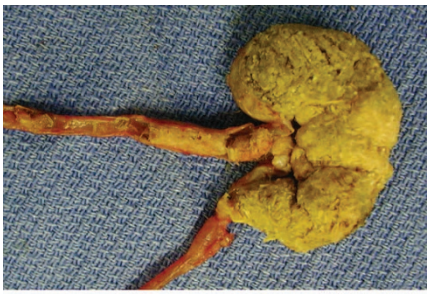

**FIGURE 2. Gastric and esophageal distension in a rat.**

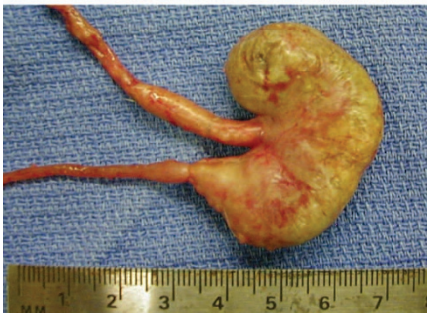

**FIGURE 3. Esophageal and gastric impaction in a rat.**

Bosgraaf is a veterinary technician of the Division of Laboratory Animal Medicine, Suchy and Harrison are research technologists in the Department of Surgery, and Toth is Director of the Division of Laboratory Animal Medicine and Professor of Pharmacology, Southern Illinois University School of Medicine, Springfield, IL. Please address correspondence to Toth at ltoth@siumed.edu.

## Diagnosis:

# Pica Secondary to Buprenorphine Administration

Based on the clinical history and gross necropsy findings, we diagnosed pica secondary to buprenorphine administration as the initiating cause of bedding ingestion and subsequent gastric and esophageal impaction. Pica is a behavior characterized by the craving for and ingesting of unnatural or non-nutrient substances. Pica in rats may indicate nausea and is perhaps analogous to emesis in other species, since treatment with anti-emetic drugs improves the behavior[1–3].

Several reports have described pica in rats after buprenorphine administration[4–7]. Various doses of buprenorphine, whether used in surgically manipulated or surgery-naive rats, or in rats treated simultaneously with other drugs, can elicit pica. Clark *et al.*[5] and Jacobsen[6] described rats ingesting non-nutrient substances, such as bedding, that are available in the environment, resulting in gastric distension that may be severe enough to cause death. The use of grid flooring in cages or the restriction of access of rats to bedding can prevent or reduce the pica and its effects after buprenorphine administration. Rats housed on synthetic bedding show a lower incidence of bedding ingestion after buprenorphine administration than rats housed on sawdust or wood-chip bedding[8].

Anestheologists and veterinarians widely recommend and use buprenorphine as a postsurgical analgesic drug in rats[8–10]. Its advantages include a relatively long duration of action and fewer cardiovascular and respiratory side effects than many other opioid analgesics, as well as relatively high analgesic potency[8]. In some surgical models, buprenorphine has superior analgesic effects as compared with fentanyl, flunixin, and acetaminophen[7]. However, adverse side effects, such as reduced weight gain, might outweigh its analgesic benefits in some situations[8]. Administration of buprenorphine in doses commonly used for analgesia has also been associated with stereotyped licking and biting, a hunched posture, and reduced intestinal motility in rats[7,11].

Less than a month after we saw the first two rats, we noted similar signs in three rats used in another laboratory. In this case, male 8- to 9-week-old [AUTHOR: Fischer?] Fischer 344 rats had undergone heterotopic heart transplantation under pentobarbital anesthesia (50 mg/kg i.p.). These rats had received one dose of buprenorphine (0.07 mg/kg s.c.) immediately after surgery and a second dose on the next morning. The research technician noted the occurrence of pica within minutes after administration of the second dose.

In our facility, both research groups whose rats experienced pica had previously used buprenorphine in similar studies without adverse effects. Both groups had previously expressed satisfaction using this agent to provide analgesia during the early postoperative period. Similarly, many reports of buprenorphine use for analgesia in rats do not mention observing this obvious side effect[12–16]. The sporadic nature of this serious side effect complicates the routine use of buprenorphine in rats, and shows that veterinary and research personnel should be alert for the development of this potentially fatal adverse drug reaction. Possible preventive interventions include use of a lower dose that retains analgesic efficacy, and maintaining rats temporarily on wire grid flooring when administering buprenorphine. Alternatively, veterinarians can recommend a different analgesic regimen.

LAB ANIMAL welcomes reader contributions to "What's Your Diagnosis?" in the case history/diagnosis format presented here; submissions should include two to five illustrations or photos. Please email your manuscript to labanimal@natureny.com or send a hard copy and an electronic copy on disk to Thomas M. Donnelly c/o Editorial Dept., LAB ANIMAL, 345 Park Avenue South, 10th Floor, New York, NY 10010. Selections are made on the basis of relevance and interest to readers.

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