Self-mutilation in rabbits following intramuscular ketamine-xylazine-acepromazine injections

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Abstract — Following hind leg intramuscular injections of ketamine, xylazine, and acepromazine, 4 of 6 rabbits exhibited self-mutilation of the digits. At necropsy, the affected sciatic nerve appeared enlarged. Lymphohistiocytic perineural inflammation and fibrosis were observed, together with nerve degeneration. Neuronal regeneration as the reason for self-mutilation is discussed.

Résumé — Automutilation chez des lapins à la suite d'injections intramusculaires de kétamine-xylazine-acépromazine. Des lapins (4/6) se sont automutilés suite à une injection intramusculaire de kétamine, de xylazine et d'acépromazine. Le diamètre des nerfs sciatiques affectés était augmenté suite à une fibrose et une inflammation périneurale lympho-hystocytique. Une dégénérescence axonale des nerfs sciatiques a été constatée. La régénération neuronale expliquant l'automutilation est discutée.

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Ketamine in combination with other drugs is frequently used to anesthetize rabbits *(Oryctolagus cuniculus)*. Following injections of ketamine-xylazine-acepromazine in the thigh muscles, self-mutilation, or self mutilation, of the digits was observed in 4 of 6 rabbits.

Rabbits (n = 6) were purchased from Charles River Canada and weighed 2 kg upon arrival. The experimental protocol was approved by the Institutional Animal Care and Use Committee. The rabbits were kept in accordance with the Canadian Council on Animal Care guidelines. They were fed standard rabbit chow and given water ad libitum. One week following arrival, the rabbits were anesthetized with 30 mg/kg body weight (BW) of ketamine (Ketaset, 100 mg/mL; Ayerst, Guelph, Ontario), 10 mg/kg BW of xylazine (Rompun, 100 mg/mL; Bayer, Etobicoke, Ontario), and 1 mg/kg BW of acepromazine (Atravet, 10 mg/mL; Ayerst) mixed in a single syringe. The anesthetic cocktail was administered in a single injection using a 21G needle. The injection site was the hamstring muscles of the left hind leg. The anterior cruciate ligament of the right hind leg was completely sectioned to induce arthritis. The objective of this study was to evaluate different experimental anti-inflammatory drugs when injected locally.

Two weeks following these procedures, digital self-mutilation of the left hind leg was observed in 4 of the 6 rabbits. Affected paws were unresponsive to topical application of proviodine. After 2 to 3 d, the situation deteriorated, as the animals continued to chew on their paws, and the decision was taken to euthanize the affected rabbits with an overdose of pentobarbital (Somnotol; MTC Pharmaceuticals, Cambridge, Ontario) 100 mg/kg BW, IV. Unaffected rabbits were euthanized at the end of the study, 3 wk following the euthanasia of the affected rabbits. At necropsy, the sciatic nerve of the affected leg appeared greatly enlarged. No lesions were observed in the semitendinosus, semimembranosus, or biceps femoris muscles surrounding the injection site. The sciatic nerve of both legs was removed, placed in 10% formalin, and processed routinely for paraffin embedding and histological examination. Sections (3 µm) were stained with hematoxylin, phloxine, and saffron, and mounted for examination by light microscopy.

Sciatic nerves of rabbits that exhibited self-mutilation had axonal degeneration evidenced by swelling and vacuolization. The perineuritis consisted mainly of lymphocytes and collagen accumulation (Figure 1). The thickening of the nerve that was noticed at necropsy was caused, therefore, by the accumulation of fibrotic tissue. The nerve from the unaffected side was surrounded by loose connective tissue and showed the typical longitudinal organization of the myelin sheaths (Figure 1).

Previous studies have shown that muscle necrosis, as well as an inflammation characterized by neutrophils, lymphocytes, and macrophages, occurs following IM injections of ketamine and xylazine (1–4). Fibroblasts surrounding the necrotic tissue are present in the inflammatory zone at 3 and 7 d (2). An increase in plasma aspartate aminotransferase was caused by local myotoxicity following ketamine IM injections in marmosets (1). Mechanisms of tissue necrosis and fibrosis following ketamine injections have not been described. Axonal degeneration and self-mutilation with ketamine-xylazine anesthesia has been shown in rabbits and guinea pigs (4,5). However, no quantification of degenerated axons was performed in either study. In rabbits, most axons underwent axonal degeneration with ketamine and xylazine at doses of 50 mg/kg BW and 10 mg/kg BW, respectively (4). In our rabbits, adding acepromazine to the cocktail and reducing the ketamine to 30 mg/kg BW did not seem to reduce the damage to the nerve or the self-mutilation behavior.

Beyers et al (4) have suggested that sciatic nerve damage results in self-mutilation. In this case report, the perineural infiltration of anesthetics must have been

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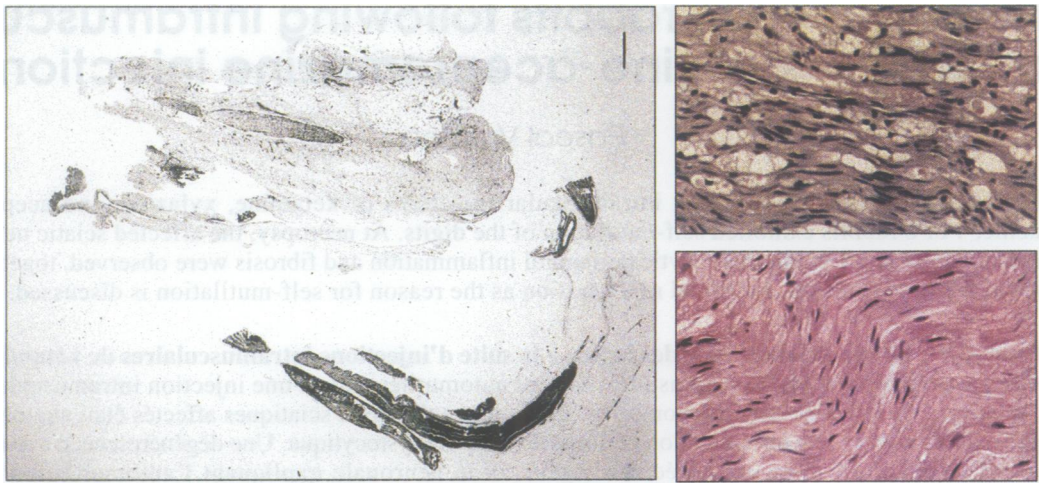

Figure 1. The photograph on the left shows the nerve affected by the injected drugs (bottom structure, tangential section) surrounded by a thick fibrotic cuff, and the normal contralateral nerve taken from the same animal (top structure, longitudinal section). On the right of this figure, 2 microphotographs of longitudinal sections of normal (top) and affected (bottom) sciatic nerves are shown (100X). Axonal degeneration, evidenced by swelling, breakdown of axons, and vacuolization is present in the affected nerve. Hematoxylin, phloxine, and saffron (HPS); bar = 0.2 mm.

more important, because there was no muscle necrosis but there was substantial perineuritis and axonal degeneration. The occurrence of self-mutilation in rats following sciatic nerve injury peaks between 7 and 14 d and self-mutilation behavior is strongly correlated with regenerating axons, as well as endoneurial macrophages (6). It is hypothesized that these regenerating axons may contribute to dysesthetic perceptions. Axons could possibly be more sensitive to biochemical factors, such as cytokines and growth factors from activated macrophages. However, chronic self-mutilation cannot be explained by these transient local and peripheral changes. Abnormal cellular hyperactivity in the spinal cord, thalamus, and cerebral cortex has been recorded for extensive periods, 6 to 18 mo, following rhizotomy (7); therefore, self-mutilation and chronic pain and/or dysesthesia could also be related to modifications occurring in the central nervous system (CNS). Evidence from a number of studies shows that self-mutilation is not related simply to axonal degeneration or lack of sensation but rather to the presence of regenerating fibers and abnormal cellular activity in the CNS.

Different environmental factors that affect stress, such as room temperature and housing, may affect abnormal behavior (6). Rats exhibit more self-mutilation when housed alone or when placed in a cold environment. The severity of self-mutilation is also variable within different rat strains and ages. Findings of a recent study show that diet may modify self-mutilation behavior (7). Proteins sources from vegetable or animal origin vary in amino acid content. Vegetable diets are known to be poor in tryptophan. Consumption of a high tryptophan diet suppresses self-mutilation. It is hypothesized that since tryptophan is a precursor of serotonin, an inhibitory neurotransmitter, self-mutilation suppression would be related to serotonergic pain modulation in the CNS. Therefore, the diet and the psychological well-being of animals exhibiting self-mutilation need to be of concern for the prevention and treatment of this condition.

Our technical error could have been avoided by injecting into the muscles and limiting the volumes injected with respect to muscle size, as suggested in the guide on laboratory animal welfare from the Canadian Council on Animal Care (9). This is important to avoid perineural infiltration of the anesthetic with subsequent damage to nerves. Since this incident, we have anesthetized more than 100 rabbits without the occurrence of self-mutilation, by dividing doses, so that no more than 1.0 mL is administered per injection site, and by changing the injection site to the lumbar muscles. CVJ

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