

## Histopathologic Changes After Repetitive Peridural Administration of Metoclopramide in Dogs

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Several groups have described an analgesic effect of metoclopramide administered IV in labor, termination of pregnancy, prosthetic hip surgery, and knee arthroscopy (1–3). Studies in albino mice demonstrated an analgesic effect with intraperitoneally administered metoclopramide (4). However, the exact mechanism of its analgesic effect has not been determined.

Metoclopramide provides analgesia for renal colic pain and improves analgesia when used for the treatment of narcotic-induced nausea during labor (3). This analgesic effect of metoclopramide in the genitourinary tract may be attributed to its antagonism of the dopamine receptor, as well as its cholinergic activity, which reduces smooth muscle spasm and increases effective peristaltic action (5,6).

We have not encountered any published reports on the peridural administration of metoclopramide. In this preliminary study, our goal was to examine possible pathological changes caused by peridural administration of metoclopramide in an animal model.

### Methods

The experimental protocol was approved by our university's animal research committee. After overnight fasting, 12 mongrel dogs (either sex), mean weight  $21 \pm 4$  kg, were anesthetized with IM ketamine 10 mg/kg and midazolam 0.1 mg/kg. A 16-gauge Tuohy needle was inserted by a midline approach at the L2-3 or L3-4 vertebral interspace. Entry into the epidural space was identified by hanging-drop technique, and a 19-gauge epidural catheter was advanced 3–4 cm into the epidural space. The catheter was then tunneled subcutaneously up to neck level (C7-T4), and

a Periplant Filtrosafe (B. Braun, Melsungen, Germany) device was implanted underneath the skin for repeated injections.

Dogs were then allocated into two groups by a coin toss. Group I ( $n = 7$ ) received metoclopramide HCl 20 mg/d through an implanted Periplant Filtrosafe for 14 days (5 mg/mL metoclopramide HCl solution: sodium metabisulfide 1.5 mg/mL, sodium chloride 7 mg/mL, distilled water 1 mL). Group II ( $n = 5$ ) received saline 4 mL/d by the same route for 14 days.

At the end of the study period, dogs were anesthetized with an IM injection of ketamine 10 mg/kg and midazolam 0.1 mg/kg. After placement of an IV catheter, thiopental 5 mg/kg and succinylcholine 1 mg/kg IV were administered, and endotracheal intubation was performed. Anesthesia was further maintained by halothane 1%–1.5% in oxygen. We then removed 10 cm of spinal cord with its dural sac 5 cm above and 5 cm below the level of epidural catheter placement. Catheter location at the epidural space was confirmed during pathological dissection of each study animal.

Paraffin slices of 5  $\mu$  thickness were obtained from the specimen and were fixed in a formaldehyde solution for light microscopy examination. Histopathological examination was performed after hematoxylin and eosin (HE) staining; Woelckes technique was used to evaluate the myelin sheaths of myelinated nerve fibers. Pathological slices obtained from spinal cord and posterior funiculi of the dorsal roots were stained with toluidine blue azure II.

For electron microscopy (EM) examinations, specimens were obtained from funiculus posterior of spinal cord and fixed in 3% glutaraldehyde in 0.2 M phosphate buffer (pH 7.4) for 5 h at 4°C, then prepared with the conventional EM procedure. Semithin sections were cut for topographic orientation and stained with toluidine blue, and ultrathin (70 nm) sections were stained with uranyl acetate and lead citrate and examined on an electron microscope.

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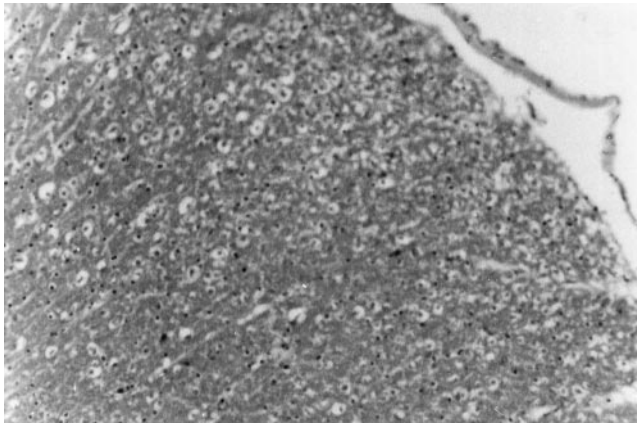


Figure 1. Hematoxylin and eosin stain. Light microscopy ( $\times 40$ ). Group I (metoclopramide).

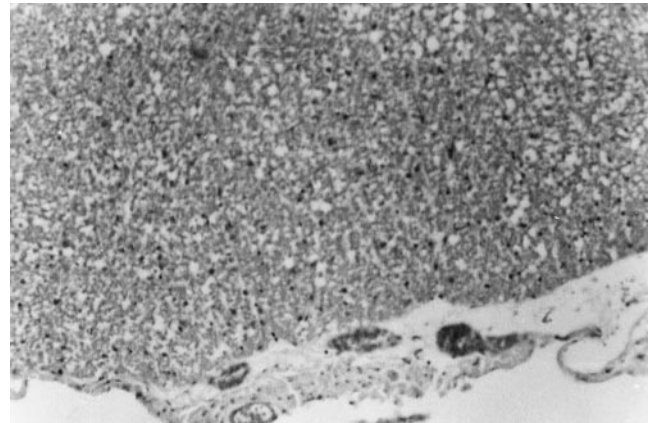


Figure 2. Hematoxylin and eosin stain. Light microscopy ( $\times 40$ ). Group II (saline).

## Results

The 5- $\mu$  paraffin slices were examined histopathologically after HE staining. Neuronal changes and myelination were evaluated, and no differences were seen between the groups (Figs. 1 and 2).

Examination of the myelin sheath of peripheral nerve fibers stained using the Woelckes technique revealed that myelin sheaths in both groups were preserved. No demyelination was observed.

In Group I, light microscopic examination of the pathological slices obtained from spinal cord and posterior funiculi of the dorsal roots, stained with toluidine blue azure II, revealed no deterioration in myelination. There was also no pathological change observed in the sensory neurons of the dorsal root in the gray matter.

Results of the EM examination showed that there was no significant pathology in small or large myelinated nerve fibers or accompanying glial cells in either group (Figs. 3 and 4). Demyelination was not observed. Myelin sheaths consisting of repeated lamellae of the glial cells were regularly arranged as series of major dense lines. Neurofilaments, microtubules, and mitochondria in axons were unaffected.

## Discussion

Metoclopramide is a structural analog of procainamide (2-methoxychlorprocainamide), but it lacks local anesthetic and antiarrhythmic activity (2). The analgesic properties of metoclopramide have been demonstrated in animal experiments. Calcium channel, opioid, or prolactin-mediated mechanisms have been suggested (2,4). Data on the analgesic potency of metoclopramide led us to evaluate its analgesic effect through epidural administration. No previous investigations concerning safety of epidural or intrathecal administration of metoclopramide have been performed. Repetitive epidural

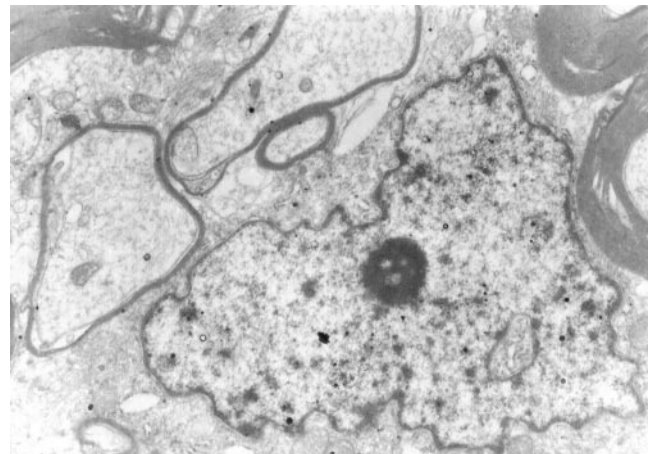
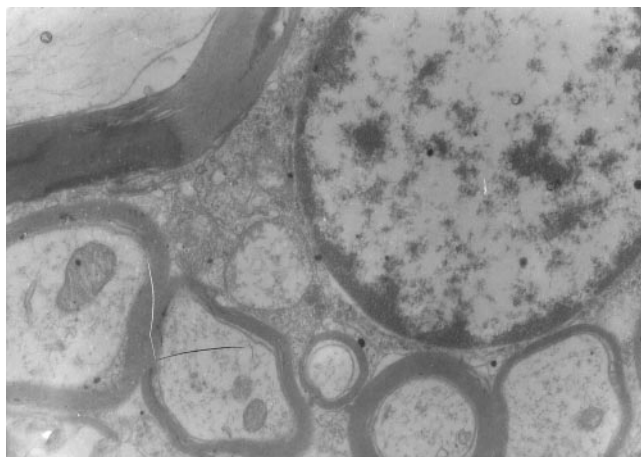


Figure 3. A glial cell from an animal in Group II (saline) is shown between the myelinated fibers ( $\times 7500$ ).

administration of metoclopramide was chosen as a study model because the epidural route is used more frequently than the intrathecal route for chronic pain management (7).

Dura has been regarded as a remarkable barrier to the deleterious effects of many drugs inadvertently administered into the epidural space (8). There are reports describing histopathologic changes after the epidural or intrathecal administration of various neurotoxic agents (9,10). Alcohol and phenol neurotoxicity is marked by demyelination, neurolysis, chromatolysis, loosened myelin lamellae, an increased number of glial cells, and extracellular edema in EM examination (9), whereas the intrathecal administration of monosialoganglioside results in demyelination, dilation of the axonal sheath, and axonal degeneration (10).

In this study, histopathologic changes after the epidural administration of metoclopramide in an animal model were studied to provide additional information regarding its neurotoxicity. The analgesic effect of



**Figure 4.** Large and small myelinated fibers from an animal in Group I (metoclopramide) have surrounded the oligodendroglia.

metoclopramide was not evaluated. The metoclopramide HCl preparation used in this study contained sodium metabisulfide as a preservative. There were no histopathological deteriorations in the metoclopramide group after repetitive use of this commercial preparation, and we found no reports concerning the neurotoxicity of this antioxidant preservative.

Metoclopramide administration in animal or human studies has resulted in an antinociceptive effect, which has been attributed to endogenous opioid mechanisms or increased serum levels of prolactin (1,2). In studies concerning ureterolithiasis and labor pain, the analgesic effects were interpreted as being mediated by an action of metoclopramide on painful contractions of smooth muscle (2,6).

The IV doses of metoclopramide shown to exert an analgesic effect are 10 mg/kg for termination of pregnancy, 0.5 mg/kg for knee arthroscopy, and 1 mg/kg for prosthetic hip surgery (1-3). In albino mice, the 50% effective dose for the analgesic effect of intraperitoneally administered metoclopramide is 2.6 mg/kg (4). In this study, a total daily dose of 20 mg was administered epidurally (approximately 1 mg/kg), which corresponds to the IV dose previously shown to have an analgesic effect.

Metoclopramide is a potent antagonist of the dopaminergic D2 receptor (2). Some researchers have suggested that dopaminergic agonists increase the efficacy of morphine analgesia, whereas others have reported an antagonism (1). This controversy may be

due to different activation characteristics of dopaminergic D1 and D2 subtypes (1). However, dopaminergic agonist and antagonist effects on mechanism of pain have not been clarified.

Ganta and Fee (11) reported that lidocaine and metoclopramide are equally effective in prevention of pain caused by the administration of propofol. They claimed that the morphine-like systemic analgesic effect of metoclopramide could be attributed to alteration of calcium transport through membranes (11). However, the role of this mechanism in the prevention of local pain is unknown.

In this study, metoclopramide was administered through the epidural route for 14 days, and there was no histopathological deterioration in the spinal cord, nerve roots, axons, or dural sac. Adequate experimental animal studies should be performed before using new drugs via the epidural or intrathecal route (9). We recommend that further dose-response and dose-related side effect studies via both the intrathecal and epidural routes be performed in animals before using metoclopramide to treat acute and chronic pain in humans.

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