

Dept. of Surgery,
 Fac. of Vet. Med., Assiut University,
 Head of Dept. Prof. Dr. N.A. Misk.

A PRELIMINARY STUDY ON THE EFFECT OF XYLAZINE BY CAUDAL EPIDURAL ADMINISTRATION IN CATTLE

By

M.A. SELEIM; I.H. AHMED and S.M. ALI
 (Received at 16/1/1990)

دراسة أولية عن تأثير الزيلازين بعد الحقن الخلفي
 فوق الأضغاف في الأبقار

مجدى سليم ، ابراهيم حسين ، منوت المختار

يستخدم التخدير الخلفي في الأبقار في كثير من حالات التوليد والجراحة والزيلازين كبنه للمستقبلات ألفا - 2 حقن حول الأضغاف في المكان الزليلي ونتج عن ذلك نوعين من التخدير وهما: مابسي تخدير عالي ومنخفض للأضغافه وذلك حسب الجرعة التي استخدمت في الحالتهن وهي 0.05 مجم لكل كيلوجرام من وزن الحيوان بالترتيب مع فترة أطول للمفعول المخدر عند استخدام الليجنوكاين.

SUMMARY

Caudal epidural analgesia in cows is indicated for various gynecologic, obstetric and surgical manipulations.

Xylazine, an α_2 adrenergic receptor agonist was injected into the caudal epidural space of cows produced a safe and effective high and low caudal epidural analgesia in a dose rate of 0.05 mg and 0.025 mg/Kg B.W. respectively, which prolonged duration of action than lidocaine.

INTRODUCTION

Caudal regional analgesia is produced by intrathecal and epidural injection of local anaesthetic drugs for a number of diagnostic and surgical procedures in human beings and animals. In addition to eliminating nociceptive input, however, this means of producing analgesia also eliminates nearly all sensory input, sympathetic outflow, and motor output, resulting in cardiovascular changes and somatic motor paralysis (BRIDENBAUGH and KENNEDY, 1987).

Recent studies of KURAISHI *et al.* (1985), and DURANT and YAKSH (1986), indicated that the intrathecal injection of opiate analgetics produce clinically useful relief of pain without loss of either ambulation or sympathetic nervous activity. In addition to the opiates, intrathecally administered α_2 -adrenergic agonists also produce antinociception in a number of species (GORDH *et al.*, 1986; POST *et al.*,

M.A. SELEIM *et al.*

1987; EISENACH and GRICE, 1988 and OSSIPOV *et al.*, 1988).

This antinociceptive effect is mediated by spinal α_2 -adrenergic receptors because the analgesia is antagonized by α_2 but not α_1 or B blockers (FLEETWOOD-WALKER *et al.*, 1985). Alpha 2 receptors inhibit the release of a spinal neurotransmitter (substance P) believed to be important in pain perception (PERNOW, 1983). Thus inhibition of spinal transmission of painful stimuli is possible, using spinal or epidural α_2 -adrenergic agonists. Spinal and epidural α_2 -induced analgesia has been achieved with clonidine Hcl and guanfacine (GORDH and TAMSEN, 1983; COOMBS *et al.*, 1985; EISENACH and GRICE, 1988; OSSIPOV *et al.*, 1988 and POST *et al.*, 1987).

Xylazine is closely related to clonidine, an α_2 -adrenergic receptor agonist used as an antihypertensive drug in human medicine. Xylazine and clonidine induce sedation via centrally located postsynaptic α_2 -adrenergic receptors (HEDLER *et al.*, 1981 and HEATCH *et al.*, 1982). Xylazine, an α_2 -adrenergic receptor agonist, is used extensively parentally as a sedative-analgesic in domestic and wild animal species (KNIGHT, 1980 and GREENE and THURMON, 1988). Xylazine was injected epidurally in horses (LeBLANC *et al.*, 1988) and intrathecally in rats and mice (OSSIPOV *et al.*, 1988).

LeBLANC *et al.* (1988) concluded that epidural administration of xylazine results in perineal analgesia in the horse, with the absence of behavioral effects commonly associated with systemically administered drugs.

The present study was undertaken to evaluate the antinociceptive and behavioral effects of xylazine in comparison to lidocaine after their epidural administration in cows.

MATERIAL and METHODS

This study was conducted on nine adult cows of native breed (weighing from 200 to 350 Kg). These animals were treated in a cross-over study at three times. They were injected xylazine in two different doses or lidocaine epidurally, with two weeks intervals between each experiment. The drugs were injected epidurally in the first coccygeal intervertebral space with a 20-gauge, 3.8-cm long needle. Confirmation of proper needle placement was based on evidence of negative pressure (hanging drop technique) and negligible resistance to injection.

Xylazine was injected in a dose of 0.05 mg/Kg B.W. which is the lowest dose used intramuscularly in cattle (GLEED, 1984), in all animals then followed by lidocaine in a dose of 0.2 mg/Kg B.W. (SKARDA, 1987). In group III experiment, the cows were injected xylazine in a lower dose of 0.025 mg/Kg B.W. The doses were given in equal volumes, diluted to 5 ml normal saline.

After injections, the animals were observed for signs of overt behavioral effects such as ataxia, salivation, tail flaccidity and anal dilatation. The analgesic effects

XYLAZINE - EPIDURALLY

of the drugs were tested by skin pin prick. Onset, duration of analgesia and the margins of desensitized area were recorded in all animals. At 5 minutes intervals after injections, the animals were allowed to walk to observe the motor effects of the drugs (ataxia of the hind limbs) except in cases of recumbency and inability to stand.

RESULTS

The mean time of onset in group I was 6.4 minutes (3-10) and in group II, 11.8 minutes (5-20). The mean duration of analgesia after xylazine, 0.05 mg/Kg B.W. was 148, 3 minutes (11-210) versus, 77.5 minutes (30-120) after lidocaine.

In group III, where the same cows were injected xylazine epidurally in a dose of 0.025 mg/Kg B.W., the onset and duration were nearly similar to group I, means were 6 minutes and 120 minutes respectively.

In group I six cows (66.7%) had marked ataxia with dragging of hind limbs, at a mean time of 9.2 minutes after xylazine injection. From these, five (55.6%) became recumbent after 20 minutes mean of time after injection, for a mean time of 40 minutes. However no apparent locomotor effects were observed in group II & III except in one cow in group III which had, mild ataxia (11.1%). The area of desensitization to skin prick was markedly extended cranially including the flank and a part of the thoracic wall and distally till the lower parts of the hind limbs in animals in group I, in comparison to group II & III, where the area was localized around the anus and the lips of valva except in one animal (11.1%) in group III in which the area of analgesia was extended distally near the hock joint. Sedation and obvious salivation were observed in all cows of group I, 1 to 5 minutes after xylazine administration.

DISCUSSION

Recent studies have demonstrated that injection of spinal and epidural α_2 agonist drugs induce analgesia with attenuation of supraspinal side effects (sedation and respiratory, and cardiovascular depression) prolonged duration of action (EISENACH *et al.*, 1987) and absence of diminished hind limb strength (REDDY *et al.*, 1980 and YAKSH and REDDY, 1981).

In the present study, epidural administration of 0.05 mg xylazine/Kg B.W. which is the lowest dose used clinically intramuscularly in cows (GLEED, 1984), induced prolonged analgesia. Furthermore, it resulted in extraspinal side effects, "sedation and pronounced salivation" in all animals. This dose was considered a high dose for caudal (low) epidural analgesia in cattle due to the extension of the local analgesic effect cranially and distally. Therefore, a lower dose (0.025 mg/Kg) of xylazine was injected epidurally in cows of group III. This dose induced analgesia for about 120 minutes, which seemed to provide a safe and effective perineal (caudal or low

M.A. SELEIM *et al.*

epidural) analgesia with a longer duration of action than that after lidocaine, about 77,5 minutes.

Recent studies have demonstrated an intraspinal site of action for α_2 -adrenergic mediated analgesia. In those studies ionophoretic application of α_2 agonists to neurons of the lumbar spinal dorsal horn inhibits the response to noxious cutaneous stimulation in various species (SATO *et al.*, 1979; FLEETWOOD-WALKER *et al.*, 1985 and SULLIVAN *et al.*, 1987). Furthermore, BOUCHENAFI and LIVINGSTON (1987) demonstrated the autoradiographic localization of α_2 adrenoceptors binding sites in the spinal cord of the sheep.

However, the locomotor effect of a high dose epidural (group I) can be explained by the local anaesthetic properties of xylazine (AZIZ and MARTIN, 1978). LeBLANC *et al.* (1988) observed also motor involvement after high doses of epidural xylazine in horses. It had been suggested that xylazine would extend sufficiently cranially in the spinal cord to block the spinal segments (L4 to S1), from which the motor innervation (femoral & sciatic nerves) to the hind limbs originated.

This investigation documented that xylazine can be used for a safe and effective high and low epidural analgesia in cows in a dose rate of 0.05 mg and 0.025 mg/B.W. respectively. The analgesic effects of epidural xylazine may be potentiated by use of other α_2 adrenergic agonists or narcotics in combination with xylazine. This needs further investigation.

REFERENCES

- Aziz, M.A. and Martin, R.J. (1978): α_2 agonist and local anaesthetic properties of xylazine. *Zbl. Vet. Med. A.*, 25: 181-188.
- Bridenbaugh, P.O. and Kennedy, W.F. (1987): Spinal, subarachnoid neural blockade. In: Cousins, M.J., Bridenbaugh, P.O. eds., *Neural blockade in clinical anesthesia and management of pain*. Philadelphia: JB Lippincott. 146-175.
- Bouchenafi, O. and Livingston, A. (1987): Autoradiographic localisation of α_2 adrenoceptor binding sites in the spinal cord of the sheep. *Research in Veterinary Science*, 42(3): 382-386.
- Coombs, D.W.; Saunders, R.L.; LaChance, D. *et al.* (1985): Intrathecal morphine tolerance: use of intrathecal clonidine, DADLE and intraventricular morphine. *Anesthesiology*, 62: 358-363.
- Durant, P.A.C. and Yaksh, T.L. (1986): Epidural injections of bupivacaine, morphine, fentanyl, lofentanyl and DADL in chronically implanted rats: a pharmacologic and pathologic study. *Anesthesiology*, 64: 43-53.
- Eisenach, J.C.; Dewan, D.M.; Rose, J.C. *et al.* (1987): Epidural clonidine produces antinociception, but not hypotension in sheep. *Anesthesiology*, 66: 496-501.
- Eisenach, J.C. and Grice, S.C. (1988): Epidural clonidine does not decrease blood pressure or spinal cord blood flow in awake sheep. *Anesthesiology*, 68: 335-340.
- Fleetwood-Walker, S.M.; Mitchell, R.; Hope, P.J. *et al.* (1985): An alpha 2 receptor mediates the selective inhibition by noradrenaline of nociceptive responses of identified dorsal horn neurons. *Brain Res.*, 334: 243-254.

XYLAZINE - EPIDURALLY

- Gleed, R.D. (1987): Tranquilizers and sedatives. In: Short, C.E., ed. Principles and practice of veterinary anesthesia. Baltimore: The Williams & Wilkins Co., 16-27.
- Gordh, T.E. and Tamsen, A. (1983): A study of the analgesic effect of clonidine in man. *Acta Anaesthesiol. Scand.*, 27 (Suppl, 27), 72.
- Gordh, T.; Feuk, U. and Norlen, K. (1986): Effect of epidural clonidine on spinal cord blood flow and regional and central hemodynamics in pigs. *Anesth. Analg.*, 65: 1312-8.
- Greene, S.A. and Thurmon, J.C. (1988): Xylazine - a review of its pharmacology and use in veterinary medicine. *J. Vet. Pharmacol. Ther* 11: 295-313.
- Hatch, R.C.; Booth, N.H.; Clark, J.D. *et al.* (1982): Antagonism of xylazine sedation in dog by 4-aminopyridine and yohimbine. *Am. J. Vet. Res.* 43: 1009-1014.
- Hedler, L.; Stamm, G.; Weitzall, R. and Starke, K. (1981): Functional characterization of central alpha-adrenoceptors by yohimbine diastereomer. *Eur. J. Pharmacol.*, 70: 43-52.
- Knight, A.P. (1980): Xylazine. *JAVMA*, 176: 454-455.
- Kuraishi, Y.; Hirato, N.; Satoh, M. and Takagi, H. (1985): Antinociceptive effects of intrathecal opioids, noradrenaline and serotonin in rats: mechanical and thermal algescic test. *Brain Res.*, 326: 168-71.
- LeBlanc, P.H.; Caron, J.P.; Patterson, J.S. *et al.* (1988): Epidural injection of xylazine for perineal analgesia in horse. *JAVMA*, 193: 1405-1408.
- Ossipov, M.H.; Saurez, L.C. and Spaulding, T.C. (1988): A comparison of the antinociceptive and behavioral effects of intrathecally administered opiates, α -2-adrenergic agonists and local anesthetics in mice and rats. *Anesth. Analg.*, 67: 616-624.
- Pernow, B. (1983): Substance P. *Pharmacol. Rev.*, 35: 85-141.
- Post, C.; Gordh, T.; Minor, B.G.; Archer, T. and Freeman, J. (1987): Antinociceptive effects and spinal cord tissue concentrations after intrathecal injection of guanfacine or clonidine into rats. *Anesth. Analg.*, 66: 317-324.
- Reddy, S.V.R.; Maderdrut, J.L. and Yaksh, T.L. (1980): Spinal cord pharmacology of adrenergic agonist-mediated antinociception. *J. Pharmacol. Exp. Ther.*, 213: 525-533.
- Satoh, M.; Kawajiri, S.I.; Ukai, Y. *et al.* (1979): Selective and nonselective inhibition by enkephalin and nonadrenaline of nociceptive responses of lamina V neurons in the spinal dorsal horn of the rabbit. *Brain Res.*, 177: 384-387.
- Skarda, R.T. (1987): Local and Regional Analgesia. In: Short, C.E., ed. Principles and practice of veterinary anesthesia. Baltimore: The Williams & Wilkins Co., 91-143.
- Sullivan, A.F.; Dashwood, M.R. and Dickenson, A.H. (1987): Alpha 2 adrenoceptor modulation of nociception in rat spinal cord: Location, effects and interactions with morphine. *Eur J Pharmacol* 138: 169-177.
- Yaksh, T.L. and Reddy, S.V.R. (1981): Studies in the primate on the analgetic effects associated with intrathecal actions of opiates alpha-adrenergic agonists, and baclofen. *Anesthesiology*, 54: 451-467.