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Epidural co-administration of neostigmine and lidocaine or xylazine enhances systemic sedation but not perineal analgesia in adult dairy cows

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ABSTRACT: The aim of this study was to evaluate the behavioural, clinical and analgesic effects of epidural neostigmine in adult dairy cattle. Five healthy, adult Holstein-Friesian dairy cows received five different treatments in a cross-over design with one-week washout period as follows: 2% lidocaine alone (0.22 mg/kg), neostigmine alone (10 μg/kg), neostigmine-lidocaine (10 μg/kg and 0.11 mg/kg), neostigmine-xylazine (10 μg/kg and 0.05 mg/kg) and 0.09% saline alone (6 ml). Analgesia of the perineal region was assessed using the superficial and deep muscle pin-prick techniques. The onset and duration of analgesia and the degree of analgesia, sedation and ataxia were assessed before drug administration (T0) and thereafter at T15, T30, T60, T120 and T180. In addition, cows were monitored for any behavioural or clinical abnormalities over the course of the entire study. Signs of agitation, increased salivation and increased frequency of defecation were observed in cows administered neostigmine epidurally alone or in combination with lidocaine or xylazine. The epidural administration of neostigmine alone did not result in any analgesic effects in any of the cows. Analgesia appeared significantly faster ($P \leq 0.05$) in the lidocaine group compared to the neostigmine-lidocaine and neostigmine-xylazine groups. The duration of analgesia produced by neostigmine-xylazine was significantly longer ($P \leq 0.05$) than that produced by lidocaine alone or neostigmine-lidocaine. Neostigmine produced a significant degree of sedation ($P \leq 0.05$) when administered epidurally alone or in combination with lidocaine or xylazine. The epidural administration of neostigmine alone did not result in any signs of ataxia, while the epidural administration of lidocaine alone, neostigmine-lidocaine and neostigmine-xylazine resulted in variable degrees of ataxia. There were no significant changes in any of the clinical parameters. In conclusion, neostigmine can be co-administered epidurally with lidocaine or xylazine for routine standing surgical procedures in adult dairy cows to enhance sedation but not analgesia.

Keywords: pain; regional analgesia; acetylcholinesterase inhibitors; standing surgery; bovine

Treatment with the acetylcholinesterase inhibitor neostigmine leads to an abundance of acetylcholine at motor end-plates (Lauretti 2015). In human as well as veterinary medicine, neostigmine has been used to treat myasthenia gravis, Ogilvie syndrome, non-obstructive urinary retention and to reverse the effects of non-depolarising muscle relaxants at the end of surgical operations (Lauretti 2015). The use of neostigmine in the epidural space is common practice in human surgery (Lauretti 2015). The exact mechanism of spinal analgesia produced by spinal or intrathecal administration of neostigmine has been suggested to involve an increased concentration, and as a consequence binding, of acetylcholine to M1, M2, M3 and M4 muscarinic receptors and to nicotinic receptors (Alkan and Kaya 2014; Lauretti 2015).

In human patients, epidurally or intrathecally administered neostigmine was found to exert

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synergistic or additive effects with α2-agonists, nitric oxide, muscimol and non-steroidal anti-inflammatory drugs (Miranda et al. 2002; Alkan and Kaya 2014; Lauretti 2015). In dogs, neostigmine was found to increase the duration of epidural analgesia compared with lidocaine alone (Marucio et al. 2014). In horses, the neostigmine-lidocaine combination was found to improve and extend the duration of perineal analgesia (DeRossi et al. 2013).

In adult cattle, epidural administration of neostigmine has not been tested before. The theory tested here was that epidural administration of neostigmine alone or in combination with lidocaine or xylazine may lead to enhanced perineal analgesia in adult dairy cows. Therefore, the aims of this study were to evaluate the analgesic effects of epidural neostigmine and to compare its effects with the analgesic effects of epidural lidocaine, neostigmine-lidocaine and neostigmine-xylazine combinations in adult dairy cattle.

MATERIAL AND METHODS

Ethical approval. This study was performed in accordance with the International Animal Ethics Committee Guidelines and in compliance with national laws and regulations. All experimental procedures were approved by the Animal Care and Use Committee of the Jordan University of Science and Technology (JUST-ACUC approval No. 516 of August 29, 2016).

Animals. Five, adult (age 2–5 years) Holstein-Friesian dairy cows with an average body weight of 550 kg were used in this study. The cows were clinically examined prior to enrolment in the study to ensure they were healthy. In a random fashion, each cow received five treatments in a cross-over design with a one-week washout period. The cows received the following treatments: 2% lidocaine alone (L; 0.22 mg/kg; 6 ml), neostigmine methylsulfate alone (N; 10 µg/kg; 2.2 ml) (Prostigmin 2.5 mg/ml, Valeant Pharmaceuticals International, Inc., Switzerland), neostigmine-lidocaine (LN; 10 µg/kg and 0.11 mg/kg; 5.2 ml), neostigmine-xylazine (Xyla-ject 2%, Adwia pharmaceuticals, Egypt) (NX; 10 µg/kg and 0.05 mg/kg; 3.5 ml) and 0.09% saline alone (S; 6 ml).

Injection technique. The injection technique used in this study was described previously (Ismail et al. 2017). Briefly, the cow was restrained in standing position in stocks. The area of the sacrococcygeal (S5-Co1) joint was clipped and surgically scrubbed using iodine disinfectant solution (10%). An 18-gauge, 4-cm-long hypodermic needle was used for the injections. Before injection, proper epidural injection was confirmed by lack of resistance to the injection of air and by the hanging drop technique using a drop of saline.

Behavioural observations. Behavioural changes such as signs of agitation, defecation, diarrhoea and salivation were recorded before drug administration (T0) and thereafter at T30, T60, T120 and T180.

Clinical parameters. The heart rate (HR), respiratory rate (RR), rectal temperature (RT) and rumen motility were determined before drug administration (T0) and thereafter at T30, T60, T120 and T180 minutes after injection of drug(s). Systolic and diastolic blood pressures were obtained from the base of the tail using an Omron digital blood pressure device (Omron Health Care, The Netherlands). This device was previously validated for use in animals in our clinic.

Degree of analgesia. The time of onset, duration and anatomic distribution of the analgesia were recorded. Time of onset of analgesia was defined as the time at which sensation was lost after drug injection while duration of analgesia was the time between loss and reappearance of pain response (DeRossi et al. 2003; DeRossi et al. 2010; Atiba et al. 2015). Analgesia was defined as the lack of response to noxious stimuli using superficial and deep muscle pin-prick applied to the tail base, anus, perineal region, caudal and cranial udder regions, medial and lateral sides of the proximal and distal regions and the hind limbs using a 23-gauge, 2.5-cm-long needle (DeRossi et al. 2003; DeRossi et al. 2010; Atiba et al. 2015). The scale used to assess analgesia (0–3) was similar to one proposed previously with slight modifications (score for normal response was changed from 1 to 0) (DeRossi et al. 2003; DeRossi et al. 2010; Atiba et al. 2015). The following scores were used to assess analgesia in this study: 0 – normal response (strong reaction to pinprick stimuli such as strong and repeated kicking, avoidance); 1 – mild analgesia (no response to pinprick stimuli, but the animal moves with no kicking); 2 – moderate analgesia (no response to pinprick stimuli, but the animal appears restless, avoidance); 3 – complete analgesia (the cow appears calm, non-responsive to pinprick stimuli). Superficial panniculus muscle

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twitching alone was not considered as an indication of painful response to pinprick stimuli.

Degree of sedation. The scale used to assess sedation (0–3) was similar to one proposed previously with slight modifications (score for normal response was changed from 1 to 0) (Dzikiti et al. 2009). The following scores were used to assess sedation in this study: 0 – no sedative effect; 1 – mild depression (upper eyelids have dropped, no other signs); 2 – moderate drowsiness (prolapsed third eyelid, ptyalism); 3 – severe (animal leans on the stocks for support).

Degree of ataxia. The scale used to assess ataxia (0–3) was similar to one proposed previously with slight modifications (score for normal response was changed from 1 to 0; DeRossi et al. 2003; DeRossi et al. 2010; Atiba et al. 2015). In cases of severe sedation, the cow was not walked out of the stocks for evaluation of ataxia. The following scores were used to assess ataxia in this study: 0 – no ataxia: no change in limb or body position from baseline; 1 – mild ataxia (occasional stumbling, but the animal continues to walk easily); 2 – moderate ataxia (marked stumbling, walking with considerable difficulty); 3 – severe ataxia (falling down).

Analgesia, sedation and ataxia were assessed before drug administration (T0) and every minute for the first 10 minutes after drug administration and then at T15, T30, T60, T120 and T180.

Statistical analyses. Data are presented as means ± SD. One-way ANOVA and Bonferroni/Dunn tests were utilised to compare the time of onset and duration of analgesia between the treatment groups. Values for HR, RR, systolic and diastolic blood pressure, RM and RT were analysed using repeated measures ANOVA. A value of $P \leq 0.05$ was considered significant.

RESULTS

Behavioural observations

Within 30 minutes after neostigmine administration, cows showed mild signs of agitation and restlessness that lasted less than 60 minutes (Table 1). There was an increased rate of salivation that started within 30 minutes after administration and lasted for up to 120 minutes. Cows also exhibited an increased frequency of defecation with the passage of soft faecal matter.

Table 1. Behavioural observations in dairy cows administered neostigmine epidurally (n = 5)

Parameters	Observation times (min)				
	T0	T30	T60	T120	T180
Agitation	–	+	–	–	–
Defecation	–	+	+	+	–
Diarrhoea	–	+	–	–	–
Salivation	–	+	+	+	–

Clinical observations

There were no statistically significant changes in the clinical values including heart rate, respiration rate and rectal temperature (Table 2). The rumen motility patterns increased significantly within 60 minutes after administration. The systolic and diastolic blood pressure decreased slightly from the baseline but not significantly.

Onset and duration of analgesia

Similar to the saline group, epidural administration neostigmine did not result in analgesic effects in any of the cows (Table 3). Analgesia appeared significantly faster ($P \leq 0.05$) in the lidocaine group (4.8 ± 2.0 minutes) compared to the neostigmine-lidocaine and neostigmine-xylazine groups (6.20 ± 3.0 minutes and 10.50 ± 2.0 minutes, respectively). The duration of analgesia produced by neostigmine-xylazine (180+ minutes) was significantly

Table 2. Clinical parameters (means ± SD) in dairy cows administered neostigmine epidurally (n = 5)

Parameters	Observation times (min)				
	T0	T30	T60	T120	T180
Heart rate (beats/min)	66 ± 4.0	64 ± 6.0	68 ± 2.0	66 ± 4.0	66 ± 6.0
Respiration rate (breaths/min)	28 ± 2.0	26 ± 4.0	28 ± 5.0	26 ± 2.0	26 ± 3.0
Rectal temperature (°C)	38 ± 0.5	38.20 ± 0.5	38.40 ± 0.6	38.20 ± 0.7	38.10 ± 0.2
Rumen motility (/3 min)	2.0 ± 0.5	3.0 ± 0.5*	3.5 ± 0.5*	2.0 ± 0.5	2.0 ± 0.5
Systolic blood pressure (mm Hg)	145 ± 5.0	138 ± 3.0	133 ± 3.0	138 ± 4.0	142 ± 2.0
Diastolic blood pressure (mm Hg)	56 ± 6.0	60 ± 3.0	54 ± 6.0	49 ± 7.0	60 ± 5.0

*Indicates significance at $P \leq 0.05$ when compared to T0 within the same treatment group

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Table 3. Onset and duration of analgesia (minutes; means ± SD) in cows administered different drugs epidurally (n = 5)

Treatment groups	Parameters	
	onset	duration
Neostigmine	0.0	0.0
Lidocaine	4.80 ± 2.0[a]	85 ± 10[a]
Neostigmine-lidocaine	6.20 ± 3.0[a]	78 ± 15[a]
Neostigmine-xylazine	10.50 ± 2.0[b]	180+[b]
Saline	0.0	0.0

Different superscript letters within the same column indicate significance at $P \leq 0.05$

longer ($P \leq 0.05$) than that produced by lidocaine alone (85 ± 10 minutes) or the neostigmine-lidocaine combination (78 ± 15 minutes). Similar to what was observed in the saline group, neostigmine administration did not result in analgesia at any of the tested sites of the body. Lidocaine alone, lidocaine-neostigmine and neostigmine-xylazine combinations produced variable degrees of analgesia at different sites of the body. The degree of analgesia was most pronounced at the base of the tail and least pronounced at the lateral side of the proximal hind limb in all groups. There was no analgesia detected at the medial and lateral sides of the distal hind limb regions in any of the groups.

Degree of sedation

The epidural administration of neostigmine resulted in significant degrees of sedation ($P \leq 0.05$) at T15, T30, T60 and T120 compared to lidocaine and saline, which produced no sedation at all (Table 4). Similar to neostigmine, lidocaine-neostigmine and neostigmine-xylazine produced a significant degree of sedation ($P \leq 0.05$) at T15 which lasted to T120. The degree of sedation produced by the neostigmine-xylazine combination, however, was the deepest.

Degree of ataxia

Similar to the saline group, epidural administration of neostigmine did not result in any signs of ataxia in any of the groups (Table 5). However, the epidural administration of lidocaine alone, lidocaine-neostigmine and neostigmine-xylazine resulted in variable degrees of ataxia, neostigmine-xylazine groups showed the highest degrees of ataxia in comparison to lidocaine alone or lidocaine-neostigmine combinations.

Table 4. Sedation scores (0–3; means ± SD) in dairy cows administered different drugs epidurally (n = 5)

Observation times (min)	Treatment groups				
	saline	neostigmine-xylazine	lidocaine-neostigmine	lidocaine	neostigmine
T0	0.0	0.0	0.0	0.0	0.0
T15	0.0	2.40 ± 0.4*	1.0 ± 0.0*	0.0	0.80 ± 0.4*
T30	0.0	2.80 ± 0.4*	1.0 ± 0.0*	0.0	1.0 ± 0.0*
T60	0.0	1.40 ± 0.4*	1.0 ± 0.0*	0.0	1.20 ± 0.4*
T120	0.0	1.20 ± 0.4*	0.0	0.0	1.20 ± 0.4*
T180	0.0	0.0	0.0	0.0	0.0

*Indicates significance at $P \leq 0.05$ when compared to T0 within the same treatment group

DISCUSSION

Although in this study all cows tolerated the epidural administration of neostigmine alone or in combination with other drugs, mild signs of restlessness such as agitation were observed. This may be a sign of abdominal discomfort due to the build-up of acetylcholine at the muscarinic receptors

Table 5. Ataxia scores (0–3; means ± SD) in dairy cows administered neostigmine epidurally (n = 5)

Observation times (min)	Treatment groups				
	saline	neostigmine-xylazine	neostigmine-lidocaine	lidocaine	neostigmine
T0	0.0	0.0	0.0	0.0	0.0
T15	0.0	1.80 ± 0.4*	1.0 ± 0.0*	1.0 ± 0.0*	0.0
T30	0.0	2.0 ± 0.0*	1.40 ± 0.4*	1.20 ± 0.4*	0.0
T60	0.0	1.80 ± 0.4*	1.20 ± 0.0*	1.0 ± 0*	0.0
T120	0.0	1.80 ± 0.4*	1.0 ± 0.4*	0.8 ± 0.4*	0.0
T180	0.0	0.80 ± 0.4*	0.0	0.0	0.0

*Indicates significance at $P \leq 0.05$ when compared to T0 within the same treatment group

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in the gastro-intestinal tract. Following epidural or intra-thecal administration, neostigmine may accumulate cranially leading to the inhibition of cholinesterase in the nervous system and, in turn, causing many cholinergic side effects (Chung et al. 1998; Nagy et al. 2014). It has also been reported that large doses of neostigmine administered epidurally may result in adverse effects due to systemic absorption (Chung et al. 1998; Nagy et al. 2014). This could explain the increased bowel movement and the passage of softer faecal material in these cows. These results are similar to previous results obtained after intramuscular injection of dairy cows with neostigmine (Ismail et al. 2017). In human surgery, epidural injection of neostigmine has been found to cause nausea and vomiting in a dose-dependent manner (Ho et al. 2005; Lauretti 2015). In addition, human patients who received epidural or intra-thecal neostigmine were found to pass gas and defecate faster than the controls, which also can be explained by the stimulatory functions of neostigmine on the intestinal tract (Chung et al. 1998; Nagy et al. 2014).

The increased salivation observed in this study is in close agreement with results obtained previously in dairy cows and human patients (Chung et al. 1998; Nagy et al. 2014; Ismail et al. 2017). This effect was found to vary according to the dose. Increased salivation was suggested to reflect peripheral cholinergic activation and to be a sign of sedation in dairy cows (Chung et al. 1998; Nagy et al. 2014).

In this study, there were no statistically significant changes in any of the clinical values including heart rate, respiration rate and rectal temperature. These results are similar to results obtained previously in dairy cows administered neostigmine intramuscularly (Ghazy et al. 2015; Ismail et al. 2017). The rumen motility patterns increased significantly within 60 minutes after administration, which was similar to previous results in cows (Ismail et al. 2017). This observation also reflects a systemic cholinergic effect (Chung et al. 1998; Nagy et al. 2014). In this study, systolic and diastolic blood pressure decreased slightly from the baseline but not significantly. These results are similar to previous findings in cows and human patients (Eldor et al. 1987; Ismail et al. 2017).

Administration of neostigmine epidurally had no analgesic effects in any of the cows in this study. This is in line with results from dogs where the analgesic effects of neostigmine alone were less pronounced than those elicited in the morphine or neostigmine-morphine groups (Marucio et al. 2014). In buffalo calves, epidural injection of the neostigmine-lidocaine combination produced complete analgesia of the perineal region (Ghazy et al. 2015). However, in a previous study in buffalo calves, neostigmine was not administered alone (neostigmine was only tested in combination with lidocaine) (Ghazy et al. 2015). The results with the lidocaine-neostigmine combination in this study are, however, similar to those reported previously (Ghazy et al. 2015). In order to minimise doses and thus side effects, in human surgery, administration of neostigmine is recommended only as part of a multimodal spinal analgesia (Grant et al. 2002).

Analgesia appeared significantly faster ($P \leq 0.05$) in the lidocaine group (4.8 ± 2.0 minutes) compared to the neostigmine-lidocaine and neostigmine-xylazine groups (6.20 ± 3.0 minutes and 10.50 ± 2.0 minutes, respectively). The duration of analgesia produced by neostigmine-xylazine (180+ minutes) was significantly longer ($P \leq 0.05$) than that produced by lidocaine alone (85 ± 10 minutes) or the neostigmine-lidocaine combination (78 ± 15 minutes). These results are similar to previously reported findings in cows that were epidurally administered lidocaine alone and xylazine alone or in combination (Singh et al. 2006; Saifzadeh et al. 2007; Singh et al. 2009).

As in the saline group, epidural administration of neostigmine did not result in any analgesia at any of the tested sites of the body. Lidocaine alone, lidocaine-neostigmine and neostigmine-xylazine combinations produced variable degrees of analgesia at different sites of the body. The degree of analgesia was most pronounced at the base of the tail and least pronounced at the lateral side of the proximal hind limb in all groups. There was no analgesia detected at the medial and lateral sides of the distal hind limb regions in any of the groups. These results are similar to previously reported findings in buffalo calves and geldings (DeRossi et al. 2012). Epidural administration of lidocaine-neostigmine was reported to result in complete analgesia of the tail, perineum and the upper parts of the hind limbs in buffalo calves (Ghazy et al. 2015).

The administration of neostigmine epidurally resulted in a significant degree of sedation. Similarly, lidocaine-neostigmine and neostigmine-xylazine produced a significant degree of sedation. However, the degree of sedation produced by the neostig-

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mine-xylazine combination was the deepest. These results are similar to findings in human patients who were administered lidocaine-neostigmine epidurally (Harjai et al. 2010). It was found that higher doses of intrathecal neostigmine can cause sedation in a dose-independent manner (Harjai et al. 2010). Mild-to-moderate sedation was also reported in cows after intramuscular administration of neostigmine (Ismail et al. 2017).

Unlike lidocaine alone, lidocaine-neostigmine and neostigmine-xylazine, the administration of neostigmine epidurally did not result in any signs of ataxia in any of the groups. These results are not in agreement with the findings reported in geldings who received neostigmine epidurally (Harjai et al. 2010; DeRossi et al. 2012). Similar to the results of our study, lidocaine-neostigmine was also found to produce mild-to-moderate ataxia in geldings (Harjai et al. 2010; DeRossi et al. 2012). In humans, the addition of neostigmine to lidocaine for epidural injections was found to enhance analgesia (dose-independent), sedation (dose-dependent) and motor blockade (Harjai et al. 2010; DeRossi et al. 2012). It has been suggested that large doses of intrathecal neostigmine alone can cause lower-extremity motor weakness in animals and volunteers because of an acetylcholine-mediated reduction in motor neuron outflow (Liu et al. 1999).

In conclusion, the data obtained in this study indicate that epidural injection of neostigmine alone produces no analgesic effects neither does it enhance the analgesic effects of lidocaine or xylazine. However, it elicits pronounced systemic sedative effects. Neostigmine could, therefore, be combined with lidocaine or xylazine to enhance sedation but not analgesia for epidural administration in routine standing surgical procedures in adult dairy cows.

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