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Research Article

Evaluation of the Analgesic and Clinical Effects Associated with the Subarachnoid Administration of Propofol in Sheep

[1]Mousa Daradka, [2]Souhaila Saoudi and [1]Zuhair Bani Ismail
[1]Department of Veterinary Clinical Sciences, Faculty of Veterinary Medicine, Jordan University of Science and Technology, Irbid 22110, Jordan
[2]Ministry of Environment and Water, Dubai, UAE

Abstract: The objective of this study was to evaluate the toxic, analgesic and clinical effects associated with intrathecal administration of propofol in sheep. Five, healthy adult non-pregnant Awassi sheep were used in the study. Propofol (2.85 mg/kg; n = 4) or normal saline (control, n = 1) was administered into the subarachnoid space at the lumbosacral intervertebral junction. Animals were assessed clinically for toxic signs, analgesia, sedation and ataxia. The heart rate, respiratory rate, rectal temperature, arterial blood pH, HCO_3^-, PaO_2 and $PaCO_2$ were recorded before (time = 0) and then at 5, 15, 30, 60, 90 and 120 min after injection of propofol. Tissues from the spinal cord and meninges were evaluated histologically for evidence of local toxic effects due to intrathecal injection of propofol. Following the administration of propofol, sheep showed signs of sedation and were ataxic within 15 min. The sheep developed sufficient surgical analgesia of the caudal abdominal wall, vagina, perinea, pelvic limbs and udder 15 to 30 min following injection of the drug and lasted for over 90 min. Sheep in the treatment group had significantly higher heart rates, $PaCO_2$ and HCO_3^- values and decreased blood pH. Values of PaO2 increased significantly initially and then decreased while the respiratory rate and rectal temperatures decreased but not significantly. Histological examination of the meninges and spinal cord showed no significant changes. Results of this study showed that a single injection of propofol into the subarachnoid space can result in sufficient surgical analgesia of the caudal abdominal wall, vagina, perinea, pelvic limbs and udder with moderate sedative effect and acceptable clinical and acid-base alterations in sheep.

Keywords: Intrathecal, propofol, regional analgesia, sedation, sheep

INTRODUCTION

General anesthesia in small ruminants is challenging and can result in life-threatening complications (Tranquilli *et al*., 2007). Local and regional analgesia including spinal analgesia techniques have been used extensively in small ruminants to overcome complications of general anesthesia (Tranquilli *et al*., 2007). Regional analgesia using lumbar subarachnoid injection is optimal for most surgical procedures in ruminants such as docking, mastectomy, cesarean, abscess drainage and surgeries of the vagina and perineum (Lucky *et al*., 2007). Lignocaine hydrochloride and bupivacaine hydrochloride are the most commonly used local and regional analgesics in ruminants (Tranquilli *et al*., 2007). Ketamine hydrochloride (DeRossi *et al*., 2009) and morphine (Wagner *et al*., 1996) were used to induce subarachnoid regional analgesia in sheep. However, subarachnoid injection of morphine caused detrimental side effects such as weakness, irritation or pruritus of the hind limbs in sheep undergoing stifle surgery (Wagner *et al*., 1996).

Propofol (2, 6 diisopropylphenol) is an anesthetic agent, emulsified in soybean oil that results in smooth induction, rapid smooth recovery, reasonable analgesia and good muscular relaxation (Duke *et al*., 1997; Tranquilli *et al*., 2007; Dzikiti *et al*., 2009). Intravenous injection of propofol to induce general anesthesia have been investigated in llamas with favorable results (Duke *et al*., 1997), however, its use for subarachnoid regional analgesia in sheep has not been investigated before. Therefore, the objective of this study was to evaluate the analgesic, clinical and acid-base effects associated with subarachnoid administration of propofol in sheep.

MATERIALS AND METHODS

Five, adult female Awassi sheep weighing 40-50 kg were used in this study. All experimental techniques

Corresponding Author: Mousa Daradka, Department of Clinical Veterinary Sciences, Faculty of Veterinary Medicine, Jordan University of Science and Technology, Irbid, P.O. Box 3030, Jordan, Tel.: +9627201000 ext. 22021; Fax: 00962 2 7095123

were reviewed and approved by the institutional animal use and care committee of Jordan University of Science and Technology (JUST-ACUC). All sheep were healthy and in good body condition as determined by physical and laboratory examination prior to their enrollment in the study. Sheep were housed freely in a fenced yard with sheltered area available in the veterinary health center located in campus. They were allowed ad libitum access to feed and water.

The skin over the lumbosacral space was clipped and aseptically prepared for injection. The area then was anesthetized using 2 mL lidocaine hydrochloride (2%) injected subcutaneously. The sheep were manually restrained in sternal recumbency on a table for injection. Propofol (1%) (Fresenius Kabi, Germany) at a dose of 2.85 mg/kg was injected into the subarachnoid space (n = 4) using an 18 g, 3½ inch spinal needle. To reduce chances of harmfully increasing the intracranial pressure, 5-10 mL of cerebrospinal fluid was removed before injecting the drug. Similar volume of normal saline (0.9% NaCl) was injected into the subarachnoid space in one sheep and served as control. Propofol and normal saline were administered at a rate of approximately 1 mL per 6 sec.

Analgesia, sedation and ataxia were assessed as described previously (Kinjavdekar *et al*., 2000; Dzikiti *et al*., 2009). Parameters were assessed on the floor before restraining the sheep (time 0) and at 5, 15, 30, 60, 90, 120 min after administration of propofol. Following the completion of drug administration, each sheep was placed on a non slippery floor for evaluation of the general behavior, analgesia, sedation and ataxia. Analgesia was assessed using pin prick and given a score of 0-3 where 0 = no analgesia (strong reaction to pin prick) and 3 = strong or complete analgesia (no response to pin prick). Sedation was assessed by clinical observation of the animal (head position and eyelids) and given a score of 0-3 where 0 = standing/no sedation and 3 = lateral recumbency/severe sedation. Ataxia was assessed by evaluating the animal while moving and given a score of 0-3 where 0 = walking without staggering and 3 = lateral recumbency.

Sheep were kept under close observation for 1 week following the completion of the study to detect any possible long-lasting clinical or behavioral toxic effects such as restlessness, agitation, seizures, or permanent hind limb paralysis.

The heart rate, respiratory rate and rectal temperature were recorded at time 0 and at 5, 15, 30, 60, 90, 120 min after administration of propofol.

Arterial blood pH, HCO_3^-, PaO2 and PaCO2 were recorded at time 0 and at 5, 15, 30, 60, 90, 120 min after administration of propofol. Arterial blood samples (1 mL) were collected into previously heparinized syringes. The syringes were capped and placed in an iced-water bath and the samples were analyzed within 20 min of collection for determination of pH, HCO_3^-, PaO2 and PaCO2 using Easy Blood Gas Analyzer (Medica, USA).

One week after the completion of the study, all sheep were humanely euthanatized and were subjected to complete postmortem examination. The spinal cord and meninges were carefully removed and grossly evaluated. Approximately, 2-3 cm spinal tissue samples were taken from the lumbosacral spinal segment as well as different locations from the cord. Samples were placed in 10% buffered formalin solutions and submitted for routine histological evaluation. Paraffin embedded sections were cut at 5 µm thickness and stained using H and E stain.

The heart rate, respiratory rate, rectal temperature, values for pH, HCO_3^-, PaO_2 and $PaCO_2$ and the scores of analgesia, sedation and ataxia are expressed as means±SD. All variables were analyzed statistically using student t-test and ANOVA test. Statistical analysis was performed using SPSS version 10.0 computer program (SPSS, Chicago, IL). Differences were considered statistically significant at p-value <0.05.

RESULTS AND DISCUSSION

In this study, subarachnoid administration of 2.85 mg/kg propofol resulted in bilateral abdominal wall analgesia and analgesia of the vagina, perinea, pelvic limbs and udder. The maximum analgesia score (2.90±0.25) was reported at 15 and 30 min after propofol administration and then gradually decreased towards the end of the observation period (120 min) (Table 1). The maximum sedation score (1.70±0.60) was reported at 30 min after propofol administration and gradually decreased towards the end of the observation period (Table 1). The maximum ataxic score (2.60±0.70) was reported at 15 min after propofol administration and gradually decreased towards the end of the observation period (Table 1). Sufficient surgical analgesia was induced 15 min following subarachnoid administration of propofol and lasted for about 90 min. Analgesia was pronounced at the perineal area, vagina, pelvic limbs, udder and bilateral abdominal wall in all treated sheep. These results are similar to those obtained by the subarachnoid administration of ketamine in sheep (DeRossi *et al*., 2009) and goats (DeRossi *et al*., 2005). The extent to which analgesia is obtained following subarachnoid administration of a particular drug is thought to be affected by the capacity of the subarachnoid space in the individual animal, neural uptake of the drug, vascular and lymphatic absorption, elimination of the drug and the physical characteristics of the animal e.g., body weight, length of the back of the animal, size of spinal canal and amount of epidural fat (Skarda and Muir, 1996).

The analgesic effects reported in this study of the lateral abdominal wall, perinea, vagina, pelvic limbs

Table 1: Analgesia, sedation and ataxia scores (0-3) in sheep administered propofol in the subarachnoid space, means±SD, N = 5

	Time (minutes)						
Parameters	0	5	15	30	60	90	120
Analgesia	0.0±0.0	2.40±0.80*	2.90±0.25*	2.90±0.25*	2.40±0.60*	1.40±0.60*	0.10±0.25
Sedation	0.0±0.0	1.40±0.50	1.60±0.50*	1.70±0.60*	0.90±0.44*	0.40±0.50	0.00±0.00
Ataxia	0.0±0.0	2.10±0.80*	2.60±0.70*	2.40±0.80*	1.80±0.75*	0.90±0.70*	0.25±0.40

*: $p<0.05$

Table 2: Heart rate, respiratory rate, rectal temperature and blood gas parameters in sheep administered propofol in the subarachnoid space, means±SD, N = 5

	Time (minutes)						
Parameters	0	5	15	30	60	90	120
Heart rate	104±14	128±20*	140±24*	140±32*	128±24*	112±16	100±12
Respiratory rate	24±6	20±6	20±5	18±3	20±3	20±8	22±4
Temprature (ºC)	39.50±0.5	39.70±0.5	38.80±0.4	38.70±0.5	38.90±0.4	39.30±0.4	39.30±0.29
Blood pH	7.46±0.05	7.43±0.03	7.44±0.06	7.46±0.05	7.43±0.03	7.41±0.03*	7.40±0.04*
$PaCO_2$ (mmHg)	36.0±3.0	35.0±3.0	35.0±4.0	34.0±6.0	36.0±3.0	37.0±3.0	39.0±3.0*
HCO_3^- (mmHg)	25.0±3.0	25.0±3.0	24.0±3.00	24.0±4.0	27.0±3.0*	28.00±3.0*	30.0±4.0*
PaO_2 (mmHg)	92.0±6.0	101.00±9.0	97.00±15.0	103.00±24.0*	92.00±7.0	92.0±6.0	89.00±7.0*

*: $p<0.05$

and udder following subarachnoid administration of propofol are consistent with the results of previous studies using epidural injection of lignocaine and xylazine in sheep and subarachnoid administration of ketamine in sheep and goats (Kyles *et al*., 1993; Eze *et al*., 2004; DeRossi *et al*., 2005, 2009). This analgesic effect is mediated by the blockade of the motor fibers which resulted in flaccidity of fat-tail and desensetization of pelvic limbs. It is well known that blockade of the parasympathetic fibers of the pelvic nerves results in the relaxation of external genitalia and dilatation of the anal sphincter (Skarda and Muir, 1996). In this study, marked pelvic limb ataxia was noticed in sheep after subarachnoid administration of propofol. The sheep had proprioception deficit in pelvic limbs and developed a dog sitting posture soon after treatment. This could be considered as a possible side effect and might indicate a local analgesic action of propofol on hind limb motor neurons (Skarda and Muir, 1996).

The heart rate, respiratory rate, rectal temperature and blood gas analysis in sheep following the subarachnoid administration of propofol are presented in Table 2. Sheep in the treatment group had significantly higher heart rates, PaCO2 and HCO3- values and a significantly decreased blood pH. Values of PaO2 increased significantly initially and then decreased. The maximum heart rate and PaO2 values were recorded at 30 min and the lowest values were recorded at 120 min after propofol administration. The heart rate remained high for the entire 120 min testing period. Maximum values for HCO3- and PaCO2 were recorded at 120 min after propofol administration and the lowest values were recorded at 30 min. The respiratory rate and rectal temperature decreased but not significantly following the administration of propofol into the subarachnoid space. Changes in blood gas analysis, tachycardia and signs of sedation observed following subarachnoid injection of propofol in sheep may have resulted from systemic absorption of the drug (Lucky *et al*., 2007) or due to direct effect of the drug on the central nervous system. It is well established that the complex venous system forms large venous plexus around the spinal cord providing large vascular surface for rapid absorption of administered drugs (Dyce *et al*., 2009). The increase in heart rate observed in treated sheep in this study is in agreement with the study of epidural lignocaine in goats (Eze *et al*., 2004). Similar increases in heart rates were also reported in sheep receiving intravenous injection of propofol (Fujimoto and Lenehan, 1985; Lin *et al*., 1997; Runciman *et al*., 1990; Bani Ismail *et al*., 2012).

Necropsy of the sheep revealed no gross abnormalities in any body system. Gross examination of the spinal cord and meninges at the lumbosacral segment revealed no abnormalities beside mild focal congestion of the meninges. In addition, histological examination of the meninges and spinal cord showed no significant changes. Sheep in this study tolerated very well the injection of relatively large volume of propofol into the subarachnoid space. There were no apparent immediate clinical or neurologic toxic-related signs such as seizure activities nor were there late appearing signs such as irreversible hind limb paralysis 24 h and 1 week later following propofol administration. Although, the administered volume in this study is large, it appears that unlike butorphanol, propofol exerts negligible neurotoxic effects on the meninges and spinal cord and could be considered as safe alternative to butorphanol for intrathecal analgesia in sheep (Rawal *et al*., 1991). It is has been determined that the volume of CSF in the lumbar region is small and that any changes in its volume or pressure could result in injury (Rawal *et al*., 1991). To prevent spinal cord injury in this study because of increased intrathecal pressure, 5-10 mL of CSF were removed before the injection of propofol.

Although, the number of animals involved in the study is a limiting factor, it can be with a certain degree of confidence concluded that a single injection of propofol into the subarachnoid space is a safe alternative and can result in sufficient surgical analgesia of the caudal abdominal wall, vagina, perinea, pelvic limbs and udder with acceptable clinical and acid-base alterations in sheep.

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