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A LONG-TERM INJECTABLE ANAESTHESIA WITH A COMBINATION OF MIDAZOLAM, KETAMINE, XYLAZINE AND PROPOFOL IN PIGS

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SUMMARY

A midazolam, ketamine, xylazine and propofol combination was evaluated as a long-term anaesthetic regimen in 18 pigs. The pigs were premedicated with intramuscular injection of atropine sulphate (0.05 mg/kg. b.wt.). Induction of anaesthesia was induced by intramuscular injection of midazolam, ketamine and xylazine at dose rates 1 mg, 4 mg and 2 mg/kg b.wt. respectively. Maintenance of anaesthesia was by intravenous injection of propofol at a dose rate 1 mg/kg b.wt. via a jugular cannula. Booster doses of propofol were given according to the duration of the concomitant surgical procedures. Body temperature, heart and respiratory rates were recorded. Assessment of analgesia, anaesthesia and recovery was by skin and tail clamp stimuli.

The combination of midazolam, ketamine, xylazine and propofol was found very effective and safe for produring long-term anaesthesia in pigs.

INTRODUCTION

The pig is physiologically more related to man than other animals. Therefore, pigs play an important role in human medical and surgical researches as an experimental model (Swindell et al., 1988; Thurmon and Benson, 1993; Lumb and Jones, 1996). Regarding major surgical interferences as in experimental research and training purposes, a long-term anaesthetic regimen was prerequisite. Many analgesic and anaesthetic protocols have been used in pigs with variable effects. Some of these anaesthetic protocols involved xylazine and ketamine (Trim and Gilroy 1985; Boschert et al., 1996), xylazine, ketamine and oxymorphone (Breese and Dodman, 1984), xylazine, and fentanyl (Vigo et al., 1993), telazole, ketamine and xylazine (Ko et al., 1993) or butrophanol, ketamine and atipamezole (Sakaguchi et al., 1996).

In comparison with other benzodiazepines midazolam possesses good anxiolytic and hypnotic properties. It has a relatively rapid onset, short duration of action, rapid recovery and can be injected by intramuscular or intravenous route (Tranquilli et al., 1991; Lumb and Jones, 1996). Midazolam is frequently given in combination with ketamine to prevent muscle rigidity, reduce undesirable effects and provide profound sedation (Nishimura et al., 1994).

Propofol (2,6 diisopropyphenol), is an intravenous short-acting, non-barbiturate anaesthetic agent that is rapidly metabolised and converted to inactive metabolites resulting in smooth rapid recovery (Morgan and Legge, 1989; Branson and Gross, 1994). It has been successfully used in dogs (Watkins et al., 1987; Ilkiw et al., 1992; Zoran et al., 1993).

Propofol, the intravenous anaesthetic agent has been evaluated in human-being and animals (Branson and Gross, 1994). However, no available literature concerning its use in pigs. Therefore the aim of the present study was to produce a long-term injectable anaesthesia with propofol after premedication with midazolam, ketamine and xylazine in pigs to serve experimental or training surgery of long durations.

MATERIAL AND METHODS

Eighteen healthy pigs of both sexes, aged 1-3 years and weighing 25-35 kg were randomly assigned into two groups. Group I (6 pigs) and group II (12 pigs) were fasted for 12 hours prior to the study. Before administration of the anaesthetic regimen, baseline values were recorded for heart rate, respiratory rate and rectal temperature. The same values were recorded at 5, 15, 30, 60, 120, 150 and 180 minutes after administration.

Both groups of pigs were premedicated with atropine sulphate (0.05 mg/kg b.wt.) i.m. Induction of anaesthesia was performed by inramuscular injection of midazolam (1 mg/kg b.wt.), and mixture of ketamine (4 mg/kg b.wt.) and xylazine (2 mg/kg b.wt.). Jugular cannulation was carried out after surgical exteriorization of the vein with 18 gauge intravenous cannula which was transfixed in the skin. Maintenance of anaesthesia was achieved by intravenous bolus injection of propofol (1 mg/kg b.wt.). Pigs were orally intubated using cuffed endotracheal tubes. Four pigs were intubated through tracheostomy.

Group I (12 trials) was given the anaesthetic cocktail on two occasions with one week interval between injections. Surgical anaesthesia was assessed after recumbency. Skin and tail clamp stimuli were used to produce moderate and high degree of nociception respectively (Tracy et al., 1988). Actual times for recumbency, beginning of skin clamp anaesthesia, beginning tail clamp anaesthesia, duration of anaesthesia, duration of maintenance, end of skin calmp anaesthesia, end of tail clamp anaesthesia, beginning of swallowing reflex, uprising, sternal recumbency, standing and walking were recorded. The assessment of the anaesthetic recovery was done according to Tracy et al., (1988).

Group II (12 trials) were subjected to long-term

surgical procedures i.e. experimental training laparoscopy which included partial hepatectomy, cholicystectomy, nephrectomy and herniorrhaphy under the effect of the same anaesthetic regimen. All data were statistically analyzed according to the method of Snedecor and Cochran, (1973).

RESULTS

Induction of anaesthesia with intramuscular injection of midazolam, ketamine and xylazine in both groups of swine was smooth. Pigs became recumbent within 3.3±1.1 min. of anaesthetic combination injection. Endotracheal intubation was easily performed in eighteen pigs while four cases required intubation through tracheostomy. The mean changes in heart rate, respiratory rate and rectal temperature before and after anaesthesia were illustrated in Table 1. The mean heart rate value in group I was significantly decreased (89.7±3.8) fifteen minutes post-induction. Such decrease was gradual till 120 min. There was significant increase in the mean heart rate value at 150 min. till 180 min. In group II, the mean heart rate value was significantly decreased (98.7±5.4) at five minutes post-induction till reached (63.1±6.1) sixty minutes of anaesthesia. There was significant increase in the mean heart rate value at 120 min. till 180 min.

The mean respiratory rate value in group I was significantly decreased (24.8±1.9) at 60 and 90 minutes and gradually increased thenafter. In group II, the mean respiratory rate value reached the highest significant decrease (19.1±1.6) at 60 min. then it gradually increased. There was a highly significant decrease (63.1± 6.1 & 19.1± 6.1) in heart and respiratory rates after injection of the maintenance anaesthetic dose in group II.

In group I, the rectal temperature was signifiantly decreased (37.6± 0.33) at 5 minutes post-induction till 180 minutes of the anaesthesia. In group II, it was significantly decreased (37.4±0.13) fifte en minutes post - induction till 180 minutes of anaesthesia.

The mean recumbency onset time after intramuscular injection of the anaesthetic combination was 3.3 ± 1.1 minutes. The mean time elapsed from the beginning of skin clamp anaesthesia and tail clamp anaesthesia were 9.9 ± 2.8 min. and 11.1 ± 1.2 minutes respectively. The mean duration of skin clamp anaesthesia was 60.8 ± 12.8 min. while that of tail clamp anaesthesia was 38.3 ± 8.3 min. (Tab. 2). Induction of anaesthesia was satisfactory in all pigs of group 1. Satisfactory degrees of skin clamp anaesthesia and tail clamp anaesthesia were observed in all pigs except two pigs that reacted to the tail clamp anaesthesia (Tab. 3). Eleven animals showed smooth recovery while only one pig showed loud howling during recovery.

Maintenance of anaesthesia was achieved by intravenous bolus injection of propofol (1 mg/kg b.wt.). The average injection of boluses to maintain long-term anaesthesia were 7 intermittent boluses. Table 4 showed the relation between propofol injection and beginning of skin and tail clamp anaesthesia and end of skin and tail clamp anaesthesia.

Table 1: Mean values of heart rate, respiratory rate and rectal temperature before and

Time	(Group I)			(Group II)		
	Heart	Resp. rate/min.	Temp. °C	Heart rate/min.	Resp. rate/min.	Temp. °C
0 min.	111.7±6.0	30.0±1.4	38.2±0.24	112±6.2	30.2±3.6	38.6±0.15
5 min.	100.6±5.9	29.4±2.2	37.6±0.33**	98.7±5.4*	28.5±1.4	38.3±0.18
15 min.	89.7+3.8**	26.4±2.8	36.9±0.37**	82.6±3.3**	29.7±1.9	37.4±0.13**
30 min.	77.0±3.1**	26.3±2.0	36.6±0.26**	75.4±4.8**	26.5±1.6	35.9±0.65**
60 min.	74.0±5.7**	24.8±1.9**	36.8±0.47**	63.1±6.1**	19.1±1.6**	36.2±0.24**
90 min.	78.1±5.0**	24.8±1.9**	36.9±0.51**	67.5±4.8**	21.8±2.3*	36.1±0.28**
120 min.	84.8±7.1**	27.2±2.4*	37.0±0.65**	71.5±6.5**	21.6±2.2*	36.0±0.17**
150 min.	88.4±8.0**	28.0±2.9*	37.6±0.42**	79.7±6.2**	21.1±1.8*	35.7±0.12**
180 min.	102.0±7.5**		37.6±0.43**	85.7±6.9**		36.9±0.28**

± = SE * P < 0.05 ** P < 0.01

Table 2: Mean times for intramuscular administration of the anaesthetic combination in pigs

Monitored parameters	Mean times ± S.D.
ACI to R	3.3 ± 1.1
ACI to BSCA	9.9 ± 2.8
ACI to BTCA	11.1 ± 1.2
BSCA to ESCA	60.8 ± 12.8
BTCA to ETCA	38.3 ± 8.3

ACI = anaesthetic combination injection, R = recumbency, BSCA = beginning skin clamp anaesthesia,
BTCA = beginning tail clamp anaesthesia, ESCA = end skin clamp anaesthesia,
ETCA = end tail clamp anaesthesia.

Table 3: Evaluation of the anaesthetic effect

Items	Satisfactory	Unsatisfactory
Induction	12	0
SCA	12	0
TCA	10	2
Recovery	11	1

SCA = skin clamp anaesthesia, TCA = tail clamp anaesthesia

Table 4: Mean times for intravenous propofol injections in pigs

Items	1st. Inj.	2nd. Inj.	3rd. Inj.	4th. Inj.	5th. Inj.	6th. Inj.	7th. Inj.
PI to BSCA	3.2±1.03	2.6±0.67	1.6±0.63	1.7±0.77	1.7±0.86	1.7±0.88	1.7±0.77
PI to BTCA	3.9±0.78	2.8±0.71	2.9±0.79	2.5±0.68	2.6±1.1	2.1±0.9	2.9±1.7
PI to ESCA	12.4±2.9	11.1±2.5	11.1±1.5	10.6±1.9	10.7±1.4	11.8±1.2	14±0.95
PI to ETCA	12.9±2.5	11.8±1.2	12.2±1.9	13.1±2.3	13.2±2.56	12.3±2.7	15.2±2.4

± S.D., PI = propofol injection, BSCA = beginning skin clamp anaesthesia, BTCA = beginning tail clamp anaesthesia, ESCA = end skin clamp anaesthesia, ETCA = end tail clamp anaesthesiasthesia

Table 5: Mean times for propofol administration and recovery in pigs

Monitored parameters:	Mean ± S.D
PI to Swallowing Reflex	11.3±1.4
PI to BR	65.3±4.4
PI to SR	73±0.4
PI to W	110±12.5

± S.D., PI = propofol injection, Swallowing R = swallowing reflex, BR = beginning righting, SR = sternal recumbency, W= walking. ESCA - end skin clamp anaesthesia

Table 6: Mean times of onset, duration and maintenance of anaesthesia

Items	Mean ± SE
Onset of anaesthesia	3.8±0.34
Duration of anaesthesia	50.2±4.37
Maintenance dose	2.7±0.27
Duration of Maintenance	23.4±1.95

Fig. 1: An anaesthetized pig with jugular cannula in situ (a). Laparoscopy in an anaesthetized pig (b).

Recovery in relation to the last bolus of propofol injection and end of skin clamp anaesthesia was illustrated in Table 5. The mean times for beginning of swallowing reflex, uprising, sternal recumbency and walking were 11.3±1.4, 65.3±4.4, 73.0±10.4 and 110±12.5 minutes from the last propofol injection respectively. Recovery was considered satisfactory when the pig did not fight the anaesthetic effect, no (or light) vocalization, when no delirium (or seizure-like activity) and ataxia was minimum and not to the extent of possible injury. Unsatisfactory recovery was recorded when the animal fought the anaesthetic effect, moderate to loud vocalization and the animal became delirious and ataxic to the extent of possible injury.

The pigs in group II were involved in practical surgical application of the used anaesthetic cocktail. The pigs of this group were used in experimental training protocol of laparoscopic surgery included partial hepatectomy, cholicystectomy, nephrectomy and herniorrhaphy (Fig. 1).

The mean time for recumbency of pigs in this group was 3.8±0.34 minutes while, the duration of anaesthesia was 50.2±4.37 minutes. Propofol as intravenously injected as intermittent boluses (average boluses = 7). Each maintenance dose of propofol prolonged the duration of deep anaesthesia from 18 to 30 min. with mean value of 23.4±1.95 min. (Tab. 6). Laparoscopic procedures were easily performed and without difficulties. Recovery of the animals was smooth, quiet and excitement free.

DISCUSSION

In the present work induction of anaesthesia with intramuscular injection of midazolam, ketamine and xylazine was satisfactory as it was smooth, quiet and excitement free. Intramuscular administration of such anaesthetic combination caused recumbency in all pigs in about 4 minutes and satisfactory anaesthesia i.e. no signs of pain to the nociceptive stimuli by skin and tail clamps for ten minutes. The same route of administration was utilized by Thurmon et al., (1988); Lumb and Jones, (1996) to immobilize such difficult subjects. This enabled the jugular cannulation for incremental doses for maintenance of anaesthesia.

Premedication with atropine sulphate (0.05 mg/kg b.wt.) was necessary as it decreased excessive salivation induced by ketamine and bradycardia caused by xylazine. This result is consistent with Tracy et al., (1988); Boschert, et al. (1996) and Lumb and Jones, (1996).

Endotracheal intubation in the pig was not an easy job and the presence of fat in the pharyngeal region makes respiratory obstruction possible in both sedated and anaesthetized animals (Hall and Clarke, 1983). However, it was succeeded in the majority of pigs and tracheostomy was performed in only four pigs. This difficulty might be due to laryngeal spasms. In Such condition tracheostomy may be less time consuming and more efficient as mentioned by Lumb and Jones, (1996). It was found that in the pigs, the ear vein is not suitable for large quantities of fluids and percutaneous puncture of jugular vein was very difficult due to presence of subcutaneous fat. Hence a cannula was surgically implanted through the jugular vein. Adding of xylazine to the anaesthetic regimen in this study (2 mg/kg b.wt.) not only provided a measurable sedative-analgesic effect, but also rendered easy administration and maintenance of anaesthesia. However, large dose caused severe hypotension and marked bradycardia (Gomez-de-Segura et al., 1977). Although pigs are resistant to xylazine or ketamine alone, a combination of xylazine and ketamine has become popular and effective anaesthetic drug combination in swine (Trim and Gilroy, 1985; Prati, 1993 and Boschert et al., 1996).

With regard to the significant decrease in heart rate in both groups, it was attributed to the parasympathomimetic action of xylazine which was moderated by the sympathomimetic action of ketamine (Trim and Gilory, 1985; Lumb and Jones, 1996).

Also the respiratory rate was significantly decreased specially after injection of propofol. This decrease was similarly noticed by Robertson et al., (1992), Marques et al.,(1995) and Softeland et al., (1995) with the use of midazolam and propofol.

Rectal temperature was significantly decreased during anaesthesia in both groups. Nevertheless hyperthermic reaction to ketamine had been reported by Benson and Thurmon, (1979).

In the present work propofol was given in repeated intermittent doses for maintenance of anaesthesia. As reported by (Morgan and Legge, 1989; Robertson et al., 1992 and Branson, and Gross, 1994), propofol is a short acting, non-barbiturate,

intravenous anaesthetic agent. In comparison with other anaesthetics, propofol is rapidly metabolized and lacks its cumulative properties (Branson, and Gross, 1994).

In conclusion, it was found that an anaesthetic regimen composed of midazolam, ketamine and xylazine and propofol was effective, safe and convenient long-term injectable anaesthesia in swine.

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