

THE EFFECT OF PANCURONIUM BROMIDE AS A MUSCLE RELAXANT ALONE OR COMBINATION WITH DIAZEPAM IN SHEEP

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ABSTRACT

The effect of pancuronium bromide (0.025 mg/kg. B.W.) alone or combined with diazepam (1mg/Kg. I.V) were evaluated in six adult ewes. Pancuronium bromide alone exhibited a muscle relaxants effect, but without analgesia.

All baseline measurements were taken before the administration the anesthetic agent and were repeated at 5,10,15,20 and 25 min. intervals after induction an aesthesia alone or combination with diazepam . it was found that heart rate decreased at 5 min.,but respiratory rate did change at 5-25 min. and it was significantly at 15,20 and 25 min.

Pancuronium bromide – diazepam combination is responsible for declined respiratory rate and decumbency position in early stage.

Pancuronium bromide – diazepam induce effective and safe an aesthesia for periods 45 minutes, due to competitive diazepam as a sedative effect of muscle relaxation. Adequate strength and duration of analgesia due to prevent impulse transmission histamine and ensured rapid and safe recovery.

INTRODUCTION

Pancuronium bromide, an amino steroid free from any hormonal action, abis – quaternary ammonium steroids, is a non – depolarizing neuromuscular blocking agent that competes with acetylcholine for cholinceptive sites at the post junctional membrane and thereby blocks competitively the transmitter action of acetylcholine resulting in muscle paralysis (1).

Clinical studies have been shown that pancuronium is approximately five times as potent as d – tubocurarine as a competitive neuromuscular blocker. Pancuronium causes moderate increase in heart rate with an attendant increase in cardiac output and blood pressure there does not cause measurable effect on systemic vascular resistance.

Pancuronium bromide causes little or no histamine release and no ganglionic blockade, and therefore anesthetic does not cause hypotension or Bronchospasm. Despite its steroid structure, the drug exhibits no hormonal activity. Cholinesterase inhibitors such as pyridostigmine and neostigmine reverse the action of pancuronium (2).

Plasma concentrations of pancuronium bromide appear to decline in a triphasic manner. In patients with normal renal and hepatic function the half – life in the terminal phase is about 2 hours. Since a large fraction of pancuronium bromide is excreted in the urine the duration of neuromuscular blockade is prolonged in patients with renal failure and the dose should be reduced. In patients with impaired hepatic function, prolonged elimination half – lives result in a higher initial dose to be given and longer duration of action respectively (3).

Since the introduction of pancuronium, many new neuromuscular blocking (NMB) agents have been brought into anesthesia practice. The large molecular size and the quaternary ammonium structure of these compounds are unique among anesthesia – related drugs. For practical purpose, understanding their structure – activity relationship (SAR) is a rational way to understand their actions and metabolism (4).

Neuromuscular blocking agents interact with many different drugs inducing general anesthesia and other NMB themselves. At a molecular level of the acetylcholine receptor, other drugs interact with NMB by direct competition at the binding sites for acetylcholine (Ach), allosteric modulation of the receptor, or direct interference with ion flux through the central ion channel of the receptor. In addition, some drugs interact with NMB at a pharmacokinetic level by interfering with their distribution and elimination (4,5).

Ach is a flexible molecule capable of adopting several conformations without significant energy penalty. This allows it to be physiologically multifunctional. Its symmetrical conformers can flip easily. The structure of Ach, $\text{CH}_3\text{-CO-O-(CH}_2\text{)}_2\text{-N}^+(\text{CH}_3)_3$, although simple, has several important functional features, namely the methonium head centered on the positively charged quaternary N atom, the alcohol O atom that forms the ester (-O-), and the acetyl group with the carbonyl O atom (-CO-) (5).

The skeletal muscle endplate Ach receptor (Ach R) is generally modeled after the electric nicotinic AChR as a pentameric structure of α_2 , β or γ subunits in a rosette around a sodium – potassium ionic channel. Each receptor has two Ach receptive sites, one on each α subunit in a pocket near where the α subunit interfaces with its neighbor β or γ subunit (6).

Various cholinergic receptors and cholinesterase have different conformational requirements or preferences of their agonists (or substrates in the case of cholinesterase) and antagonists of the cholinergic compounds.

Amino steroids as pancuronium bromide are among the amino steroid NMB agents. The steroid nucleus provides a rigid bulky of the two Ach moieties of pancuronium, with both functional groups pointing up. The amino steroids several structure activity relationship (SAR) and conformation activity relationship (CAR), and the structure of the pancuronium bromide as the following (4)

The aim of this study was to evaluate the effects of Pancuronium Bromide as a Muscle Relaxant Alone or Combination with Diazepam on heart, respiratory rate and induction of anesthesia stage of ewes.

Intravenous anesthetics have a lower muscle – relaxing effect than volatile anesthetics. The reversal of neuromuscular blockade, as currently done with inhibition of the enzyme acetylcholine esterase as neostigmine has important limitations (6,7,8):

- The mechanism of reversal is indirect such as administration of the acetylcholine esterase inhibitor; enzymatic degradation of acetylcholine in the synaptic cleft is reduced thereby increasing the numbers of Ach molecules compacting for the binding sites with the NMB.
- The efficacy is limited and residual block occurs because reversal is dependent on the increase of Ach concentration and the decrease of the concentration of the NMB according to its inherent rate of elimination.
- Reversal is inadequate or impossible against profound block because of the competitive nature of the interaction between Ach and NMB.
- True rescue reversal in a (cannot ventilate – cannot intubate) situation does not exist.
- The effect of Ach esterase inhibitors is not selective, but also potentiates neurotransmission at muscarinic Ach receptors leading to bradycardia, hypotension, bronchoconstriction, nausea and diarrhea. Therefore, in clinical practice, Ach esterase inhibitors are combined with atropine or glycopyrrolate to antagonize the muscarinic effect of the Ach (3,4).

Depolarizing agent, which act peripherally at the neuromuscular junctions? Anticholinesterases such as pyridostigmine and edrophonium are antagonistic to the non – depolarizing agent. The agents are used as adjuncts to general anesthetics where profound muscle relaxation is desired. Because these agents produce motor paralysis only and don't produce either sedation or analgesia, their use for euthanasia is unacceptable as it results in an unnecessarily stressful death due to asphyxia (9).

The use of muscle relaxant drugs in conjunction with a general anesthetic agent to induce complete skeletal muscle relaxation gives rise to difficulty in evaluating the depth of anesthesia. The use of NMB agents is not acceptable because more effective and human drugs are available for this purpose (10).

MATERIALS AND METHODS

Six adult ewes Awassi breed, ranging in weight between 40-50 kg, and 3-4 years old, experimental animals were divided into two main groups. In group one treated included three ewes each ewe was given (0.025-mg/kg B.W) intravenously of pancuronium¹ bromide, and group two gives (0.025 mg/kg B.W.) of pancuronium bromide with (1 mg/kg W.B.) of Diazepam² intravenously. In alone and combination group, as the anesthesia started the animals were laid on lateral recumbency and observed until recovery and spontaneous standing.

Data were analyzed by using student's *t* - test. And one way analysis of variance, to a certain the statistical difference at $P < 0.05$.(11).

RESULTS

Intravenous administration of pancuronium bromide, recumbency within 45-90 second. The animal showed muscle relaxant. The onset and duration of anesthesia in treated sheep are shown in (table 1).

Table 1: Intravenous injection pancuronium alone or combination

Parameter (min)	Group 1	Group 2
**Sleeping time	20 ± 1*	45 ± 2*
***Time to sternal recumbency	13.6 ± 21*	33 ± 31
****Time If standing position	15 ± 1*	35 ± 3.1*
* significantly $P < 0.05 \pm sD$		
** sleeping time from recumbency until movement to head		
*** sternal recumbency from recumbency until sternal position		
**** Standing position from recumbency until standing		

In both treatment, as the anesthesia started the animals were laid to recumbency and standing during the stages of the experiment should be the following recorders above, along from 45 second to 45 minutes. But the physiological reactions are following shown in (table 2).

1. Cardiovascular: Increased pulse rate and cardiac output was frequently recorded.
2. Gastrointestinal: Salivation is sometimes noted during anesthesia.
3. Injection site reaction: pain or local skin response.
4. Respiratory: Bronchospasm has been reported.

Table (2) physiological reactions

Time (min)	Heart rate		Respiratory rate	
	Pan.	Pan+diazepam	Pan.	Pan+diazepam
0	74.6±5	80.5 ± 11	49.2 ± 11	34 ± 11
5	96±21	79 ± 92	60.6 ± 21	43 ± 21
10	74.1±10	80 ± 21	55 ± 12	40 ± 11
15	76.5±21	81 ± 12	57 ± 10	31 ± 21*
20	75.6±90	82 ± 30	58 ± 30	32 ± 41*
25	77.3 ± 29	78 ± 12	57 ± 51	32 ± 61*

¹ Lisapharam-S.P.A. Italy 2mg/ml.

² (Valium 10, Roch & Co.Ltd., Basle; Switerland) ,

DISCUSSION

In ewes, limited data are available on pancuronium bromide as a muscle relaxant effect. However, the pancuronium is potent muscle relaxant effect by the agents, which act peripherally at the neuromuscular junctions. This agent produces motor paralysis only. There is no sedation or analgesia, their use on conscious, abolishes some of the signs used to judge the depth of anesthesia where, profound muscle relaxation is desired (10).

The use of muscle relaxant drugs in conjunction with a general anesthetic agent to induce complete skeletal muscle relaxation gives to difficulty in evaluating the depth of anesthesia, for reason, artificial respiration may be needed, and appropriately experienced personnel and proper equipment should be available (12).

Monitoring the depth of anesthesia in a sheep that has been paralyzed a neuromuscular blocking agent is both critically important and challenging (13).

Results indicated that pancuronium bromide is induce sleeping to standing position less than combination with diazepam due to the diazepam increase the intensity and prolong the duration of action pancuronium bromide, and significantly different from the treated groups, $P < 0.05$, but the pancuronium – diazepam group is significantly decrease the respiratory rate .

Pancuronium bromide causes moderate increases in heart rate with an attendant increase in cardiac out put and blood pressure, there does not appear to be any measurable effect on systemic vascular resistance (13,14).

Pancuronium bromide cause, little or no histamine release and no release and no ganglionic blocked, and therefore does not cause hypotension or Bronchospasm. Intravenous administrations of 0.025 mg/kg of pancuronium normally produce muscular relaxation with 45-90 seconds, a peak effect about 4 – ½ minutes and average duration of effect of 45 minutes. However, it should be remembered that there is wide variation in individual sheep responses to muscle relaxants (13).

The symptoms of overdoses are those of prolonged apnea, reparatory and / or persistent muscle weakness, and death may follow respiratory failure. The animal should be remaining under mechanical ventilation. And in conclusion, pancuronium is given by intravenous administration, it is not recommended to be given be intravenous infusion due to induce acute respiratory failure (15).

A competitive diazepam as a sedative effect and muscle relaxation as well as does intern uncial neurons. However, the pancuronium is act motor paralysis, the result should be to competitive drugs are adequate strength and duration of analgesia and ensured rapid and safe recovery. More than

Use pancuronium bromide alone.

At the same time the neuromuscular action of pancuronium may be reversed by the administration of atropine sulphate (15,16).

In animals with normal renal and hepatic function the half life in the terminal phase is about 2 hours. Since a large fraction of pancuronium is excreted in the urine, the duration of neuromuscular blocked is prolonged in animal with renal failure and the dose should be reduced. As well as the animals with impaired hepatic function, prolonged distribution and elimination half-life result in a higher dose to be given and longer of action respectively. The pancuronium bromide is metabolized by the liver, but the kidney is the major route for elimination (17,18).

In this study demonstrates that pancuronium bromide can be combination with diazepam to increase the intensity and prolong the duration of pancuronium and safe anesthesia with good muscle relaxants.

Molecular structure of most NMB agents relates to their metabolic pathways, although, exception exist. Even without enzymatic catalysis, short acting NMB agent especially the ultra-short ones, may be break down spontaneously (19).

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تأثير بروميد البانكورونيوم كمرخي للعضلات لوحدة أو بعد مزجه مع الديازيبام في الأغنام

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الخلاصة

قيمت في ستة نعايج نتائج استخدام بروميد البانكورونيوم لوحدة (بجرعة 0.025 ملغم/كغم من وزن الجسم بالحقن في الوريد) أو بالمزج مع الديازيبام (بجرعة 1 ملغم/كغم من وزن الجسم بالحقن في الوريد). سجلت كافة المعايير بفترة قيل البدء بالعمل ثم 5,10,15,20 و 25 دقيقة بعد إعطاء المخدر لوحده أو كخليط . حيث لوحظ إن انخفاض معدل ضربات القلب في فترة خمسة دقائق ، لكن معدل مرات التنفس انخفض بفترة من خمسة إلى خمسة وعشرون دقيقة . وقد سجل فرق معنوي بفترة 15 - 25 دقيقة . وتبين من النتائج بأن بروميد البانكورونيوم أعطى تأثيراً مرخياً للعضلات في حين وفر مزيج الديازيبام مع بروميد البانكورونيوم أسلوب تخدير مثالي وأمين ولفترة 45 دقيقة وذلك بسبب منع انتقال النبضات عبر العقد الذاتية مع قلة إفراز الهستامين . بالإضافة إلى إن الإفاقة كانت أمينة وسريعة لذا فأن استخدام المخدر في حالة المزيج هو المسؤول عن انخفاض عدد مرات التنفس ووضع النعاج في حالة الرقود بوقت مبكر .

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