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ANTAGONISTIC EFFECT OF NIKETHAMIDE AND CAFFIENE AGAINST XYLAZINE WITH SPECIAL REFERENCES TO ACID-BASE BALANCE IN SHEEP

(With 4 Tables)

By

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التأثير المضاد للنيكثاميد والكافين للزيلازين وخاصة على الإتزان الحمضى القاعدى فـى الأغنـــــــــام

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أجريت هذه الدراسة على ٩ أغنام من الجنسين حيث قسمت إلى ثلاث مجموعات متساوية حقنت المجموعات الثلاثة بالزيلازين فى العضل بجرعة ١ ملجم / كجم من وزن الجسم · تركـــت المجموعة الأولى بدون حقن للمواد الأخرى للمقارنة بينما حقنت المجموعة الثانية فى الوريد بجرعة ٤٠ ملجم / كجم من وزن الحيوان من النيكثاميد بعد ٥٠ دقيقة من حقن الزيلازين · أما المجموعة الثالثة فقد حقنت بالكافين فى الوريد بجرعة ٢٠ ملجم / كجم من وزن الجسم بعد ٥٠ دقيقـة مـن حقن الزيلازين · كما تم الفحص الأكلنيكي للحيوانات وخاصة درجة الحرارة ومعـــدل النبـــض والتنفس قبل وأثناء التجربة · وكذلك غازات الدم والإتزان الحمضى القاعدى قد تم تـجينهـــا ووجد أن النيكثاميد والكافيين لهم تأثير منشط للأغنام المهدئة بإستخدام الزيلازيـــن ·

SUMMARY

Nine sheep of both sexes were used in this study. The animals were divided into three groups. The first group received xylazine only in a dose rate of 1.0 mg/kg B.Wt. intramuscularly, the second group injected intravenously nikethamide in a dose of 40 mg/kg B.W.t 50 minutes after intramuscular administration of xylazine, while the third group received caffiene 20 mg/kg B.Wt. in intravenously 50 minutes after intramuscular xylazine injection. Time and state of sedation, recumbendy, muscles condition, salivation and urination were noticed and recorded. Clinical examination including body temperature, pulse and respiratory rate before and during experiment were recorded. Blood gases and acid-base balance were also demonstrated. Nikethamide and caffiene gave a stimulant effect for sheep sedated with xylazine.

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INTRODUCTION

Xylazine is a potent non narcotic, sedative, analgesic and muscle relaxant frequently used in ruminants. Because ruminants are more sensitive to xylazine than other animals, they require only 10% or less the dose of horses, dogs and cats to induce the equivalent state of sedation (KNIGHT, 1980).

Most sheep can be sedated by intramuscular injection of 0.15-0.30 mg/kg b.wt. xylazine (STRAUB, 1972; KOSUCH, 1973; MOHAMMED, et al. 1976; SHOKRY, et al. 1976 and BOLBOL and MISK, 1979).

The clinical application of xylazine in ovine practice was in maximum dose of 1.0 mg/kg b.wt. (BAUDITZ, 1972 and ALI, et al. 1988).

The overdose of xylazine can induce marked central nervous system depression characterized by prolonged recumbency and bradycardia as well as tachypnea (RAPTOPOULOS, et al. 1985; BROWN, 1986 and HSU, et al. 1987).

Durgs that causes C.N.S. depression are usually accompained by alteration in the function of respiratory system and subsequently changes in oxygenation process through the lungs (DONAWICK and BAUE, 1968 and CLARK, et al. 1981). Lung plays an important role in the buffering mechanism of acid-base balance (HILLS, 1974). Respiratory distress is usually accompanied with disterbance in values of blood gases and acid-base values (CARAWAY, 1962 and EL-SEBAIE, et al. 1985).

The aim of this investigation is to study the possible antagonistic effect of both nikethamide and caffiene in sheep against the depression action of xylazine. Special attention was directed towards the clinical signs and alteration in acid-base balance and blood gases.

MATERIAL and METHODS

Nine clinicaly healthy (3 males and 6 females) sheep of the native breed were used. Their ages ranged between 2 and 4 years and their body weights between 30-60kg.

The animals were divided into three groups each of three. They were injected intramuscularly with xylazine in a dose of 1.0 mg/kg b.wt. According to JONES, et al. (1978), nikethamide in a dose of 40 mg/kg b.wt. (group II) and caffiene in a dose of 20 mg/kg b.wt. (group III) were administered intravenously 50 minutes (averaged needed time for many surgical operations in sheep) after xylazine injection.

Pulse, rectal temperature and respiratory rate were recorded before, 30,60,90,120, 150,180 and 210 minutes after xylazine injection. The other clinical signs were also observed and recorded.

Venous blood samples were collected anaerobically at the same time intervals from jugular vein using 1 ml disposable syringes, whose dead space had been previously filled with 1:1000 I.U. sodium heparin. Samples were immediately placed on ice-bath

and processed within 45 minutes using Corning pH-blood gas analyser (Model 168. Halstead, Essex, Great Britain). The analyser directly measured at 37°C blood pH, carbon dioxide tension (pC02:mm Hg) and oxygen tension (p02:mm Hg). Bicarbonate ($HC03^-$: mmol/L), total carbon dioxide (tC02:mmol/L) and base excess (B.E.: mmol/L) were calculated automatically by the same apparatus.

RESULTS

Group I, received 1.0 mg/kg b.wt. xylazine I.M.:

The onset of sedation was manifested after an average period of 5 minutes postinjection. Sheep showed lowered head and neck, excessive salivation, repeated urination of a considerable amount of urine and have a tendency to lie down. Fifteen minutes postinjection, the animals lay down with head and neck laterally turned backward as in milk fever position. At this stage pronounced serous salivation, protrusion of the tongue, drooping of the upper eyelid, protrusion of the nictitating membrane and skin sensibility were completely absent.

Ninety minutes postinjection, the animals tried to stand up. The animals began to stand and move 120 minutes after xylazine injection.

Group II, received nikethamide I.V. after xylazine I.M.:

The clinical findings after xylazine injection were similar to those in group I. but after nikethamide injection the animals regained awarness and stood up immediately after its injection. Coughing was noticed in two animals for few seconds then disappeared. One animal lay down again (sternal) after 30 minutes and another one after 35 minutes while the third animal lay down after 40 minutes.

Group III, received caffiene I.V. after xylazine I.M.:

The clinical findings after xylazine injection were the same in comparison to those of group I. Salivation was ceased post caffiene injection and there was no signs of central nervous system excitment.

Three minutes after I.V. injection of caffiene, the animals changed the lateral recumbency into sternal recumbency and began to raise th head. After five minutes from caffiene injection the animals stood up. The animals were retained to sternal recumbency again after about one hour.

Findings of respiration, pulse and temperature are presented in table (1). Values of blood gases and acid-base balance are shown in tables (2,3 & 4).

Respiratory rate showed a marked polypnae in the different groups 30 and 60 minutes after injection and retained their normal values 120 minutes after injection, while marked oligopnae was continued in the group III. Pulse rate slightly decreased specially in the third group table (1). Body temperature was decreased in group (I) while no specific changes was marked in the two other groups.

Data concerning blood gases and acid-base of group (I) showed increase in the blood pH in the late time postinjection and this accompanied with increased bicarbonate and base excess values. In group (II) the pH values increased to their maximum values at the time between 60 and 120 minutes post administration. Accompanied increase in the base excess values were observed at the same time.

The same findings were observed in group (III) in which blood pH values were increased at 150, 180 and 210 minutes postinjection. Concomitant elevation were also noticed in the base excess values.

DISSCUSION

In this study, the use of xylazine (1.0 mg/kg B.Wt. I.M.) induced marked central nervous system depression characterized by prolonged recumbency, head drooping and third eyelid protrusion in addition to tachypnea and bradycardia.

Xylazine injected I.M. induced tachypnea which was characterized by rapid and shallow breathing. Similar findings were reported after RAPTOPOULOS, et al. (1985) and HSU, et al. (1987). Injection with either nikethamide or caffiene in time interval of 50 minutes post xylazine administration counteract the tachypnea produced after its injection.

Observed bradycardia after I.M. injection of xylazine could be explained due to central depression effect of the substance used. Injection of nikethamide caused an initial decrease in pulse rate followed by a gradual recovery toward base line measurments. These changes were probably due to an increae in blood pressure which was preceded by a brief decrease after nikethamide injection (JONES, et al. 1978). Similar results were reported after I.V. caffiene injection.

The decrease in body temperature after xylazine, nikethamide and caffiene was within the normal levels (table 1).

Blood gases and acid-base alteration following the administration of xylazine indicated that a slight alkalosis would occurred conjugated with marked increased in the base excess (table 2). Such changes may be due to the alteration in the respiratory rate (polypnae) which occurred at the end of the experiment.

On the other hand, in group (II) similar changes in the mean values of blood gases and acid-base balance, but to less extent clear than those in group (I) after this time the both blood pH and base excess returned back to their normal values. Such rapid regulation of these values may refered to the antagonstic action of nikethamide. Moreover, in group (III) which treated with caffiene, the values of blood pH and base excess still high until the end time of experiment without ability to return back to their normal values (table, 4). It could be suggested that caffiene have had a less but longer antagonstic action than nikethamide.

In conclusion, xylazine in a dose of 1.0 mg/kg B.Wt. produced a marked degree of sedation in sheep for more than two hours.

The results of this study indicated that both Nikethamide and caffiene at the studied doses have a marked antagonistic effect on the sedative, bradycardiac, and tachypneic effects of xylazine in sheep. These antagonistic effects of Nikethamide and caffiene on xylazine suggest that each drug would be a useful antidote for xylazine overdose in sheep.

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Table (1)

The mean values of respiration, pluse and temperature before and after treatment

Time (min.)	respiratory rate Group			pluse rate Group			temperature Group		
	I	II	III	I	II	III	I	II	III
0	18	31	13	120	123	113	39.7	39.3	39.5
30	47	58	67	80	81	73	38.8	38.8	38.5
60	43	47	51	80	67	76	37.3	38.5	37.4
90	41	40	45	68	84	71	36.2	38.5	36.5
120	38	36	28	77	71	67	36.1	38.7	36.2
150	39	36	26	87	90	103	36.1	38.1	36.2
180	38	48	15	87	97	120	36.2	39.4	37.1
210	40	40	13	89	107	120	36.7	39.6	38.1

Table (2)

Group I: Mean values of blood gases and acid-base parameters in sheep after i.m. injection of xylazine (1.0 mg/kg B.wt.)

Time	pH	$P_v CO_2$ mm Hg	$P_v O_2$ mm Hg	HCO_3^- mmol/L	TCO_2 mmol/L	B.E. mmol/L
0	7.454	33.4	28.3	21.2	22.2	-2.3
30	7.420	36.4	48.3	24.7	25.7	1.5
60	7.420	42.2	42.0	27.6	28.9	3.7
90	7.374	35.9	49.4	25.2	26.4	1.2
120	7.395	38.9	44.6	27.0	28.3	1.8
150	7.410	43.1	48.7	28.1	29.4	3.8
180	7.438	48.1	46.1	29.0	30.5	5.3
210	7.463	44.8	45.2	30.1	31.3	6.6

Table (3)

Group II: Mean values of blood gases and acid-base parameters in sheep (Nikethamide was injected i.v. after xylazine administration i.m.)

Time	pH	P_vCO_2 mm Hg	P_vO_2 mm Hg	HCO_3^- mmol/L	TCO_2 mmol/L	B.E. mmol/L
0	7.402	36.2	28.6	22.6	23.7	-1.1
30	7.413	39.3	44.4	25.1	26.3	1.2
60	7.445	41.2	48.2	28.2	29.5	4.5
90	7.452	41.5	40.2	28.9	30.2	5.3
120	7.448	41.6	37.0	29.1	30.5	5.7
150	7.415	43.6	36.6	28.4	29.8	4.6
180	7.415	43.2	42.8	27.4	28.8	3.7
210	7.403	43.3	32.1	27.2	28.6	2.7

Table (4)

Group III: Mean values of blood gases and acid-base parameters in sheep (Caffiene was injected i.v. after xylazine administration i.m.)

Time	pH	P_vCO_2 mm Hg	P_vO_2 mm Hg	HCO_3^- mmol/L	TCO_2 mmol/L	B.E. mmol/L
0	7.291	34.9	31.3	17.0	18.4	-8.5
30	7.404	36.9	40.5	23.3	24.4	-0.5
60	7.425	40.4	38.1	26.5	19.4	2.6
90	7.377	40.9	39.2	24.2	25.4	-0.5
120	7.470	39.6	42.4	26.3	27.9	4.0
150	7.492	36.9	43.2	28.6	29.7	5.8
180	7.474	39.8	43.2	27.8	29.2	5.4
210	7.491	40.9	42.9	29.5	30.7	7.0