EVALUATION OF HORMONAL, METABOLIC AND CARDIORESPIRATORY EFFECTS OF MEDETOMIDINE IN ONE HUMPED CAMELS

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SUMMARY

This study was aimed to evaluate the effects of alpha 2-adrenoceptor agonist medetomidine on some hormonal, metabolic and cardiorespiratory responses in healthy one humped camels . Five apparently healthy male camels ageing 3-4 years, weighing 220-280 Kg were used . The experiment was designed to investigate the physiological effects of different intravenous doses of medetomidine (20, 30 and 40 µg /Kg) . All animals were treated with each dose with an interval of one week and each animal served as control (zero line) before injection . Physiological findings heart rate, respiratory rate, rectal body temperature and electrocardiogram were monitored pre- and post-injection of medetomidine after 5, 30,60 and 120 min . Complete hematological changes were measured pre- and post-injection . Both blood glucose and insulin level were estimated . Cortisol was measured by single antibody radioimmunoassay (RIA) technique . Medetomidine suppressed insulin secretion and induces initial hypoglycemia followed by increased blood glucose levels . The hyperglycemic effects of medetomidine was not dose- dependent . There was non significant changes in hematological events. Plasma cortisol levels were showed non significant increases within dose 20 µg/ kg body weight while there was significant increases with dose 30 and 40 µg /kg.. Body temperature was moderately decreased . The heart rate was showed a bradycardia with irregular rhythm, and decreases the conduction in the conductive system of the heart, affected T waves. The respiratory rate was affected with an initial slowing for few seconds to 1-2 min. post-injection, and increasing to normal within 120 min.

It could be concluded that healthy camels can usually compensate for these physiological changes during sedation and analgesia; however medetomidine are contraindicated in cardiovascular and respiratory diseased camels. Moreover, animal ECG must be applied before pre anaethetic medication or anesthesia in order to prevent the sudden death of the animals during anesthesia specially in large animals as camels.

INTRODUCTION

Medetomidine hydrochloride (Domitor) a veterinary non-narcotic sedative , muscle relaxant and analgesic used in dogs only. Domitor, is a synthetic ∝ 2-adrenorceptor agonist which produces sedation and analgesia **(Ambrisko and Ilkasa 2002)**. It is also useful for gastrointestinal surgery and endoscopy **Greene et al (1999)**. Moreover, it is also used as reliable emetics for small animals **(Maze & Tranquilli 1991; Ilkasa et al 1992)**. The effects of medetomidine on respiration and cardiovascular were recorded in different animals species of dogs **(Ko et al.,1996; Kogima et al., 1999 & 2002)**. In sheep **Kastner et al., (2001)**. **Chimpanzes Adams et al., (2003)**, and recently in camels **(Alsobayil and Mama, (1999)**. In India, **Peshen et al (2006)** reported that detomidine Hcl produces some physiological changes during sedation and analgesia in camels. α-2 agonists alters the cardiovascular functions and decreases myocardial contractility **(Dart.,1999; Paddleford and Harvey.,1999)**.

The aim of the present investigation was to evaluate the physiological changes such as blood hormones levels, hematological findings and cardiorespiratory effects after medetomidine Hcl injection in one humped camels(dromedary).

MATERIALS & METHODS

Animals :

Five apparently healthy male camels (Camelus dromedaries) ageing 3-4 years , weighing 220-280 Kg were used. They were examined hematological, biochemical and clinically before the experiments. All recorded values are within the physiological ranges. Animals were fasting for 20-24h before the injection of drug , but water was available ad libitum.

Drugs:

Domitor® (medetomidine hydrochloride) is a synthetic alpha 2- adrenoreceptor agonist with sedative andanalgesic properties. The chemical name is [1-(2.3 di - methylphenyl) ethyl] -1 H-imidazole mono hydrochloride. Its molecular weight is (236.7). Medetomidine was available as a 1mg /ml solution (Domitor, Orion Corporation, Espoo, Finland).

Experimental design:

The experiment was designed to study the effects of different intravenous doses of medetomidine (20, 30, and 40 ug/Kg). Five animals were used in each group for treatment in deferent dos-

es with one week interval and each animal was served as control. Blood samples were collected from each animal under local anesthesia with 2 % lidocaine . Through fixation of five gauge central venous (CV) catheter was introduced into the jugular vein . The catheter was flushed with 0.5 ml of heparin physiological saline solution, capped, and fixed . The catheter was placed in the evening before the experiment and removed after the last blood sampling . In heparin tube 5 ml of blood was collected from each animal before injection and considered as control (0 - line) and then at 5 , 30 , 60 and 120 min post injection . Moreover, heart, respiratory, rates and rectal body temperature were recorded as previously described . Blood samples were divided into 2 parts . One for hematologieal analysis and the other samples were centrifuged immediately at 3000 r.p.m for 15 min , then plasma was separated and frozen at -20°C for biochemical and hormonal analysis.

Electrocardiogram (ECG):

It was recorded for each animal before and after medetomidine injection. Bipolar standard limb leads that measure the potential difference between two limbs. Lead I which measure the potential difference between right forelimb - ve pole and left forelimb + ve pole. Lead II which measure the potential difference between right forelimb -ve pole and left hind limb + ve pole. Lead III which measure the potential difference between left forelimb -ve pole and left hind limb + ve pole. Using a modified electrocardiogram(by change the human ECG leads using special clepses fixed on the skin of the fore and hind limbs of camels to record the electrical changes of the heart from the skin), the previously described leads were applied on each camel before and after injection of medetomidine and the ECG waves were recorded as lead I,II,III bipolar standers limbs leads .

Analytical methods:

Heparin blood samples were used for measuring complete blood analysis using cell dyne according to **Coles 1980**. Blood glucose was estimated by commercially Kits (Bio-Merieux-France). Plasma cortisol was measured by single antibody radioimmunoassay (RIA) technique using a commercially available kit. Insulin hormone was measured by double antibody RIA technique .

Statistical analysis of the data obtained were analyzed by means ANOVA using **Spsswin. (1995)**. Mean of data and stander errors were represented in table No. (1) .

RESULTS

Hormonal effects of medetomidine :

These were showed in table (1). Camels endocrine glands were respond to medetomidine through inhibition of insulin hormone which secreted from beta cells of I lets of Langerhans, medetomidine induces initial hypoglycemia five min. after injection followed by increase of blood glucose (hyperglycemia). The response of blood glucose is not doses dependent. The cortisol hormone levels show non significant changes within dose 20µg /kg , but there was significant increases within dose,30 and 40 µg / kg.

Clinco-physiological responses:

Effects of medetomidine on ECG:

The ECG were represented as five waves P, QRS complex and T waves Fig (1), Fig (2). There was several changes in the conductivity and contractility of the cardiac muscles of camel after injection of the drug in different doses 20,30, and 40 µg /Kg BW, generally but the dose 40 µg/ Kg BW induces delays the rate of conduction between SAN and AVN. It increases P-R intervals from 0.25 to 0.35 millisecond. In addition, it decreases contractility of the ventricles specially QRS complex were decreased in the strength of contraction "systole", the T - waves were inverted after 5min. of injection of dose 40 µg /kg BW. Medetomidine induced bradycardia with irregular rhythm, the results of the heart rates were shown in fig. (4), it were decreased by 50% as normal heart rate. Immediately after injection of the medetomidine Hcl of the 40µg/ Kg. After 30 and 90 min. there were still prolonged P-R intervals and inverted T weaves and still decreased contractility of the ventricles. While the heart rate began to increase to its near normal levels. After 120 min. of injection the T weaves still inverted but the ventricles became to contract near to its normal levels .

The respiratory rates were shown in fig. (4). Respiratory responses included an initial slowing of respiration within a few seconds to 1-2 min. Post-injection, increasing to normal within 120 min.

Body temperature was moderately decreases as presented in Fig.(5)

Hematological findings:

RBCs , Hb, PCV, MCV, total and differential leucocytic count all these parameter within different doses have no significant changes.

DISCUSSION

The α- 2-adrenoceptor agonists acts through inhibition of the sympathetic out flow in the nervous system. Medetomidine binds the α-2adrenoceptor, then inhibits the secretion or release of plasma catecholamine **(Ambrisko and Hikasa 2002). Benson et al. (2000)** found that medetomidine administered preoperatively reduced catecholamine levels in both operated and non operated dogs. **Ambrisko and Hikasa (2000)** reported that medetomidine has greater effects on reducing plasma epinephrine levels than xylazine. The results of the present investigation revealed that camels under the effects of sedation and analgesia showed an increases in blood glucose, these hyperglycemia is essential to compensate the requirements of the internal environment of the body during sedation and analgesia. Our finding revealed that the hyperglycemic effects of medetomidine was not dose -dependent. Moreover, the blood insulin hormone levels were decreased in the present study these may leads to increase blood glucose levels. Benson et. al. (2000) have reported that injection of medetomidine induced a decrease in insulin level. **Burton et, al. (1997)** found that medetomidine at the same doses in dogs induces hyperglycemia. Moreover, **Nishimura et al (1994) & Ranheim et al., (2000)** they found the same results in sheep ,cattle and pigs respectively. The plasma cortisol levels were showed a significant changes at doses 30 and 40µg / kg BW. The cortisol hormone secretion was influenced by both the peripheral site at the adrenal cortex, and through corticotrophin releasing factor (CRF) and through adrenocorticotrophic hormone (ACTH) which secreted from the hypothalamus and anterior pituitary glands respectively **Guyton and Hall (1996).** The effects of the _ 2-agonists on the plasma cortisol level have been assessed in different animals. **Maze et al (1991)** reported that an IM injection of 80 µg / kg BW of dexmedetomidine decreased the basal level of cortisol 3 hours post-injection in dogs, and concluded that only high dosages of the drug inhibits the adrenal cortex steroidogenesis. In contrast, the in dogs it produces hyperglycemia. Pre-medication with medetomidine was reported to reduce or delay the increase of cortisol secretion in ovariohysterectomy female dogs **(Maze et., al. 1991; Benson et al. 2000 & Ko et al 2000).** Sedation with xylazine or clonidine , show inhibitory effect on the release of cortisol level. However, whether it is due to the a 2- adrenoceptor- mediated specific action, other receptor- mediated actions, or the result of non- specific effects by providing sedation and analgesia which reduce stress response, is unknown. An in vitro study reveled that 2-adrenoreeepotr agents, medetomidine, detomidine, and atipamezol, all suppressed the release of cortisol from porcine adrenocortical cells **Jager et al. (1998).** In the present study, medatomidine Hcl induce bradycardia five mins. after injection and decreases rate of conduction from SAN to AVN, delay conduction may be produce dangerous in camels during deep analgesia, or contraindication in animals suffered from heart block, the effects of drug extended to 120min. after injection. Medatomadine Hcl inhibit the

rhythmcity of SAN and decreased heart rate also it delay rate of conduction at AVN . Moreover, decreases strength of contractility and ST segments were prolonged which represent delay in re-polarization of the ventricles due to inhibit of sod. pot. Pump at cardiac muscle cell membrane . T weave represents the changes of direction of action potential of the cardiac muscle membranes of the ventricles from the base to the apex of the heart .

Therefore ,it was recommended that medetomidine Hcl in high doses are contraindicated in the heart disease specially in partial heart block that can be produce complete heart block and induce death to the animals during anesthesia .alpha two agonists decrease myocardial contractility and alter the cardiovascular functions **(Dart, 1999; Paddleford and Harvey, 1999 and Peshen P et al, 2006)**.

The respiratory rate was affected with an initial slowing for few seconds to 1-2 min. post-injection, and increasing to normal within 120 min.

It could be concluded that healthy camels can usually compensate for these physiological changes during sedation and analgesia ; however medetomidine are contraindicated in cardiovascular and respiratory diseased camels . Moreover, animal ECG must be applied before pre anaethetic medication or anesthesia in order to prevent the sudden death of the animals during anesthesia specially in large animals as camels.

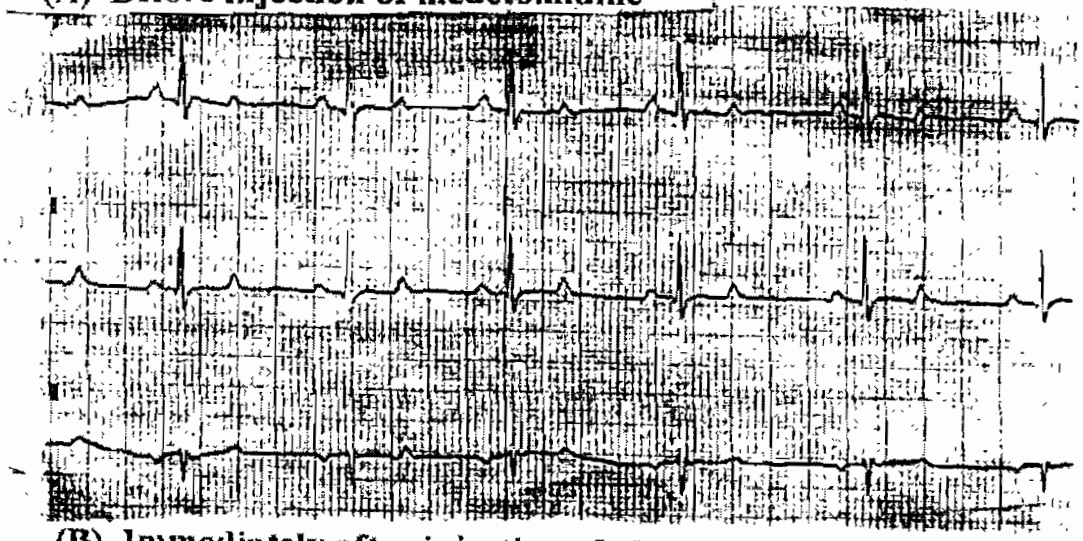
Table (1): The effects of Medetomidine Hcl on blood glucose ,Insulin , Cortisol hormone of different doses 20, 30 ,40. µg per Kg BW.

Parameter		Blood glucose levels mg / dl		Insulin levels as U / ml			Cortisol hormone levels µg / dl	
Dose	20 µg /kg	30 µg/kg	40 µg/kg	20 µg/kg	30 µg/kg	40 µg/kg	20 µg/kg	30 µg /kg	40 µg/kg
Control 0 mins	92.14±2.01	86.4±1.17	86.3±0.98	13.32±0.5	14.2±0.62	13.4±1.2	2.4±0.16	2.4±0.18	2.54±0.20
5 mins	82.6±1.5	49.6±1.3	73.2±1.39	9.4±0.51	10.2±0.5	9.64±0.40	2.24±0.09	2.46±0.18	2.26±0.16
30 mins	117±2.6	106.6±1.2	73.6±1.66	6.7±0.25	5.44±.29	4.64±0.26	2.7±0.10	2.3±0.10	2.9±0.07
60min	150.8±2.8	172.8±2.3	164.6±2.54	4±0.47	4.92±0 29	4.7±0.34	2.36±0.15	2.7±0.13	3.92±0.16
120 mins	132.6±1.36	122.8±1.5	162.±2.66	7.86±0.98	8.4±0.20	7.26±0.25	2.44±0.16	3.36±0.15	4.0±0 14
f. value	167.5**	817.1**	579.01**	32.8**	84.12**	36.16**	1.80	7.07**	25.46**

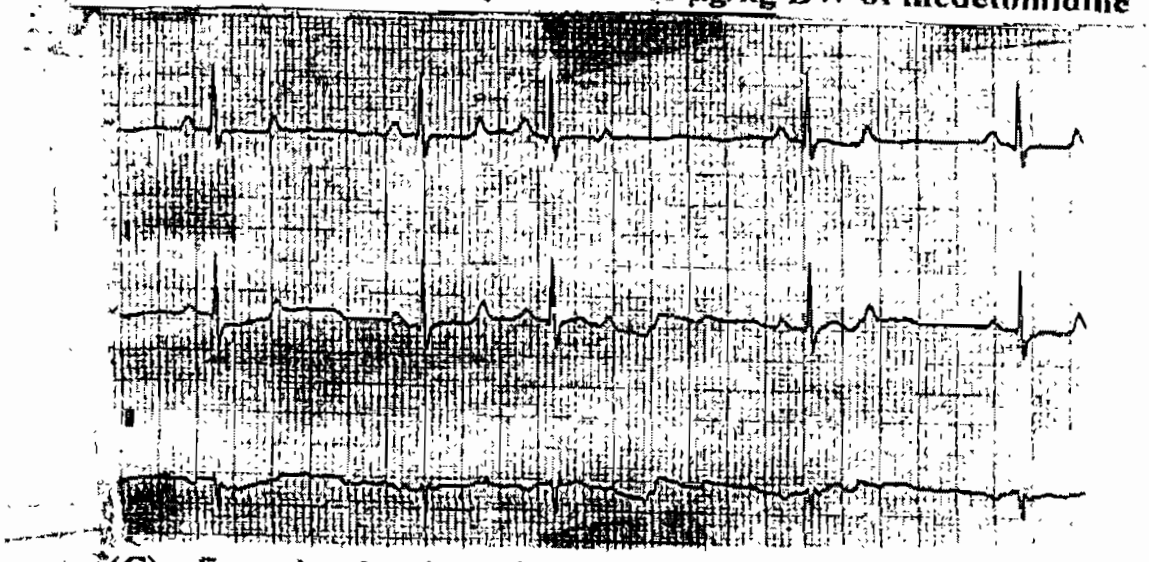
Mean+ SE. * Significance at (P<0.01)

Fig. (1)

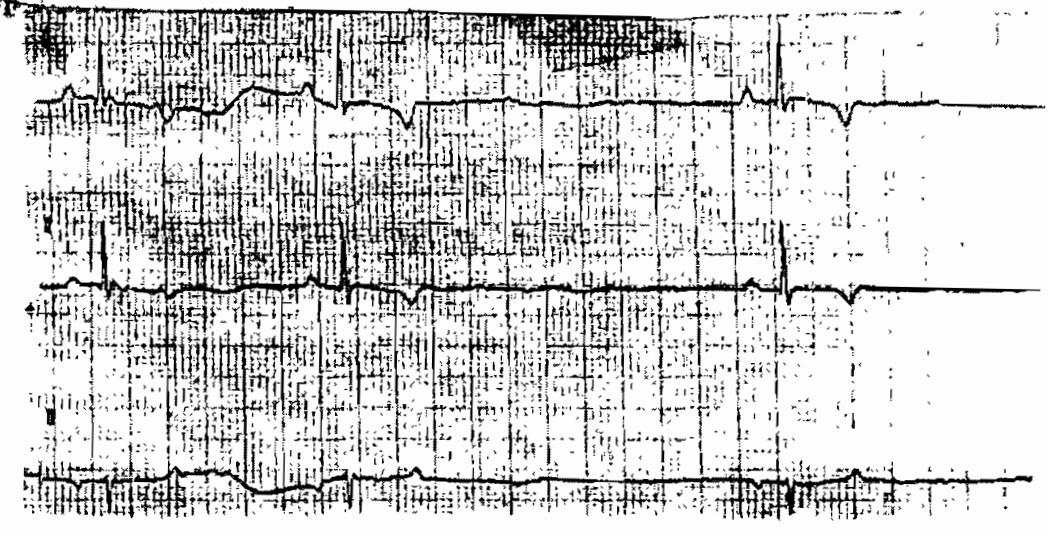
(A) Before injection of medetomidine



(B) Immediately after injection of 40 µg/kg BW of medetomidine



(C) five min after injection of previous dose of medetomidine



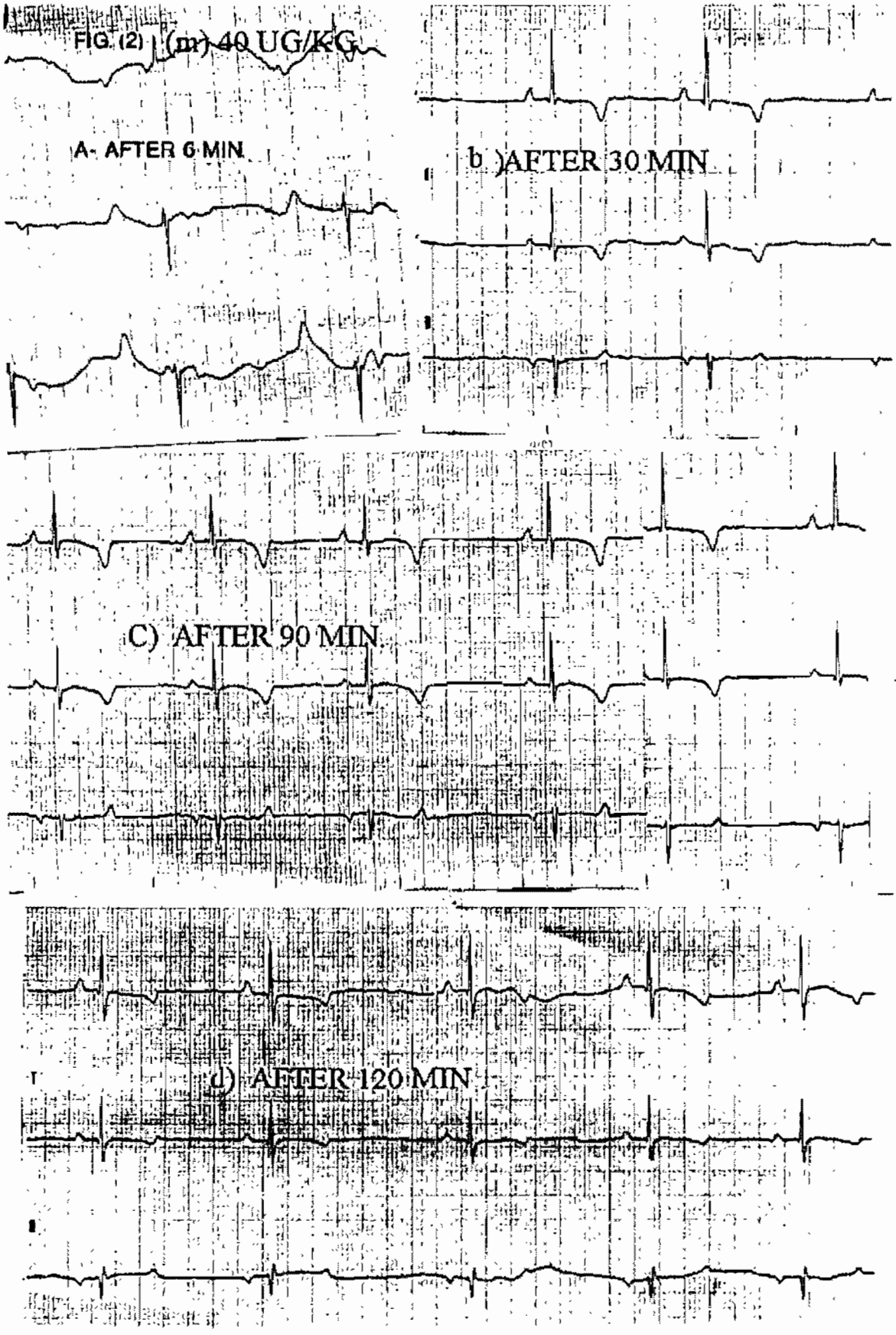


FIG. (2) (m) 40 UG/KG
A- AFTER 6 MIN
b)AFTER 30 MIN
C) AFTER 90 MIN
d) AFTER 120 MIN

fig.(3) Effects of medetomidine on the heart rate.

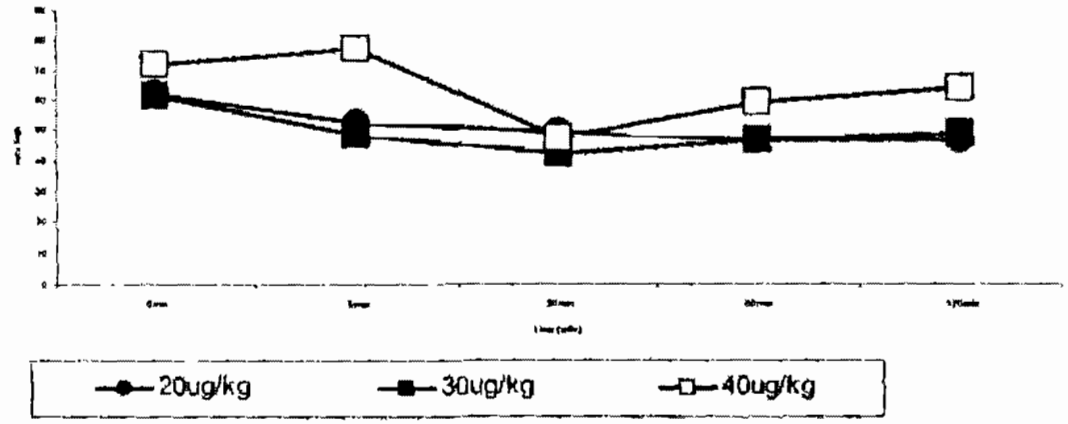


fig (4) Effects of medetomidine on the respiratory rate .

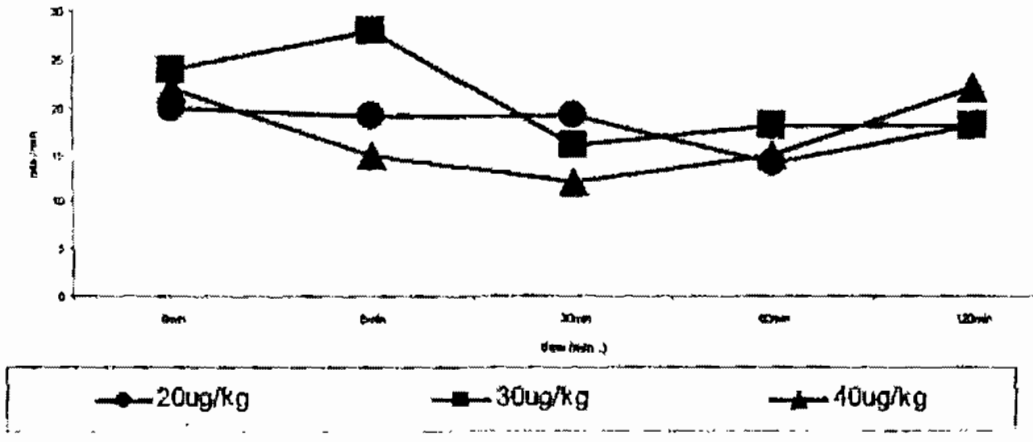
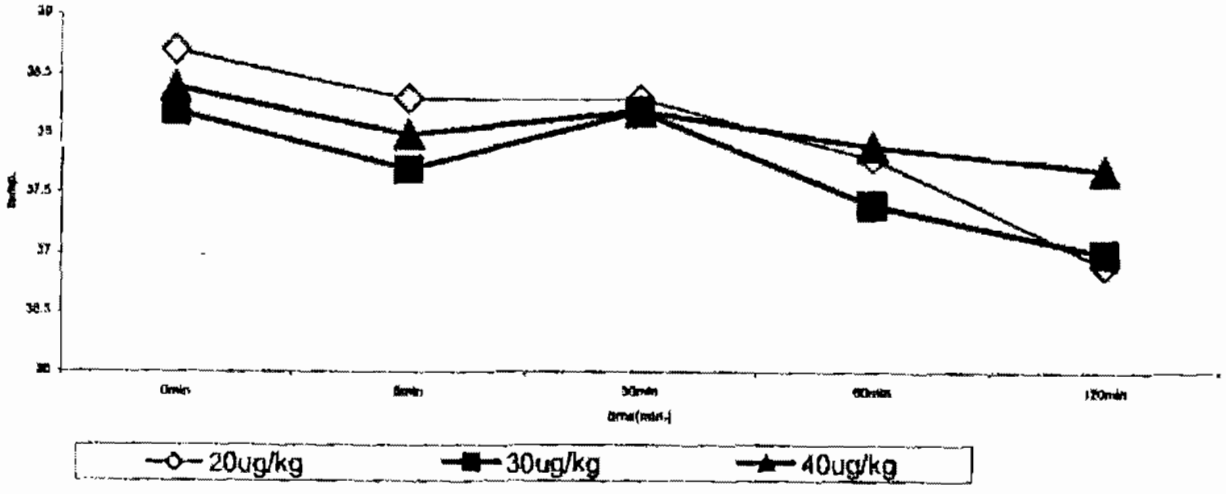


fig.(5) Effects of medetomidine on rectal body temperature



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