Yamaguchi University, Japan

The United Graduate School of Veterinary Science

The Stress Related Neuroendocrine and Metabolic Effects of Alpha-2 Adrenergic Agents and Their Combinations with Injectable Analgesics in Dogs

Structured summary of Ph.D. Thesis

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Table of Contents

Introduction

The alpha-2 adrenoceptor agonists, medetomidine and xylazine, are widely used in veterinary practice for different purposes. Because of their good sedative, muscle relaxant and analgesic properties they can be used for chemical restraint or in combination with other drugs they can provide balanced anaesthesia. By reducing gastric and intestinal motility, alpha-2 agonists are useful for gastrointestinal surgery or endoscopy. These drugs are also reliable emetics for small animals. In addition, xylazine is used as a diagnostic agent for congenital or acquired hyposomatotropism in dogs and cats. Another advantage of this class of drugs, that their actions can be reversed by specific antagonists. Although, alpha-2 adrenergic agents are multipotent drugs, they should be used carefully because unexplained and sometimes fatal accidents may be associated with their use in the healthy small animal patient. These are usually associated with the cardiovascular side effects of these drugs. However, whether the neuroendocrine and metabolic effects of alpha-2 agonists are involved in the causes of these accidents are not fully understood.

Recently, there is an increasing interest in using medetomidine as a pre-anaesthetic adjuvant because it can attenuate the endocrine stress response to surgical pain. The endocrine and metabolic stress response is characterised by the increase of catecholamine, cortisol, glucose, and nonesterified fatty acid (NEFA) blood levels, and the decrease of insulin levels. Adrenoceptors play an important role in the co-ordination of these events; therefore, alpha-2 adrenergic agents may interfere to the pathophysiology of stress response. Other analgesics like opioid drugs (butorphanol and fentanyl) and ketamine have endocrine and metabolic effects also. These drugs are often combined with medetomidine to provide balanced anaesthesia. The purpose of anaesthesia is to induce an unconscious, painless condition and attenuate stress response in the majority of cases. Proper management of the endocrine status is crucial for the surgical patient, therefore examination of the endocrine and metabolic effects of different analgesics and anaesthetics are very important. Therefore, I accomplished this study to gain further information on these effects of alpha-2 adrenergic agents and their combinations with opioids or ketamine in dogs.

Materials and methods

Experimental protocols

I completed four experiments to examine the neurohormonal and metabolic effects of different intramuscularly injected sedative and analgesic drugs. In the first experiment, I compared medetomidine (10, 20, 40, 80 µg/kg) and xylazine (1, 2, 4, 8 mg/kg). In the second experiment, I antagonised the effects of medetomidine (20 µg/kg) with atipamezole (40, 120, 320 µg/kg) or yohimbine (110 µg/kg). In the third experiment, I compared butorphanol (0.1 mg/kg) fentanyl (10 µg/kg) and ketamine (10 mg/kg), and then in the fourth experiment, I combined these drugs with medetomidine (20 µg/kg).

Animals

Healthy adult beagle dogs have been used in this study from the Department of Veterinary Internal Medicine of the Tottori University. There were males and females among them with the mean body weight of 12 kg and mean age of 3 years. The dogs were assigned to different treatment groups in randomised order. Five dogs participated in each group. At least one week elapsed between experiments on the same dog to allow time for excretion of the applied medicines. The study protocol was approved by the Animal Research Committee of Tottori University.

Sample collection

One day before the experiment I inserted a central venous catheter into the jugular vein of the dogs. This catheter was used for sampling blood before and after the treatments. I collected blood samples for 24 hours in the first experiment and for 6 hours in the following experiments. The blood samples were immediately centrifuged and the plasma was preserved under minus 80 degree until measurement.

Sample and data analysis

I measured the following variables in each plasma sample: epinephrine, norepinephrine, cortisol, glucose, insulin, glucagon, NEFA and lactic acid. High Performance Liquid Chromatograph and electrochemical detector was used for catecholamine measurement. Cortisol, insulin, and glucagon were measured by a RIA (Radio Immuno Assay) technique; glucose and NEFA were measured by a spectrophotometer. I used ANOVA and Tukey's test for statistical analysis.

Results

First experiment

Medetomidine and xylazine similarly, dose-dependently inhibited norepinephrine release and lipolysis. Medetomidine suppressed epinephrine release dose-dependently with greater potency than xylazine. Xylazine also tended to decrease epinephrine levels dose-dependently. The cortisol and glucagon levels did not change significantly in any treatment group. Both drugs suppressed insulin secretion and increased glucose levels. The hyperglycaemic effect of medetomidine was not dose-dependent at the tested dosages and the glucose values only moderately increased. In contrast, xylazine caused dose-dependent hyperglycaemia and the glucose values increased to a high level especially in those groups, where large doses of xylazine were administered.

Second experiment

Medetomidine decreased the plasma levels of norepinephrine, epinephrine, insulin, and NEFA, and increased the glucose levels 30 minutes after injection. Both atipamezole and yohimbine antagonised these effects. The reversal effects of atipamezole were dose-dependent, except on epinephrine, where all doses were equally effective. Yohimbine caused prolonged increases in plasma norepinephrine and insulin levels comparing to atipamezole, possibly because of its longer elimination half-life. Only yohimbine increased the cortisol levels. Neither glucagon nor lactate levels changed significantly.

Third experiment

Plasma levels of epinephrine and cortisol significantly increased after every treatment. Norepinephrine levels only increased after ketamine treatment and glucose levels increased after fentanyl and ketamine treatments. Changes in epinephrine levels were not in correlation with those of the cortisol levels in any treatment group, but significantly correlated to the glucose levels after butorphanol and fentanyl but not after ketamine treatments. The epinephrine levels also significantly correlated to the NEFA levels in the butorphanol group and had a tendency for correlation in the fentanyl group but not in the ketamine group.

Fourth experiment

Norepinephrine, epinephrine, insulin, and NEFA levels significantly decreased in every treatment groups. However, the norepinephrine levels were significantly higher in the medetomidine-ketamine than in the medetomidine-saline groups. Cortisol levels did not change significantly. Plasma glucose levels significantly increased in every group except for the medetomidine-butorphanol group where only increasing tendency was observed. Interestingly, the glucose levels in the balanced anaesthesia groups were significantly lower than in the medetomidine and saline treated control group.

Conclusions and recommendations

Surgical pain induces stress response in the body. This is characterised by an increase in catecholamine, cortisol and glucose blood levels and the decrease of insulin levels. Attenuation of this endocrine and metabolic stress response is desirable in most of the cases. Alpha-2 agonists can be helpful because they decrease the blood level of catecholamines and cortisol. On the other hand, they may worsen hyperglycaemia and further decrease the insulin levels. The results of the first experiment suggest that unknown mechanisms may suppress hyperglycaemia after high doses of medetomidine injection, but if xylazine was overdosed, the plasma glucose levels would freely increase to an extreme level. The hyperglycaemic effect of alpha-2 agonists is a secondary effect, which may be harmless but not desirable. In this respect, the use of medetomidine is preferable over xylazine.

According to the results of the second experiment, yohimbine is not an ideal drug to antagonise the effects of medetomidine because it increases the cortisol, norepinephrine, and insulin levels, and may cause excitement. On the other hand, I did not notice adverse effects of atipamezole, even when applied in high doses. Based on these findings, when medetomidine-induced sedation is antagonised in dogs, I recommend using atipamezole intramuscularly, from 2 to 6 folds the dose of medetomidine, unless otherwise indicated.

In the third experiment, single injections of butorphanol and fentanyl induced hormonal and metabolic changes similar to the physiological stress response but the effects of ketamine were somewhat different. Epinephrine seems to be the key mediator of these changes after butorphanol and fentanyl but not after ketamine treatments. The effects of ketamine can not be explained with its antagonistic actions on N-methyl-D-aspartate receptors and the involvement of other receptor systems is highly probable. The hormonal and metabolic changes observed in this study are undesirable for the stress free management of the patients, therefore butorphanol, fentanyl and ketamine are recommended to use as part of a balanced anaesthesia and not as single treatments.

In the fourth experiment, the neurohormonal and metabolic effects of medetomidine were dominant in the balanced anaesthesia protocols. The norepinephrine levels were less depressed in the medetomidine-ketamine group probably because of the potency of ketamine to increase sympathoneural activity. The balanced anaesthesia combinations were advantageous comparing to single butorphanol, fentanyl and ketamine treatments because medetomidine suppressed their stress response like effects. The other advantage of the anaesthesia combinations was that they provided lower plasma glucose levels than medetomidine alone.

References

1. **Ambrisko TD**, Hikasa Y. The antagonistic effects of atipamezole and yohimbine on stress-related neurohormonal and metabolic responses induced by medetomidine in dogs. *Can J Vet Res* 2003;67:64-67.

2. **Ambrisko TD**, Hikasa Y. Neurohormonal and metabolic effects of medetomidine compared with xylazine in beagle dogs. *Can J Vet Res* 2002;66:42-49.

Secondary publications in Hungarian

3. **Ambriskó Tamás**, Yoshiaki Hikasa. Az atipamezol és a yohimbin hormonális és metabolikus hatásai medetomidinnel nyugtatott kutyákban. *Magy. Állatorv. Lapja.* 2003 (accepted for publication).

4. **Ambriskó Tamás**, Yoshiaki Hikasa. A medetomidin és a xilazin hormonális és metabolikus hatásai kutyákban. *Magy. Állatorv. Lapja.* 2003;125:219-223.

Manuscripts submitted to Journals

5. **Ambrisko TD**, Hikasa Y, Sato K. Stress-related neurohormonal and metabolic effects of butorphanol, fentanyl and ketamine in dogs.

6. **Ambrisko TD**, Hikasa Y, Sato K. Stress-related neurohormonal and metabolic effects of medetomidine combined with butorphanol, fentanyl or ketamine in dogs.