EFFECTS OF YOHIMBINE AND ATIPAMEZOLE ON PLASMATIC GLUCOSE CONCENTRATION AND BLOOD GAS ANALYSIS IN DOGS INTOXICATED WITH TRIATOX®

(REFEREIS DA IOIMBINA E ATIPAMEZOLE NA CONCENTRAÇÃO PLASMÁTICA DE GLICOSE E HEMOGASOMETRIA EM CÃES INTOXICADOS COM TRIATOX®)

(EFECTOS DE LA YOHIMBINA Y DEL ATIP AMEZOL SOBRE LA CONCENTRACIÓN PLASMÁTICA DE GLUCOSA Y LA HEMOGASOMETRÍA EN PERROS INTOXICADOS CON TRIATOX®)

S. F. ANDRADE1, M. SAKATE2, A. J. CROCCI3

SUMMARY

This study compared the effectiveness of either yohimbine or atipamezole in the reversion of hyperglycemia and blood gas alterations induced by Triatox®. Thirty dogs were equally divided into 3 groups (T, TY, and TA). Group T was given 2.5% Triatox® i.v. at 1 mg/kg; Group TY received the same dose of Triatox® followed by 0.1 mg/kg (2 mg/mL) yohimbine i.v. 30 minutes later; and Group TA received the same dose of Triatox® followed by 0.2 mg/kg (5 mg/mL) atipamezole i.v. 30 minutes later. Blood samples of every animal were drawn to measure plasma glucose concentration and blood gases at 0, 30, 60, 120 and 360 minutes after amitraz administration. Hyperglycemia was observed in group T (Triatox®); yohimbine (group TY) reverted the hyperglycemia induced by Triatox®, whereas atipamezole (group TA) was less effective than yohimbine to do so. There were no significant (p<0.05) changes on blood gas analysis in all studied groups. Our results demonstrate the importance of more studies regarding the reversion of amitraz-induced hyperglycemia by the a2-adrenergic antagonists yohimbine and atipamezole. This procedure may be a crucial factor in the treatment of patients with alterations of the cardiorespiratory parameters and increased blood glucose levels owing to intoxication by this acaricide.


RESUMO

Este estudo comparou a eficácia entre ioimbina e atipamezole na reversão da hiperiglicemia e das alterações de hemogasometria induzida pelo Triatox®. Trinta cães foram divididos igualmente em 3 grupos (T, TY, e TA). Grupo T recebeu Triatox® a 2.5% IV a dose de 1 mg/kg; Grupo TY recebeu a mesma dose de Triatox® e após 30 min ioimbina na dose de 0.1 mg/kg (2 mg/mL) IV; e Grupo TA recebeu a mesma dose de amitraz e após 30 min atipamezole na dose de 0.2 mg/kg (5 mg/mL) IV. Amostras de sangue de cada animal foram coletadas para análise da concentração de glicose plasmática e hemogasometria nos tempos 0, 30, 60, 120 e 360 minutos após a administração de Triatox®. A hiperiglicemia, induzida pelo amitraz e observada nos três grupos, foi revertida no grupo da ioimbina (grupo TY) e, de maneira menos afetiva, no do atipamezole (grupo TA). Não houve alteração significante (p<0,05) da análise da hemogasometria em todos os grupos estudados. Os resultados obtidos neste trabalho demonstram a importância de mais estudos na reversão da hiperiglicemia induzida por Triatox®, pelos antagonistas a2-adrenérgicos, ioimbina e atipamezole, que pode ser um fator crucial no

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tratamiento de pacientes diabéticos intoxicados por este acaricida.


RESUMEN
Este estudio comparó la eficacia entre la yohimbina y el atipamezol en la reversión de la hiperglycemia y de las alteraciones de la hemogasometría inducidas por el Triatox®. Treinta perros fueron distribuidos equitativamente en tres grupos (T, TY y TA). El grupo T recibió Triatox® a 2,5%, IV, a la dosis de 1mg/kg; el grupo TY recibió la misma dosis de Triatox® y después de 30 minutos yohimbina, a la dosis de 0,1mg/kg (2mg/mL), IV; y el grupo TA recibió la misma dosis de amitraz y después de 30 minutos, atipamezol, a la dosis de 0,2mg/kg (5mg/mL), IV. Muestras de sangre de cada animal fueron colectadas para el análisis de la concentración de glucosa plasmática y de la hemogasometría, en los tiempos 0, 30, 60, 120 y 360 minutos, después de la administración de Triatox®. Fue observada hiperglicemia en el grupo T (Triatox®), pero la yohimbina (grupo TY) revirtió la hiperglicemia inducida por el amitraz, mientras el atipamezol (grupo TA) fue menos efectivo que la yohimbina en la reversión de ese efecto. No hubo alteración significativa (p<0,05) en el análisis de la hemogasometría en todos los grupos estudiados. Los resultados obtenidos en este trabajo demuestran la importancia de la realización de más estudios sobre la reversión de la hiperglicemia inducida por el Triatox®, por los agonistas adrenérgicos α₂, yohimbina y atipamezol, que pueden ser un factor crucial en el tratamiento de pacientes diabéticos intoxicados por este acaricida.


INTRODUCTION
Amitraz is a pesticide from the group of formamidines used as ectoparasiticide in veterinary medicine (HUGNET et al., 1996). In Brazil a recent study showed that one of the most common intoxications, 13.9%, was from pesticides for farm use (39.3% organophosphorous, 35.7% carbamate insecticides and 25.0% amitraz) (XAVIER et al., 2002). Amitraz is a highly lipid-soluble compound that is absorbed through skin and mucous membranes, being primarily biotransformed by the kidneys (PASS e MOGG, 1991) and also by the liver (JONES, 1990). The degradation products present in the urine include N’-(2,4-dimethylphenyl)-N-methylformamidine (BTS 27271), 2,4-dimethylformanilide, 2,4-dimethylaniline, 4-formamido-3-metylbenzoic acid, 4-amino-3-methylbenzoic acid, and several unknown metabolites, BTS 27271 being the more potent amitraz active metabolite (KNOWLES e BENEZET, 1981).

Classical signs of intoxication are characterized by nervous system alterations such as sedation, loss of reflexes and motor incoordination. Other signs include bradycardia, hypotension, hypothermia, polyuria, hyperglycemia, emesis, mydriasis and a decrease in the intestinal transit. The mode of action responsible for these undesirable effects consists of the interaction with α₂- adrenoceptors in a similar way to the agonists xylazine and clonidine. Amitraz also stimulates peripherally α₁- adrenergic receptors producing vasoconstriction (CULLEN e REYNOLDS, 1990; HSU, 1996).

Recent studies demonstrate more specifically the subtypes of α₂- adrenergic receptors where amitraz and its active metabolites act. Studies have proven amitraz interaction with α₂D pre-synaptic receptors in the hypothalamus of rats (ALTOBELLI et al., 2001). Other authors studied the effect of amitraz and its active metabolite, BTS 2727, in the inhibition of insulin and stimulation of glucagon secretion within the pancreas of rats, mediated by a high affinity for binding of the pesticide and its metabolite with α₁D receptors at the pancreatic islets (ABU-BASHA et al., 1999).

Therefore, the use of α₂- adrenergic antagonists such as yohimbine (SCHAFFER et al., 1990; HOVDA e MACMANUS, 1993) or atipamezole (HUGNET et al., 1995) is the treatment of choice for the intoxication by amitraz, besides other therapeutic procedures, such as gastrointestinal decontamination (HUGNET et al., 1996). In the present experiment the product used was the acaricide Triatox® that has as main component the amitraz diluted in xilene. However, until the present moment, there is no comparative study between the efficiency of these two antagonists for the reversion of hyperglycemia induced by amitraz or the acid-base alterations that this acaricide may induce, which is the objective of the present experiment.

MATERIALS AND METHODS

Experimental animals
The present experiment was approved by the Ethics Committee of the Universidade do Oeste Paulista.
Laboratory of the Veterinary Hospital of UNOESTE in agreement with the routine and technical norms of this laboratory. The following moments were usual: M0 (control) before amitraz administration; M1, 30 min after amitraz administration and the moment of the $\alpha_2$-adrenergic antagonist administration; M2, 60 min after amitraz administration and 30 min after administration of the $\alpha_2$-adrenergic antagonist; M3, 120 min after amitraz administration and 90 min after administration of the $\alpha_2$-adrenergic antagonist; and M4, 360 min after amitraz administration and 330 min after administration of the $\alpha_2$-adrenergic antagonist.

The experimental model proposed and developed in this study was first described by Andrade & Sakate (2003) and consists of Triatox® diluted in distilled water, administered iv in dogs, causing an acute intoxication without fatal consequences. Dosages used for each group were: Group T - Triatox® (n=10), 5 males and 5 females, administered as a 2.5% concentration (25 mg/mL) by dilution of 1 mL of Triatox® Mallinckrodt Vet (125 mg of amitraz) in 4 mL of bi distilled water for a dose of 1 mg/kg iv; Group TY - Triatox®/Yohimbine (n=10), 4 males and 6 females, received 1 mg/kg of 2.5% Triatox® iv and, 30 min later 0.1 mg/kg of yohimbine (Yobine®Vet-A-Mix) (2mg/mL) iv and Group TA - Triatox®/Atipamezole (n=10), 4 males and 6 females, received 1 mg/kg of 2.5% Triatox® iv and 30 min later 0.2 mg/kg of atipamezole (Antisedan® – Pfizer) (5 mg/mL) iv.

Experimental Procedure

All dogs were randomly allocated in three groups of 10 animals each one: group T (Triatox®), group TY (Triatox®/yohimbine) and group TA (Triatox®/atipamezole). Blood samples (4 mL) were obtained from the femoral artery. From the collected blood, 3 mL was transferred to a flask containing fluoride of sodium to measure plasma glucose concentration by a colorimetric enzymatic method using a spectrophotometer (model CELM E 225 D) and 1 mL was used for arterial blood gas analysis (equipment model AZL OMNI-5) at 0, 30, 60, 120 and 360 minutes. The blood samples were processed on the Clinical Laboratory of the Veterinary Hospital of UNOESTE in agreement with the routine and technical norms of this laboratory.

The following moments were usual: M0 (control) before amitraz administration; M1, 30 min after amitraz administration and the moment of the $\alpha_2$-adrenergic antagonist administration; M2, 60 min after amitraz administration and 30 min after administration of the $\alpha_2$-adrenergic antagonist; M3, 120 min after amitraz administration and 90 min after administration of the $\alpha_2$-adrenergic antagonist; and M4, 360 min after amitraz administration and 330 min after administration of the $\alpha_2$-adrenergic antagonist.

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Statistical Analysis

For each variable evaluated in the experiment the

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>M0</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
<th>M4</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>90.6±11.5</td>
<td>101.5±18.3</td>
<td>114.8±44.6</td>
<td>116.6±48.0</td>
<td>128.8±34.2</td>
</tr>
<tr>
<td>n=10</td>
<td>(Aa)*</td>
<td>(Aa)</td>
<td>(Ba)</td>
<td>(Ba)</td>
<td>(Ba)</td>
</tr>
<tr>
<td>TY</td>
<td>93.6±11.2</td>
<td>99.3±12.2</td>
<td>105.9±14.0</td>
<td>102.8±18.5</td>
<td>97.2±15.9</td>
</tr>
<tr>
<td>n=10</td>
<td>(Aa)</td>
<td>(Aa)</td>
<td>(Ba)</td>
<td>(Ba)</td>
<td>(Ab)**</td>
</tr>
<tr>
<td>TA</td>
<td>98.0±12.7</td>
<td>103.4±22.5</td>
<td>119.6±18.2</td>
<td>120.2±20.0</td>
<td>122.9±20.0</td>
</tr>
<tr>
<td>n=10</td>
<td>(Aa)</td>
<td>(Aa)</td>
<td>(Ba)</td>
<td>(Ba)</td>
<td>(Ba)</td>
</tr>
</tbody>
</table>

**M1**: Time moment of administration of $\alpha_2$-adrenergic antagonists

Group T - Triatox® (n=10), 1 mg/kg of 2.5% amitraz iv

Group TY - Triatox®/Yohimbine (n=10) 1 mg/kg of 2.5% amitraz iv and 30 min later 0.1 mg/kg of yohimbine (2mg/mL) iv

Group TA - Triatox®/Atipamezole (n=10) 1 mg/kg of 2.5% amitraz iv and 30 min later 0.2 mg/kg of atipamezole (5 mg/mL) iv

* Capital letters compare moments for each group and small letters compare groups for each moment. Same letters indicate differences that were not significant (p>0.05). A significance level of 5% (p<0.05) was adopted.

** Statistically different (p<0.05)
Table II – Mean (±SD) values obtained for concentration of hydrogen ions (pH), partial pressure of oxygen (PO2), partial pressure of carbon dioxide (PCO2), sodium (Na+), potassium (K+), chloride (Cl-) and bicarbonate (HCO3⁻), by blood gas analysis, according to the different groups and time intervals in dogs experimentally intoxicated by Triatox®.

<table>
<thead>
<tr>
<th>Blood Gas Normal Values</th>
<th>Groups</th>
<th>Moments (in minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>pH</td>
<td>T (n=10)</td>
<td>7.40±0.04 (Aa)**</td>
</tr>
<tr>
<td></td>
<td>TY (n=10)</td>
<td>7.40±0.03 (Aa)</td>
</tr>
<tr>
<td></td>
<td>TA (n=10)</td>
<td>7.41±0.03 (Aa)</td>
</tr>
<tr>
<td>PO2 (mmHg)</td>
<td>T (n=10)</td>
<td>87.7±16.4 (Aa)</td>
</tr>
<tr>
<td></td>
<td>TY (n=10)</td>
<td>91.3±6.8 (Aa)</td>
</tr>
<tr>
<td></td>
<td>TA (n=10)</td>
<td>87.5±3.3 (Aa)</td>
</tr>
<tr>
<td>PCO2 (mmHg)</td>
<td>T (n=10)</td>
<td>34.9±5.4 (Aa)</td>
</tr>
<tr>
<td></td>
<td>TY (n=10)</td>
<td>32.1±3.1 (Aa)</td>
</tr>
<tr>
<td></td>
<td>TA (n=10)</td>
<td>36.5±4.3 (Aa)</td>
</tr>
<tr>
<td>Na⁺ (mmol/L)</td>
<td>T (n=10)</td>
<td>144.2±4.6 (Aa)</td>
</tr>
<tr>
<td></td>
<td>TY (n=10)</td>
<td>144.7±5.9 (Aa)</td>
</tr>
<tr>
<td></td>
<td>TA (n=10)</td>
<td>146.7±6.7 (Aa)</td>
</tr>
<tr>
<td>K⁺ (mmol/L)</td>
<td>T (n=10)</td>
<td>3.7±0.2 (Aa)</td>
</tr>
<tr>
<td></td>
<td>TY (n=10)</td>
<td>3.9±0.4 (Aa)</td>
</tr>
<tr>
<td></td>
<td>TA (n=10)</td>
<td>3.8±0.3 (Aa)</td>
</tr>
<tr>
<td>Cl⁻ (mmol/L)</td>
<td>T (n=10)</td>
<td>113.5±2.3 (Aa)</td>
</tr>
<tr>
<td></td>
<td>TY (n=10)</td>
<td>116.1±5.5 (Aa)</td>
</tr>
<tr>
<td></td>
<td>TA (n=10)</td>
<td>112.0±2.1 (Aa)</td>
</tr>
<tr>
<td>HCO₃⁻ (mmol/L)</td>
<td>T (n=10)</td>
<td>21.1±2.7 (Aa)</td>
</tr>
<tr>
<td></td>
<td>TY (n=10)</td>
<td>19.4±2.2 (Aa)</td>
</tr>
<tr>
<td></td>
<td>TA (n=10)</td>
<td>23.8±5.5 (Aa)</td>
</tr>
</tbody>
</table>

Values according to Kaneko et al. (1997). ** Capital letters compare moments for each group and small letters compare groups for each moment. Same letters indicate differences that were not significant (p>0.05). A significance level of 5% (p<0.05) was adopted.

Group T - Triatox® (n=10), 1 mg/kg of 2.5% amitraz iv
Group TY - Triatox®/Yohimbine (n=10) 1 mg/kg of 2.5% amitraz iv and 30 min later 0.1 mg/kg of yohimbine (2mg/mL) iv
Group TA - Triatox®/Atipamezole (n=10) 1 mg/kg of 2.5% amitraz iv and 30 min later 0.2 mg/kg of atipamezole (5 mg/mL) iv
multivariated analysis profile was used (MORRISON, 1990) for comparison, on average, of the effect of the several time moments in each group, as well as the comparison, on average, of the effect of the groups in each time moment. This analysis considers the structure of existent correlation among time moments in each group.

**RESULTS**

The glucose concentrations in mg/dL are displayed in Figure 1. Normal limits for glucose levels were considered as 65-118 mg/dL (KANEKO et al., 1997). Significant differences were detected between the moments of each group beginning in M2 (Table I).

Values of glucose concentrations increased gradually in Group T (Triatox®) beginning in M0 (90.6±11.5) and rising up to 128.8±34.2 at M4. Group TA (Triatox®/Atipamezole) also demonstrated a gradual increase of glycemia from moment M0 (98.0±12.7), reaching 122.9±20.0 at M4 (Figure 1). No significant differences were detected between groups T and TA. Otherwise, Group TY (Triatox®/Yohimbine) demonstrated a reduction of glucose concentration beginning at M2 (105.9±14.0) until M4 (97.2±15.9) (Figure 1). A significant difference was detected (p<0.05) between Group TY and Groups T and TA at M4 (Table I).

The following parameters were evaluated by blood gas analysis: concentration of hydrogen ions (pH), partial pressure of oxygen (PO₂), partial pressure of carbon dioxide (PCO₂), sodium (Na⁺), potassium (K⁺), chlorine (Cl⁻) and bicarbonate (HCO₃⁻).

Mean values obtained by blood gas analysis in the animals are demonstrated in Table II. No significant difference was detected (p>0.05) among groups T, TY and TA, neither among the different moments in each group.

**DISCUSSION**

Some intoxications can modify the normal homeostasis and result in significant hydro-electrolytic and acid-base unbalances including a potential risk of life for the animal (CORNELIUS, 1996). Until the present moment, there are no reports in the literature about the acid-base disturbances produced by the IV administration of amitraz or amitraz associated with its α₂-adrenergic agonists, yohimbine or atipamezole in dogs. In the present experiment it was evidenced that there are no significant modifications in blood gas values in dogs intoxicated by amitraz intravenously, or by amitraz and treated with its antagonists, yohimbine and atipamezole, intravenously.

Amitraz causes hyperglycemia and hypoinsulinemia when administered by the cutaneous, oral and intravenous routes, like others α₂-adrenergic agonists (HSU e SCHAFFER, 1988). The probable mechanism of action of amitraz and its active metabolite, BTS 27271, for induction of hyperglycemia, is by inhibiting insulin secretion mediated by α₂-adrenergic receptors, possibly by inhibition of adenylcyclase that is mediated by G PTX-sensitive proteins (CHEN e HSU, 1994). The subtype of α₂-adrenergic receptor involved in that action is α₂D located within the pancreatic islets (ABU-BASHA et al., 1999).

According to the report of HUGNET et al. (1996), atipamezole reverted hyperglycemia induced by amitraz administered orally. However, data from the present experiment did not demonstrate this fact. Possible causes for this difference may be listed as follows: 1º) different routes used for amitraz administration, in this study it was administered by iv route which could cause higher concentration and occupation of receptors by the agonist when compared to oral route; 2º) in the refered study the administration of an antagonist occurred when the glycemia curve was already decreasing, while in the present experiment the antagonist was administered when the curve was still ascending (Figure 1); 3º) atipamezole is a reversible and competitive antagonist with fast dissociation (KUKKONEN et al.,1997). Thus, inhibition is surmountable when the concentration of the agonist is increased (dose-dependent). It is presumed in this experiment that amitraz was found in high concentrations at the moment of atipamezole administration and 4º)
yohimbine has longer half-life elimination when compared to atipamezole (AMBRISKO e HIKASA, 2003).

In this study the efficacy of yohimbine to revert hyperglycemia induced by amitraz may be due to its mode of action. Yohimbine is $\alpha_2$ adrenoceptor antagonist (KAUMMANN, 1983, KALSNER e ABDALI, 2002), that blocked the inhibitory effects of amitraz and BTS27271 on cyclic AMP and insulin release (CHEN e HSU, 1994). Other authors, considered yohimbine as an irreversible and competitive antagonist with slow dissociation (KUKKONEN et al., 1997). This action occurs even though yohimbine has less affinity with $\alpha_{2D}$ receptor than atipamezole (HAAPALINNA et al., 1997, SCWARTZ e CLARK, 1998). There is an increasing interest in human medicine for the possible role of $\alpha_2$-adrenergic receptors in the decreasing function of $\beta$-pancreatic cells in patients with diabetes type 2 (ROBERTSON et al., 1976, ORTIZ-ALONSO et al., 1991). It is evident that these patients are more sensitive to intoxication by amitraz than other healthy individuals, requiring more studies to rule out this hypothesis (ABU-BASHA et al., 1999).

The results obtained demonstrate the importance of more studies on the reversion of hyperglycemia induced by amitraz, by the $\alpha_2$-adrenergics antagonists, yohimbine and atipamezole. Possibly larger doses of atipamezole could revert the hyperglycemia induced by amitraz in high concentration, even so more research need to be done in this sense. The hyperglycemia is transitory in amitraz intoxication, but this can be a crucial factor in the treatment of diabetic patients’ cases intoxicated by this acaricide. In humans, over 16 cases have been reported in which hyperglycemia was one of the most prominent signs (AYDIN et al., 1997, ULUKAYA et al., 2001, DOGANAY et al., 2002, KALYONCU et al., 2002, ATABEK et al., 2002). Exposure to amitraz would be expected to pose a greater hazard to patients with type 2 diabetes, who already have impaired insulin secretion and/or utilization (ABU-BASHA et al., 1999).

Andrade e Sakate (2003) in recent study, observed that amitraz caused sedation, loss of reflexes, hypothermia, bradycardia, hypotension, bradypnea and mydriasis, with 3rd eyelid prolapse, increased diuresis and vomiting in some animals. Yohimbine reversed all alterations induced by amitraz, but induced significant cardiorespiratory effects such as tachycardia and, tachypnea. Atipamezole also reversed all alterations, but caused less cardiorespiratory effects. In the present study yohimbine at a dose of 0,1 mg/kg iv was more effective in reverting the hyperglycemia induced by amitraz at a dose of 1 mg/ kg iv than atipamezole at a dose of 0,2 mg/kg iv. These results may be useful in the treatment of serious intoxicated patients with amitraz that have significant alterations on cardiorespiratory parameters and blood glucose levels.

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