

# Action of *tacrolimus* in arginine induced experimental acute pancreatitis

## *Ação do tacrolimus na pancreatite aguda experimental induzida pela arginina*

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### A B S T R A C T

**Objective:** To determine whether tacrolimus administered to rats, in the presence of pancreatitis induced by L-Arginine, interferes with the serum levels of amylase and glucose and the histological pattern of the pancreatic parenchyma. **Methods:** Forty Wistar rats were divided into four groups with 10 rats each: control group (C), tacrolimus group (T), pancreatitis group (P) and pancreatitis-tacrolimus group (PT). We evaluated serum levels of amylase, glucose, and tacrolimus and made histological assessments of the pancreas. Induction of pancreatitis was made by inoculation of L-Arginine at a dose of 500mg/100g body weight intraperitoneally, and tacrolimus treatment at a dose of 11g/kg subcutaneously for four days. **Results:** Serum amylase was higher ( $p = 0.0000$ ) in groups PT, P and T than in the control group. The PT group mean was higher ( $p = 0.0009$ ) than in the T group, but did not differ ( $p = 0.6802$ ) from the average of the P group. There was no difference between groups P and T ( $p = 0.2568$ ). Neither in mean blood glucose between the groups ( $p = 0.4920$ ); serum levels of tacrolimus were similar in PT and T groups ( $p = 0.7112$ ). There were no histological changes in groups T and C and no hemorrhage in the pancreas of rats in groups P and PT. In group P, there was no edema in 30%, mild edema in 20% and in 50%, moderate; as for inflammatory infiltration, it was moderate in 80% and absent in 20%, and atrophy of the parenchyma was moderate in 60% and severe in 40%. In the PT group, there was edema, inflammatory infiltration or atrophy in the pancreas in all rats. **Conclusion:** treatment with Tacrolimus induced an increase in serum amylase in normal mice, but did not affect blood glucose or the histological pattern of the pancreatic parenchyma. In the presence of pancreatitis induced by L-Arginine tacrolimus induced edema, inflammatory infiltration and more severe atrophy in the pancreatic parenchyma.

**Key words:** Immunosuppressants. Tacrolimus. Pancreatitis. Arginine. Amylase. Glucose. Disease / pathology. Animal experimentation. Rats.

### INTRODUCTION

The improved outcomes in solid organ transplantation, demonstrated by the increase in graft and patient survival, is due primarily to improvement in surgical techniques, progress in immunological techniques for selection of donors, effectiveness of solutions for organ preservation and a new immunosuppressive drugs<sup>1</sup>.

Among these stands out tacrolimus, which has a macrolide structure originally isolated from culture of *Streptomyces tsukubaensis*<sup>2</sup>. Its immunosuppressive effect is mediated by its binding to a cytosolic protein (FKBP12) responsible for its intracellular accumulation. The tacrolimus-FKBP12 complex binds specifically and competitively to calcineurin, with consequent calcium-dependent inhibition of transduction of cytotoxic T lymphocytes and activation

of B lymphocytes proliferation. It also inhibits the transcription of different genes of lymphokines, such as interferon-gamma, and expression of interleukin-2 receptors, thus leading to immunosuppression<sup>3</sup>.

The continuous use of immunosuppressive drugs require regular blood monitoring to perform individual adjustments and maintain blood levels stable enough to prevent rejection and, at the same, below the toxic threshold to avoid adverse effects<sup>4</sup>. The main adverse effects observed with tacrolimus are tremors, headache, hypertension, nausea, diarrhea and renal dysfunction, which can be controlled by dose reducing<sup>5</sup>.

Little known, and still of hypothetical character, is the occurrence of acute pancreatitis (AP) associated with the chronic use of tacrolimus<sup>6-8</sup>. The AP is a disease caused by multiple etiologies that present with a common central

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phenomenon, intraparenchymal activation of pancreatic enzymes, which induce a process of autodigestion manifested by edema, hemorrhage, and pancreatic or peripancreatic necrosis, accompanied by systemic repercussions, with involvement of multiple organs and systems and, in some cases, death<sup>9</sup>. However, its pathophysiological mechanisms are not yet completely understood. It is known that excessive doses of basic amino acids, such as arginine, cause injury to the pancreas of rats<sup>10,11</sup>.

Due to the high protein metabolism in pancreatic acinar cells, it is likely that these cells are the first target of excess arginine, resulting in degeneration, atrophy or necrosis with, severe mitochondrial damage and reduction in cellular energy supply<sup>12</sup>. Experimental models of pancreatitis have contributed to the understanding of cell biology and pathophysiology of this disease, but for the best interpretation of experimental results it should always be considered that the pathogenesis of the disease in humans may differ from the one of the animal model<sup>13</sup>.

Regarding the occurrence of acute pancreatitis with the use of tacrolimus there is no consensus<sup>7,8,14,15</sup>. Its possible pancreatic toxicity is not considered a side effect of immunosuppressive treatment, but the incidence of these problems is high among patients who underwent transplantation of the organ. There is no background for this drug to be appointed as a trigger point of the process, since the target organ undergoes intense manipulation and ischemia during transplantation.

This study aims to determine whether tacrolimus administered to rats in the presence of pancreatitis induced by L-Arginine interferes in serum amylase and glucose and the histological pattern of the pancreatic parenchyma.

## METHODS

### Sample characterization

Were used 40 Wistar rats (*Rattus norvegicus*, Rodentia, Mammalia), not inbred, weighing  $282.4 \pm 12.6$ g, obtained from the vivarium of the Universidade Federal do

Paraná. The rats were kept in groups of five in polypropylene boxes suitable for the species, in an environment with controlled temperature and humidity, under cycles of light automatically set every 12 hours. They were fed diets specific to the species (Nuvilab, Nuvital®) and water *ad libitum*. Ethical Principles in Animal Experimentation of the Colégio Brasileiro de Experimentação Animal (COBEA) were followed<sup>16</sup>, and the Walker Nomina Anatomica<sup>17</sup>. The project was approved by the Ethics Committee for Animal Research of the Hospital Angelina Caron, according to the protocol 023/08.

### Experimental design

The sample was separated into four groups (Table 1).

### Induction of pancreatitis by arginine

Pancreatitis was induced by intraperitoneal inoculation of L-arginine solution (Merck 1.01542 Articleã) with rats under inhalation sedation with halothane (Tanohalo®, Cristália). The 20% (w/v) solution was prepared in phosphate buffer pH 6.8 and inoculated at a dose of intraperitoneal 500mg/100g of weight for the groups P and PT. C and T groups received phosphate buffer pH 6.8, at a dose proportional to weight, the same route of inoculation of the other groups<sup>18,19,20</sup>.

### Treatment by tacrolimus

We used the product Prograf® (Janssen-Cilag/Fugisawa), in the form of 5mg/ml injectable tacrolimus. The dose used was the 11g/kg weight and the solution was prepared from dilutions in phosphate buffer pH 6.8. The rats in groups T and PT subcutaneously received this treatment for four days from the day of induction of pancreatitis and the rats of groups C and P were treated with phosphate buffer pH 6.8, at a dose proportional to weight, also subcutaneously.

### Sample collection and laboratory analysis

On the fourth day of evolution, the rats were anesthetized by inhalation with halothane in closed circuit

**Table 1** - Groups of rats in the study.

Groups		N	Goals
Control	(C)	10	Establish reference values for serum levels of amylase and glucose and pancreas histological evaluations of normal mice.
Tacrolimus	T	10	Verify the occurrence of the changes in serum amylase and glucose and histological evaluations of pancreas of rats under tacrolimus treatment.
Pancreatitis	P	10	Verify the occurrence of the changes in serum amylase and glucose and histological evaluations of pancreas of rats under induction of pancreatitis by L-arginine.
Pancreatitis and Tacrolimus	PT	10	Verify the occurrence of the changes in serum amylase and glucose and histological evaluations of pancreas of rats under induction of pancreatitis by L-arginine and treatment with tacrolimus.

and subjected to transthoracic cardiac puncture. We collected volumes of blood sufficient to induce cardiac arrest. After separation of the serum samples were allocated for the measurement of tacrolimus, amylase and glucose. Once death of the mice was evidenced, we performed laparotomies and resections of the pancreas for histopathological evaluations.

**Measurement of amylase and glucose**

We performed the measurements in an automated equipment - COBAS System - MIRA "S", with specific reagents, following the manufacturer's guidelines and included positive and negative standards<sup>21</sup>.

**Dosing of tacrolimus**

We used the IMx Tacrolimus II assay (Abbott csc 0800-11-90-99), which is based on microparticle immunoenzymatic methodology (MEIA). The results are expressed in ng/ml<sup>22</sup>.

**Histopathological evaluations**

The removed pancreas was fixed in formaldehyde 10% for at least 48 hours, and sections were made through the long axis of the gland, stained with hematoxylin-eosin and examined by light microscopy. All sections were examined without knowledge of the group and period. We considered the following histological patterns: edema, inflammatory infiltration, hemorrhage and parenchymal necrosis. The histologic pattern (Table 2) was defined according to the presence and predominance of microscopic changes<sup>19,23</sup>.

**Statistical analysis**

We applied statistical methods of ANOVA and Student-T and adopted the significance level of  $p \leq 0.05$ . During induction of pancreatitis in the arginine group there were two deaths, so the sample of this group had  $n = 8$ . In order to assess whether there were differences in serum amylase, glucose, and tacrolimus between groups C, T, P and PT, we tested the null hypothesis that the average level of amylase in the groups would be equal to the average

Group C versus the alternative hypothesis that these levels were different.

**RESULTS**

**Measurement of amylase**

As shown in figure 1, the amylase of the rats was significantly higher ( $p = 0.0000$ ) in the PT group ( $2788.1 \pm 531.1$  U/L), T ( $2009.7 \pm 310.8$  U/L) and P ( $2577.5 \pm 1501.5$  U/L) compared to the control group ( $1000.0 \pm 87.14$  U/L). The group PT mean was significantly higher ( $p = 0.0009$ ) than the average of the group T, but did not differ ( $p = 0.6802$ ) from the average of the group P. Among the groups P and T there was no significant difference ( $p = 0.2568$ ).

**Levels of glucose**

Blood glucose was similar in all groups ( $p = 0.4920$ ) and, when compared to the control group, the groups P, PT and T also displayed no significant difference, as shown in figure 2.

**Levels of tacrolimus**

Serum levels of tacrolimus in rats was similar in PT and T groups ( $p = 0.7112$ ), as shown in figure 3.

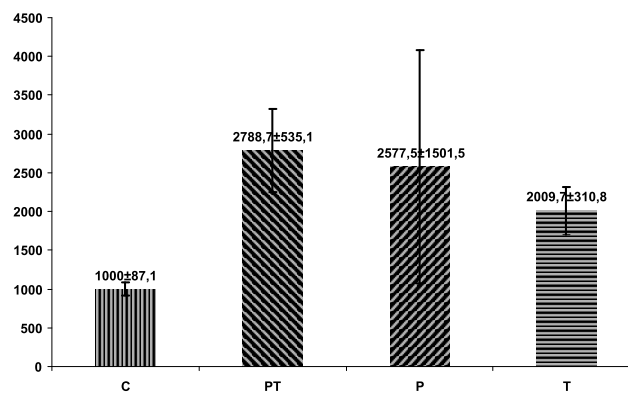


Figure 1 - Means and standard deviations of the amylase measurements (units/liter).

Table 2 - Histological Criteria for the evaluation of pancreatitis.

Histological Findings		Classification		
Atrophy	Absent	Mild	Moderate	Severe
Edema	Absent	Mild	Moderate	Severe
Inflammatory infiltration	Absent	Mild	Moderate	Severe
Inflammatory Population	Absent	Mild	Moderate	Severe
Neutrophils				
Macrophages				
Lymphocytes				
Mista				
Haemorrhage	Absent	Mild	Moderate	Severe
Necrosis	Absent	Mild	Moderate	Severe

### Histological examinations

No histological changes were observed in the tacrolimus and control groups and no cases of hemorrhage in the pancreatic parenchyma of rats in groups P and PT. As shown in figure 4, in the pancreatitis group there was no edema in 30%, and edema occurred in 20% as mild and 50% moderately; inflammatory infiltration occurred moderately in 80% and did not occur in 20% of the animals; atrophy of the parenchyma was moderate in 60% and severe in 40%. In the PT group, there was edema, inflammatory infiltration and atrophy of pancreatic parenchyma in all rats, with moderate edema in 60% and severe in 40%; inflammatory infiltrate occurred in 90% moderately and in 10%, severely; and atrophy of pancreatic parenchyma occurred moderately in 30% and severely in 70%.

### DISCUSSION

The experimental model of this study was based on previous experiments that have described a new form of acute necrotizing pancreatitis induced in rats by a single intraperitoneal injection of arginine at a concentration of 500mg/100g body weight<sup>18,19</sup>. During the pilot study of this work it was observed that the inoculation of the total dose given by the authors caused immediate death of all animals and at necropsy a widespread occurrence of mesenteric thrombosis was observed. For this reason, the proposed dose was split in two 250mg/100g interval of thirty minutes.

This non-invasive model proved to be easily reproduced and affordable when compared to invasive experimental models of acute pancreatitis<sup>20</sup>. The experimental model used herein displays, as its basic features, the elevation of serum amylase in the first 24 hours, with return to normal until the seventh day; it does not induce changes in glucose levels and the histological changes of the pancreatic parenchyma (edema and necrosis) are more severe in the period between 72 and 96 hours of onset<sup>23</sup>. As seen in figure 2, injection of L-arginine did not alter the endocrine function of the pancreas because the serum glucose levels were maintained in groups P, PT and T levels similar to those of group C. For this reason, in this study we chose the collecting samples within 96 hours of onset (fourth day) to coincide with the timing of more severe pancreatic histopathological changes, allowing time for the action of tacrolimus, which was administered daily during the four days of evaluation.

As shown in figure 3, groups T and PT – treated with tacrolimus – had similar serum levels, which endorses the procedure and demonstrates the bioavailability of the drug. It is known that the increase of serum amylase does not correlate with the severity of acute pancreatitis and also with the histological changes observed in the pancreas<sup>23,24</sup>. In this study, as shown in figure 1, serum amylase levels remained normal in group C ( $1000 \pm 87.1$

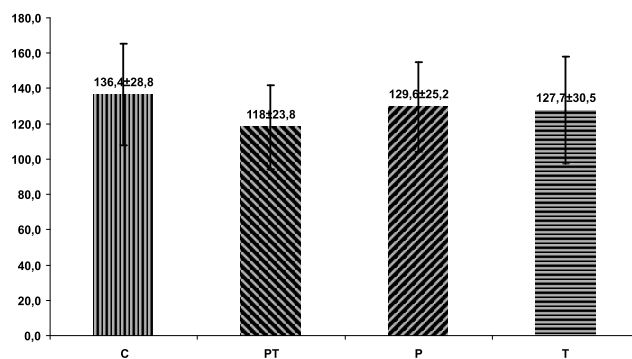


Figure 2 - Means and standard deviations of blood glucose (mg/dl).

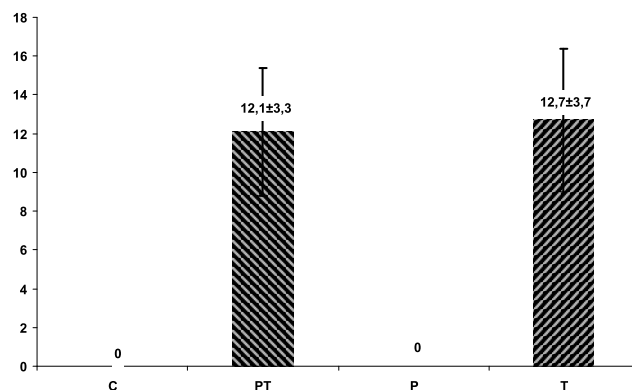


Figure 3 - Means and standard deviations of the doses of tacrolimus (ng/ml).

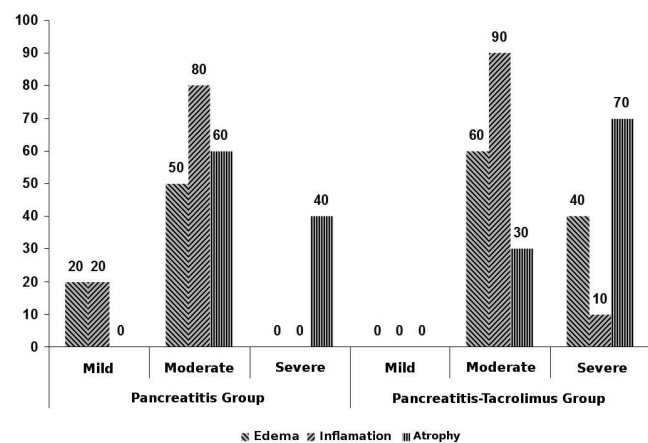


Figure 4 - Percentages of occurrence and the classification of histological criteria for evaluation of pancreatitis.

U/L) but rose significantly in groups P ( $2577.5 \pm 1501.5$  U/L) and PT ( $2788.7 \pm 531.1$  U/L), injected with L-arginine ( $p = 0.0000$ ). Noteworthy is the amylase average observed in rats of group T, receiving treatment with tacrolimus ( $2009.7 \pm 310.8$  U/L), which was also significantly higher than group C ( $p = 0.0000$ ). Although the efficacy of tacrolimus in the suppression of chronic pancreatitis in Wistar rats, variant Bonn/Kobori, was documented<sup>25</sup>, these results cannot be compared to the present study because they were obtained

in a distinct animal model, whose autoimmune mechanism is of chronic evolution and inducer of fibrosis of the pancreatic parenchyma. In this pathophysiological context, an immunosuppressive drug such as tacrolimus has effects on the autoimmune mechanism, which explains those results. Still on the results of measurements of amylase in the present study, it appears that tacrolimus treatment for four days at a dose of 1 mg/kg effectively induced an increase in serum enzyme, showing, however, a protective effect against the action of arginine because the results of the T groups ( $2009.7 \pm 310.8$  U/L) are significantly smaller than the PT group ( $2577.5 \pm 1501.5$  U/L). The justification for these results can be based on the fact that tacrolimus at therapeutic doses may increase the secretion of pancreatic enzymes, with deteriorating effect on the organ, culminating in acute pancreatitis when the pancreas is stimulated<sup>24,25</sup>.

It is known that the pancreas is considered the tissue that has the highest level of protein synthesis. There are reasons to believe that damaged, but still viable, acinar cells may cause greater and longer lasting elevation of serum amylase than necrotic cells, unable to maintain production of enzymes<sup>26,27</sup>.

From the results obtained in the histological analysis of this study, it can be argued that tacrolimus, when inoculated into normal mice, did not alter the pancreatic histological architecture (group T), these results being consistent with another study<sup>28</sup>.

There was no bleeding from the pancreatic parenchyma of rats in groups Pancreatitis and Pancreatitis-Tacrolimus, however, as the other criteria of histological assessment, there were differences between these groups, as in the PT group, edema, inflammatory infiltration and atrophy of pancreatic parenchyma was more severe than in the P group, as shown in figure 4. Few reports observed pancreatic histological changes caused by tacrolimus and described the occurrence of nuclear pyknosis and cytoplasmic vacuolation as a cause of necrotic degeneration of the acinar cells<sup>28</sup>.

Treatment by tacrolimus induced a significant increase in serum amylase in normal mice and did not alter blood glucose levels and histological pattern of the pancreatic parenchyma. In the presence of pancreatitis induced by L-Arginine, tacrolimus induced edema, inflammatory infiltration and atrophy more severe in the pancreatic parenchyma.

## R E S U M O

**Objetivo:** verificar se o tacrolimus administrado em ratos, em vigência de pancreatite induzida pela L-Arginina, interfere nos níveis séricos da amilase e glicose e no padrão histológico do parênquima pancreático. **Métodos:** quarenta ratos Wistar foram distribuídos em quatro grupos com 10 ratos cada. Grupo controle (C), grupo tacrolimus (T), grupo pancreatite (P) e grupo pancreatite-tacrolimus (PT). Foram avaliados os níveis séricos de amilase, glicose e tacrolimus e feitas avaliações histológicas do pâncreas. A indução de pancreatite foi feita pela inoculação de L-Arginina na dose de 500mg/100g de peso corporal por via intraperitoneal e o tratamento com tacrolimus na dose de 1mg/kg por via subcutânea durante quatro dias. **Resultados:** a amilase estava mais elevada ( $p=0,0000$ ) nos grupos PT, T e P do que no grupo controle. A média do grupo PT foi maior ( $p=0,0009$ ) que a do grupo T, mas não diferiu ( $p=0,6802$ ) da média do grupo P. Entre os grupos P e T não houve diferença ( $p=0,2568$ ). Não houve diferença nas médias de glicemia entre os grupos ( $p=0,4920$ ) e os níveis séricos de tacrolimus foram similares nos grupos PT e T ( $p=0,7112$ ). Não ocorreram alterações histológicas nos grupos T e C e não ocorreu hemorragia no pâncreas dos ratos dos grupos P e PT. No grupo P, em 30% não se observou edema, em 20% observou-se a forma leve e em 50%, a moderada; quanto à infiltração inflamatória, em 80% moderada e em 20% não ocorreu, e a atrofia do parênquima foi de 60% moderada e 40% acentuada. No grupo PT, houve ocorrência de edema, infiltração inflamatória e atrofia do pâncreas em todos os ratos. **Conclusão:** o tratamento pelo tacrolimus induziu aumento nos níveis séricos de amilase em ratos normais, não alterou a glicemia nem o padrão histológico do parênquima pancreático. Na vigência de pancreatite induzida pela L-Arginina o tacrolimus induziu edema, infiltração inflamatória e atrofia com maior gravidade no parênquima pancreático.

**Descritores:** Imunossuppressores. Tacrolimo. Pancreatite. Arginina. Amilase. Glicemia. Doença/patologia. Experimentação animal. Ratos.

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