THE POTENTIAL THERAPEUTIC EFFECT OF APRIMELAST (OTEZLA) ON L-ARGININE INDUCED ACUTE PANCREATITIS IN RATS

Rabab Shaban Elshafey a Salwa A. Elgendi b

a Department of Forensic Medicine & Clinical Toxicology, b Department of Pharmacology, Faculty of Medicine, Benha University, Egypt

Corresponding author E-mail: shabanrabab@yahoo.com
Submit Date 10-11-2021
Revise Date 15-02-2022
Accept Date 2022-02-20

ABSTRACT

Background: Acute pancreatic inflammation is an emergency worldwide. Aprimelast (Otezla) is an orally active drug inhibiting phosphodiesterase-4 (PDE4) & modulate the inflammatory mediators. NO research was done to detect its role in treatment of acute pancreatitis (AP). Aim: this research was designed to determine the role of Aprimelast on AP produced by L-arginine. Materials & methods: A rat model of AP was developed by two injections of L-arginine 250 mg/kg body weight, intraperitoneal (IP), separated by a one-hour period. The treatment group received Aprimelast at a single daily oral dosage of 20mg/kg body weight for five consecutive days after IP injections of L-arginine at the same dose as before. At the last of treating period, blood samples were taken for the assessment of the parameters of oxidative stress glutathione [GSH], malondialdehyde [MDA], then rats were sacrificed. The pancreas of all treated animals was excised, prepared for estimation of tumor necrotic factor (TNF- alpha) & interleukin-10 (IL-10) in tissues and histopathological examination. Results: Rats with AP had histological alterations consistent with pancreatic tissue impairment, and elevated blood glucose, serum amylase, and lipase enzyme activities. Additionally, AP rats had increased levels of the pancreatic inflammatory biomarker TNF-alpha and decreased levels of the anti-inflammatory biomarker IL-10. Additionally, the oxidative stress biomarker MDA was elevated in AP, whereas the antioxidant GSH level was reduced as contrasted to control group. Co-administration of Aprimelast led to substantial improvements in both pre-existing parameters and histology. Conclusion: These results suggested that Aprimelast may have beneficial therapeutic effect on L-arginine induced AP in adult albino rats owing to its anti-inflammatory and anti-oxidative stress effects.

Keywords: Aprimelast, Pancreatic inflammation, Phosphodiesterases, L-arginine, Oxidative stress

INTRODUCTION

Acute pancreatitis (AP) is a life-threatening inflammatory disease that can range from a moderate self-limiting condition in 15% to 20% of patients to a severe necrotizing inflammation in the remaining 80% of cases, which is associated with a danger of death of up to 30% (Liu et al., 2018). The systemic inflammatory response causes adversity and death associated with pancreatitis spreading to numerous organs adjacent and distant, which may result in multiple organ failure (Garcia and Calvo, 2010). This is mostly due to a lack of target-specific treatment choices for this disease due to a lack of knowledge of its etiology. Pathogenic pathways such as inflammation, apoptosis, necrosis, and oxidative stress impact the disease's onset and progression, with the end result being irreversible deformation of the pancreas' morphology and structure (Hammer, 2014). It's generally known that inflammation, especially severe pancreatitis, is aided by the formation of free radicals (Onderet et al., 2012). In living tissues, an imbalance between pro-oxidant
and antioxidant molecules is termed oxidative stress, which is caused via increasing the production of reactive oxygen species and decreasing the antioxidant potential (Okita et al., 2015). Various medications which have antioxidative &anti-inflammatory capacity have been tried to stop the inflammatory cascade and therefore prevent irreversible pancreatic damage, but no acceptable results have been achieved, necessitating the development of new therapies (Kambhampati et al., 2014).

Phosphodiesterase-4 (PDE4) isoenzymes are the main PDEs produced in leukocytes, including basophils, eosinophils, macrophages, mast cells, monocytes, neutrophils, and T lymphocytes; anti-inflammatory reactions of these cells to pro-inflammatory substances are mediated by the enzyme adenosine 3’,5’-cyclic monophosphate (Kwak et al., 2008).

Aprimelast is an orally administered phosphodiesterase-4 (PDE4) inhibitor that prevents the synthesis of pro-inflammatory mediators (Schafer, 2012). Aprimelast is a novel small molecule that selectively inhibits intracellular PDE4. This enzyme is a phosphodiesterase (PDE) that is implicated in the cyclic adenosine monophosphate hydrolysis (cAMP). cAMP serves as a signaling molecule for a pro- and anti-inflammatory mediators' integrated network (Taskén and Aandhl, 2004). Inhibition of PDE4 results in an increase in the quantity of cyclic adenosine monophosphate (cAMP) in cells, hence modulating inflammatory responses. Aprimelast inhibits a broad range of inflammatory mediators implicated in the development of psoriasis. Inhibition of PDE4 results in a decrease in inducible interleukin 23 (IL23) and nitric oxide synthase (iNOS) levels, and an increase in the anti-inflammatory cytokine IL10 (Schafer, 2012). Until date, limited research has been performed on aprimelast's preventive impact against a variety of illnesses. Thus, this research was intended to determine the potential therapeutic impact of Aprimelast in adult albino rats after L-arginine-induced acute pancreatitis.

**MATERIAL & METHODS**

**Drugs & Chemicals:**
Sigma-Aldrich Corp. (St. Louis, MO, USA) provided the L-arginine powder, which was dissolved in 0.9 percent saline to a concentration of 500 mg/ml and the pH set to 7 with 5N HCl as per the manufacturer's instructions (Aziz et al. 2017).

Aprimelast (Otezla) was obtained from 'Beijing Mesochem Technology co., Ltd., Beijing, China'.

**Animals:**
The present investigation used 40 adult albino rats weighing between 200 and 250 gm (bought from the animal house of the Faculty of Veterinary Medicine, Mushtohor, Banha University). Throughout the experimental period, they were kept in clean, properly ventilated cages in the same environmental factors with free access to food and water. They were exposed to their environment for two weeks prior to the experiment's commencement. The research was conducted in accordance with the ethics committee of scientific research at Banha University's Faculty of Medicine and in accordance with the National Institutes of Health's Guide for the Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985).

**Groups of animals and treatment:**
A 40 adult albino rats were distributed equally into 5 groups (8 rats per each):

1- Group I (-ve control group): These animals didn't take any medications & access their food and water freely to assess the basic parameters.

2- Group II: Rats in this group received normal saline (0.9 percent NaCl) as the vehicle through a double intraperitoneal (IP) injection of (2.5 mg/kg body weight with a 1-hour interval) and subsequently were gavaged orally with
normal saline for 5 consecutive days.

3- Group III (Aprimelast group): Animals of this group were treated with Aprimelast 20mg/kg, once daily, orally for five days according to (Imama et al.,2018).

4- Group IV: (Acute pancreatitis or L- arginine group): Animals of this group treated with L-arginine (250 mg/100g body weight, double intraperitoneal (IP) injections with 1 h interval (Melo et al., 2010).

5- Group V: The therapeutic group (L-arginine + Aprimelast treated group): Animals were treated with L-arginine injections at the same dose as group IV with a 1-hour interval to induce acute pancreatitis (AP), and then Aprimelast was given (20 mg/kg body weight by oral gavage every 24 hours for five consecutive days).

Procedural details
1. AT the beginning of study.
   Induction of Pancreatitis was done by L- arginine as previously explained in rats of groups IV. A combination of L-arginine & Aprimelast was given to rats in a group V.

2. By the end of treating protocol
   Overnight fasting (12-14 h) was performed on all animals in the various experimental groups, then anesthetized with ether and sacrificed by cervical decapitation.

3. Sampling
   1. Preparation of blood samples
      Blood was collected from hearts by direct puncture into a dry clean labeled glass centrifuge tube and left to coagulate for 30 minutes, then rapidly centrifuged at 5000 rpm for 10 minutes and the clear sera were separated and kept in clean stopper plastic vials, some of them was stored at – 80°C until the analysis of oxidative stress parameters (MDA, GSH) & the others stored at -20 °C for assessment of serum amylase and lipase) & blood sample for glucose level.
   2. Collection of tissue homogenate & histological samples

Pancreatic tissues were quickly removed after animal scarification and cut into two parts; First part was immediately frozen, and temperature should be maintained at 80°C till the tissue homogenate was produced for inflammatory and anti-inflammatory marker estimation. (TNF-α & IL10 respectively). The second portion was imbedded in 10% formalin for histopathology examination (Zhang et al., 2017).

Analysis:
1. Estimation of blood glucose level (FPG):
   Diagnostic kits (Pars Azmoonkit, IRI) were used to estimate blood glucose levels on an automated analyzer (Abbott, model Alcyon 300, USA) (Samarghandian et al.,2017).

2. Assessment of serum lipase and amylase levels:
   Serum lipase and amylase levels were estimated spectrophotometrically using commercial kits on Olympus AU-2700 autoanalyzer (Hamburg, Germany) was used in this research (Man Company, Tehran, Iran). In this case, the findings are presented as a U/I ratio (Burtis and Ashwood., 1994).

3. Measurement of malondialdehyde (MDA) in serum:
   Using a thiobarbituric acid reactive material, the production of MDA, a byproduct of fatty acid peroxidation, was determined spectrophotometrically at 532 nm (TBARS) (Genet et al. 2002).

4. Assessment of Reduced glutathione (GSH) in serum:
   The determination of GSH level in serum was done by using ELISA kits that purchased from Life Span Biosciences company (LSBio), Shanghai Blue Gene Biotech CO., LTD for GSH as per the manufacturer’s instructions (Hussein et al.,2018).

5. Assessment of tumor necrosis factor-alpha (TNF-α):
   Enzyme-linked immunosorbent assay (ELISA) kit was used to detect TNF
amounts in tissue homogenates (Boster Biological Technology, Wuhan, China). An ELISA reader was used to read the ELISA microplate with a maximum absorbance of 450 nm (Dynatech Laboratories, USA). After drawing the standard curves, the cytokine levels were computed and represented as pg/ml (Xuetal., 2021).

6. Measurement of interleukin-10 (IL 10):
After following manufacturer’s instructions, Thermo Fisher Scientific Inc./Lab Vision, Fremont, CA, USA, measured pancreatic tissue IL 10 levels using ELISA kits (IL-10 BMS629s EMMPO) (Diketal.,2018).

Histopathological examination
Other pancreatic slices coated in paraffin wax and kept in 10% formalin. Staining with hematoxylin and eosin (H&E) and photographing sections (Yoon et al., 2001). Histopathological examination was processed at pathology department, Faculty of Medicine Benha university.

Statistical analysis:
For univariate, bivariate, and stratified analysis of the data, a software package (SPSS, Version 20.0 for Windows, SPSS Inc., Chicago, IL) was used. The K-S test of normality was used to determine the non-normalcy of quantitative variables, and the Man-Whitney test was used to compare them. The ANOVA (F) and Kruskal-Wallis tests were used to compare quantitative variables for both parametric and nonparametric variables in multiple comparisons. Differences were regarded statistically significant at Probability (P) values of 0.05.

RESULTS
1- As regard to both control groups (negative & positive) and aprimelast treated group:
There were no statistically significant differences of all the studied biochemical parameters between these groups (group I, II, III respectively) (p value > 0.05) by ANOVA test (F test) regarding:
1- Blood glucose, serum lipase & amylase levels (Table 1).
2- Oxidative stress parameters: serum malondialdehyde [MDA] level and reduced Glutathione [GSH]) (Table 2).
3- Inflammatory and anti-inflammatory biomarkers. (TNF-α & IL10 respectively) biomarkers in pancreatic tissue (Table 3).

So the negative control group was chosen as a representative group to be compared with the biochemical results of the other treated groups; [L- arginine treated group (group IV) and L-arginine + aprimelast (group V) treated group].

2- As regard to L- arginine (group IV) and L-arginine + aprimelast (group V) treated groups:
The present study showed a substantial rise in blood glucose, serum lipase & amylase levels as well as increased serum MDA and decreased GSH activities in L-arginine treated (AP) group as compared to control group. Also, there were elevation of TNF-α & reduction of IL-10 levels in pancreatic tissues of rats in this group as compared to control. Furthermore, there were significant reduction in blood glucose, serum lipase & amylase levels, increased serum MDA & decreased GSH in L- arginine + aprimelast group as compared to L- arginine (AP) group. In addition, there was significant decrease in TNF-α & increased IL-10 in pancreatic tissues of rats in this group in comparison with rats treated with L-arginine. These results were statistically significant (P<0.001) (Table 1, 2&3 respectively).

2-Histopathological results:
a- H & E light microscopic examinations:
1- In –ve control, +ve control & aprimelast treated group (group I, II & III respectively):
The light microscopic examinations of pancreatic tissues stained with hematoxylin and eosin (H&E) from rats of these groups revealed similar results. There were normal
acinar cells that are triangular in shape with darkly pigmented basal nuclei and pink cytoplasm. The pancreatic islets of Langerhans are shown as clusters of cells (Figure 1 A, B & C respectively).

2- In L-arginine treated group (group IV):

Histopathological examination of stained sections in the pancreas of L-arginine treated rats showed hydropic degeneration of acinar cells, inflammatory cell infiltration, with predominance of neutrophils (Figure 1 D&E).

3- In L-arginine + Aprimelast treated group (group V):

Histopathological examination of stained pancreatic sections of treated rats in this group demonstrated near normal architecture of pancreas with minimal inflammatory cell infiltration (Figure 1 F).
Table 1: Effect of Aprimelast on Blood Glucose Level, Serum Amylase & Lipase.

<table>
<thead>
<tr>
<th></th>
<th>Control (-ve) group</th>
<th>Control (+ve) group</th>
<th>Aprimelast group</th>
<th>L-argin (AP) group</th>
<th>L-argi+ a prim group</th>
<th>ANOVA</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ±SD</td>
<td>Range</td>
<td>Mean ±SD</td>
<td>Range</td>
<td>Mean ±SD</td>
<td>Range</td>
<td></td>
</tr>
<tr>
<td>BI Glucose</td>
<td>104.13 ±11.39</td>
<td>81.0-115.0</td>
<td>103.88 ±11.85</td>
<td>80.0-116.0</td>
<td>102.0 ±11.81</td>
<td>84.0-116.0</td>
<td>102.0 ±11.81</td>
</tr>
<tr>
<td>Amylase</td>
<td>472.63 ±35.01</td>
<td>415-503</td>
<td>475.75 ±30.66</td>
<td>414-502</td>
<td>465.25 ±32.71</td>
<td>421-505</td>
<td>896.63 ±46.44&lt;abcd</td>
</tr>
<tr>
<td>Lipase</td>
<td>11.38 ±2.13</td>
<td>9.0-15.0</td>
<td>11.75 ±1.67</td>
<td>10.0-15.0</td>
<td>11.25 ±1.98</td>
<td>9.0-14.0</td>
<td>52.0 ±3.70&lt;abcd</td>
</tr>
</tbody>
</table>

Table 2: Effect of Aprimelast on Serum Levels of MDA & GSH

<table>
<thead>
<tr>
<th></th>
<th>control (-ve) group</th>
<th>control (+ve) group</th>
<th>Aprimelast group</th>
<th>L-argin (AP)group</th>
<th>L-argi+ aprim group</th>
<th>ANOVA</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ±SD</td>
<td>Range</td>
<td>Mean ±SD</td>
<td>Range</td>
<td>Mean ±SD</td>
<td>Range</td>
<td></td>
</tr>
<tr>
<td>MDA</td>
<td>4.25 ±1.01</td>
<td>2.8-5.76</td>
<td>4.44 ±0.70</td>
<td>3.47-5.50</td>
<td>3.94 ±1.01</td>
<td>2.45-5.20</td>
<td>10.27 ±1.79&lt;abc</td>
</tr>
<tr>
<td>GSH</td>
<td>138.83 ±6.85</td>
<td>129.5-149.0</td>
<td>139.27 ±5.90</td>
<td>130.0-148.6</td>
<td>138.7 ±8.34</td>
<td>129.0-149.5</td>
<td>47.17 ±3.24&lt;abc</td>
</tr>
</tbody>
</table>

Table 3: Effect of Aprimelast on pancreatic tissue Levels of TNF-alpha & IL-10

<table>
<thead>
<tr>
<th></th>
<th>control (-ve) group</th>
<th>control (+ve) group</th>
<th>Aprimelast group</th>
<th>L-argin (AP) group</th>
<th>L-argi+ aprim group</th>
<th>ANOVA</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ±SD</td>
<td>Range</td>
<td>Mean ±SD</td>
<td>Range</td>
<td>Mean ±SD</td>
<td>Range</td>
<td></td>
</tr>
<tr>
<td>TNF</td>
<td>4.38 ±1.41</td>
<td>2.0-6.0</td>
<td>4.5 ±1.51</td>
<td>2.0-6.0</td>
<td>4.38 ±1.41</td>
<td>2.0-6.0</td>
<td>168.5 ±16.33&lt;abcd</td>
</tr>
<tr>
<td>IL-10</td>
<td>71.91 ±1.43</td>
<td>70.2-74.34</td>
<td>71.64 ±1.10</td>
<td>70.2-73.0</td>
<td>72.21 ±1.75</td>
<td>70.0-74.9</td>
<td>42.53 ±7.30&lt;abcd</td>
</tr>
</tbody>
</table>

a:sig& control (-ve) group b:sig&control (+ve) c:sig&Aprimelast group d:sig& L-argin (AP)group
Figure (1): Photomicrograph sections of rat pancreatic tissue demonstrated the potential therapeutic effect of Aprimelast on histopathological changes in rats injected with L-arginine. All [Hematoxylin and Eosin (H&E) X 400], Histopathological Findings:

Fig. (A, B & C): Pancreatic slices from rats in groups I (-ve control group), II (+ve control group), and III (Aprimelast group) show typical pancreatic tissue topologies consisting of acinar cells that are triangular and have darkly pigmented basal nuclei and pink cytoplasm. The pancreatic islets of Langerhans are shown as clusters of cells.
DISCUSSION

Acute pancreatitis is a mortal disease & a major cause of critical care unit admissions globally. L-arginine has a long history of inducing experimental inflammatory AP (Chen et al., 2012; Wang et al., 2017). Although L-arginine is an amino acid that is just semi-essential that may be found in our diet., it is transformed to nitric oxide (NO), a gas that has a variety of physiological effects at modest quantities. It has been shown to induce destruction of pancreatic acinar cells as well as the development of necrotizing pancreatitis caused by a high dosage (Saka et al., 2004).

L-arginine was chosen for AP induction in the present research because it is a frequently used sports agent, is In addition to being non-invasive, the procedure causes biochemical and histological changes in the pancreas that are similar to those seen in people (Melo et al., 2010).

In the current study, two IP injections of L-arginine caused AP, as indicated by the increase amylase and serum lipase enzyme levels, as well as a higher blood glucose level that reveal affection of its exocrine &endocrine functions. These results agreed with Mirmaleket et al. (2016). Also, this agreed with the study of Abd El-Rahman, (2019) who discovered that IP injection of L-arginine increased serum lipase and amylase levels.

Raised serum lipase & amylase are important in detection of AP. Pancreatic enzymes being activated inside acinar cells and then released into the bloodstream may explain these increases, which are followed by a significant decrease in pancreatic enzyme production owing to severe pancreatic damage after 72 hours (Sidhu et al., 2012 and Sandhya et al., 2012).

The current findings indicate a condition of oxidative stress, as indicated by a large increase in MDA, a marker of lipid peroxidation, and a considerable decrease in antioxidant enzymes, GSH in acute L-arginine treated group compared to control.

These findings corroborated previously reported findings. (Lau and Bhatia 2012; Simsek et al., 2018). Abdel-Aziz et al. (2020) stated that increased MDA, myeloperoxidase (MPO), nitric oxide (NO) & decreased GSH activities in rats treated with L-arginine.

Oxidative stress has a crucial role in AP pathogenesis and its subsequent complications. Inflammatory cells generate free radicals which cause damage to cellular lipids and proteins (Kahraman et al., 2017). MDA is an excellent indicator of AP severity owing to its early elevation after 3–5 hours and subsequent return to its original after 12 hours(Abu-Hilal et al., 2006).

In the recent results, there was an increased plasma level (TNF-α) and decreased interleukin-10 (IL-10) in L-arginine administered rats as contrasted with the control.

This agreed with the study of Yu-ling and Li-min (2006) who observed a substantial rise in serum interleukin-1 and interleukin-6 levels in animals with severe AP produced by high dosages of L-arginine injection, which is directly linked to histopathological alterations.

The primary pro-inflammatory mediators are TNF-α, IL-1β and IL-6, according to several research. TNF-α triggers the intracellular protease (trypsinogen), which results in cellular necrosis and the stimulation of granulocytes and other pro-inflammatory mediators (Yang et al., 2007). TNF-α and IL-10 are both synthesized in different parts of the body. Antagonizes the TNF-α impact, which protects the body(Mayer et al., 2000).

In contrast to the control group, the AP group exhibited histological abnormalities (cellular vacuolization, deformed acinar structure, and inflammatory cell infiltration). This was corroborated by prior research (Chen et al., 2012; Wang et al., 2017).

Phosphodiesterase (PDE) enzyme is a
cyclic nucleotide which breaks up cyclic guanosine monophosphate (cGMP) to 5-GMP, a relatively inactive isomer that interferes with the NO signaling pathway. (Buchwalow et al., 2018). When faced with circumstances associated with oxidative stress and inflammation combination of NO with superoxide radicals (O2-) led to formation of nitrogen species and reactive oxygen (RNS and ROS) producing harm to the cell from which several illnesses, including AP is generated (Qader et al., 2003).

There is an FDA approved PDE4 inhibitor called Aprimelast in treatment of psoriasis by maintaining antiapoptotic and anti-inflammatory actions (Cory, 2014). It induces the CREB/ATF-1 family of transaction factors to accumulate intracellularly so that the inflammatory process can be stopped, and lipid peroxidation prevented (Erdogan et al., 2007).

The recent study dedicated those acute changes in pancreas induced by L-arginine had been blunted by Aprimelast. It is demonstrated by improvement of all tested parameters as well as attenuation of histopathological changes in Aprimelast + L-arginine treated group as compared L-arginine group.

The present study agreed with Imam et al. (2018) who reported that Aprimelast treatment significantly reduced oxidative damage& apoptosis in cardiotoxicity induced experimentally by doxorubicin rats.

Hatzelmann and Schudt, (2001) recorded that roflumilast and other PDE4 inhibitors had significant inhibition of reactive oxygen production under experimental studies.

The attenuating impact of aprimelast on AP produced by L-arginine may be explained by PDE4 inhibitors’ capacity to decrease cytokine production, neutrophilic degranulation, and TNF-driven neutrophil adhesion to endothelial cells, which is the main stage in the inflammatory cascade.

**CONCLUSIONS**

the current research concluded that Aprimelast (Otezla) can improve L-arginine triggered acute pancreatitis in rats through its antioxidant and anti-inflammatory effects.

**RECOMMENDATIONS**

- Further research should be conducted to determine the survival benefit of Aprimelast in acute pancreatitis in order to fully appreciate the drug’s clinical use.
- Clinical trials should be conducted to investigate Aprimelast therapeutic benefits.

**REFERENCES**


Chen, J.; Cai, Q.P.; Shen, P.J.; Yan, R.L.; Wang, C.M.; Yang, D.J.; et al. (2012): Netrin-1 protects against L-arginine-induced acute pancreatitis in mice. PLoS One, 7(9): e46201


Melo, C.M.; Carvalho, K.M.; Neves, J.C.; Morais, T.C.; Rao, V.S.;


Xu, H.; Wang, Y. and Luo, Y. (2021): Outline is a new target of EA treatment in the alleviation of brain injury and glial cell activation via...

Zhang, Fh.; Sun, Yh.; Fan, Kl.; Dong, Zb; Han, N.; Zhao, H. and Kong, L. (2017): Protective effects of heme oxygenase-1 against severe acute pancreatitis via inhibition of tumor necrosis factor-α and augmentation of interleukin-10. BMC Gastroenterology 17, 100 0651-4.
التأثير العلاجي المحتمل للأبريميلاست (أوتيزلا) على التهاب البنكرياس الحاد المحدث بواسطة الارجينين لـ الفئران

رباب شعيان الشافعي 
سطو. ن. الجندی 
أ/قسم الطب الشرعي والسموم، ب.قسم الفارماكولوجي، كلية الطب البشري، جامعة بنها، مصر.

التهاب البنكرياس الحاد هو مرض تهابي يهدد الحياة.
الأبريميلاست (أوتيزلا) هو دواء صغير فعال عن طريق الفم يثبط إنزيم الفوسفوداي استيراز 4. حتي الآن لا يتم اجراء ابحاث لمعرفة دوره في علاج التهاب البنكرياس الحاد المحدث.
هذه الدراسة هدفت إلى إثبات المحاولة لمعرفة دوره في علاج التهاب البنكرياس الحاد عن طريق حقن الفئران التجارب.

تم إعداد الارجينين لـ داخل الغشاء البريتوني 250 مجم/ كجم من وزن الجسم مفصولة بفترة ساعة.
أما المجموعة المعالجة تم إعطائها الأبريميلاست 20 مجم/ كجم من وزن الجسم لمدة خمسة أيام متتالية بعد حقن الارجينين.

تم قبض العينات من الدم بعد الإجراءات السابقة. في نهاية الدراسة تم اجراء ابحاث لقياس مستوى الجلوکوز والليباز والأميلاز ومعاملات الأكسدة.

تتناول الأپتافات ونتائج الدراسة 춮 البينكيراس على فئة الارجينين، وفترة التثبيت ونسبة النجا.

وطفر نتائج هذه الدراسة إلى أن الأبريميلاست قد يكون له تأثير علاجي مفيد على التهاب البنكرياس الحاد المحدث بواسطة الارجينين، لـ الفئران التجارب البيضاء بسبب خصائصه المضادة للالتهاب والأكسدة.