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HISTOLOGICAL STUDY OF THE POSSIBLE PROTECTIVE EFFECT OF ALLOPURINOL ON EXPERIMENTALLY INDUCED PANCREATITIS OF ADULT ALBINO RATS

Thesis

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(Histology)

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ABSTRACT

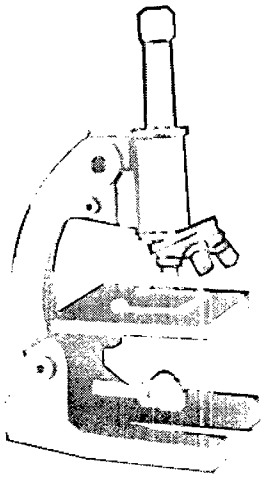
Key words: L-arginine- pancreatitis – allopurinol -rat

Allopurinol is a drug which provides an effective therapy in the treatment of primary hyperuricemia of gout and that secondary to haematological disorders or antineaplasic therapy. Many previous reports have pointed out the protective effects of allopurinol on various forms of ischemic and inflammatory diseases. The aim of this study was to evaluate the possible protective effect of allopurinol on the experimentally L-arginine induced pancreatitis of adult male albino rat employing histological and histochemical methods. Sixty adult male albino rats were selected and divided into two groups; control group and experimental group. The experimental group was subdivided into six subgroups; the first three subgroups were injected intra-peritoneally with L-arginine for one, two and four weeks to induce pancreatitis, the second three subgroups were injected likewise the first three subgroups group but treated with allopurinol before the L-arginine injection. Light microscopic examination of the pancreas of animals that received L-arginine, showed variable degrees of distorted acinar pattern. The blood vessels showed variable degrees of dilatation and congestion, with peri-vascular mononuclear cellular infiltration. The cytoplasm of both exocrine and endocrine parts appeared vacuolated. The connective tissue septae were markedly increased in thickness with advanced periods of L-arginine injection. The collagen fibers were progressively increased, particularly around the congested blood vessels and the dilated ducts, and also extended in-between the lobules and acini of the pancreas. Animals that were pretreated with allopurinol showed that the normal pancreatic architecture was preserved and the inflammatory cells and cytoplasmic vacuoles were markedly decreased. In L-arginine injected groups, there was a gradual decrease in the succininc dehydrogenase activity that became apparently very weak at the end of the experiment. The acid phosphatase activity was markedly increased after two weeks of L-arginine injection, however it became markedly decreased at the end of the experiment. In the groups that received allopurinol before L-arginine injection,

normal moderate activity of both the succininc dehydrogenase and acid phosphatase was noticed.

Conclusion: prophylactic allopurinol treatment exerted a protective effect against the development of histopathological degenerative changes of L-arginine.

يعد عقار الألوبيورينول هو العقار المتميز فى علاج حالات النقرس الأولية والثانوية التى قد تنتج عن الاضطرابات الدموية أو مضادات التورم. وقد أثبتت العديد من الدراسات الدور الوقائى الفعال لهذا العقار فى علاج أمراض الالتهابات المختلفة. وقد كان الهدف من هذا البحث هو دراسة الدور الوقائى المحتمل لعقار الألوبيورينول فى علاج التهاب البنكرياس المستحدث معملياً بحقن مادة الإل-أرجينين لفئران التجارب البيضاء البالغة. وقد استخدم فى هذا البحث ستون فأراً من ذكور فئران التجارب البيضاء البالغة، وتم تقسيمهم إلى مجموعتين رئيسيتين، المجموعة الأولى (المجموعة الضابطة) ، والمجموعة الثانية (مجموعة التجارب) التى قسمت إلى ست مجموعات فرعية، حقنت الثلاث مجموعات الأولى بمادة الإل-أرجينين يومياً لمدة أسبوع، أسبوعين وأربعة أسابيع بالترتيب. أما المجموعات الثلاث الثانية فقد عولجت بعقار الألوبيورينول قبل الحقن بمادة الإل-أرجينين بنصف ساعة وذلك يومياً لمدة أسبوع، أسبوعين وأربعة أسابيع بالترتيب. لوحظت الأعراض الخلوية لمرض التهاب البنكرياس فى المجموعات التى تم حقنها بمادة الإل-أرجينين؛ حيث ظهر احتقان واتساع لبعض الأوعية الدموية، كما ظهرت العديد من التجويفات الهوائية فى سيتوبلازم خلايا حويصلات البنكرياس وكذلك خلايا جزر لانجرهانز. سجلت زيادة تدريجية فى الألياف الكولاجينية حول الأوعية الدموية وامتدت بين الفصيصات والمعنبات. فى مراحل متأخرة من التجربة، اضمحلت تماماً أجزاء من البنكرياس تاركة مواد متحللة وفقدت الخلايا الترتيب والشكل الطبيعى لها. وقد سجل انخفاض ظاهرى وتدريجى فى نشاط انزيم السكسينيك دى هيدروجينيز حتى وصل الى ضعيف جدا فى نهاية التجربة، وهذه نتيجة طبيعية نظراً لتآكل الخلايا. وبدراسة نشاط انزيمات الفوسفاتيز الحمضية، وجد أنه ازداد ظاهريا بعد أسبوعين من إعطاء مادة الإل-أرجينين، وذلك نتيجة لحدوث التهاب حاد فى البنكرياس، ثم انخفض انخفاضا ملحوظاً فى نهاية التجربة، وهذه نتيجة طبيعية نظراً لتآكل الخلايا. أما فى الحيوانات التى عولجت بعقار الألوبيورينول فقد أظهرت العينات التركيب الهستولوجى والهستوكيميائى للبنكرياس الطبيعى، حيث وجد أن الخلايا الالتهابية والتجويفات السيتوبلازمية قد قلت بدرجة كبيرة. لذلك نستنتج أن العلاج بعقار الألوبيورينول قد أدى إلى حماية خلايا البنكرياس وذلك بتقليل الالتهاب وتقليل التغيرات التلفية لمادة الإل-أرجينين.



INTRODUCTION

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Acute pancreatitis is a life threatening disease with putatively high mortality rates, particularly in the setting of systemic inflammatory response and multiple organ failure when super-infection of necrosis occurs. Although there are many clinical scores that are widely accepted to predict the disease prognosis, current medical treatment is still based upon the state of the art intensive care treatment largely unrelated to the pathogenesis of the disease. chronic pancreatitis resulting from the repeated acute inflammatory episodes is a progressive and irreversible disease characterized by loss of pancreatic exocrine and endocrine functions, loss of parenchymal cells and fibrosis which contributes to the irreversibility of the disease ***(Grady et al., 1999 , Felderbauer et al., 2005 and Lankisch and Lerch 2006).***

Pancreatitis has a wide variety of clinical etiologies including alcoholism, biliary stones, viral infections as mumps and hepatitis types A&B, metabolic disorders such as hyperlipidemia, hypercalcemia and structural abnormalities. In addition, retrograde cholangio-pancreatography (ERCP) that is continuously used in the diagnosis and management of pancreatico-biliary diseases can cause pancreatitis. Certain medications especially esterogens, corticosteroids, thiazide diuretics and azathioprine may also cause acute pancreatitis. Moreover, it was reported that obesity is a risk factor in the development of severe acute pancreatitis ***(Topazian and Gorelick, 2003 and Martinez et al., 2006).***

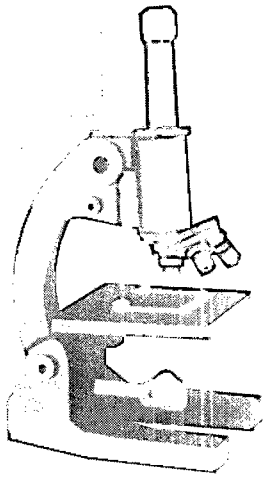
Allopurinol is an inhibitor to the enzyme xanthine oxidase (XO), the enzyme which is involved in the production of uric acid, as it catalyzes the conversion of hypoxanthine into xanthine and xanthine into uric acid,

which are the terminal biochemical reactions of the purine degradation pathway. Therefore, any defect in purine metabolism results in an increase in the level of uric acid, and this eventually will lead to deposition of urate monohydrate crystals in joints, resulting in gouty arthritis ***(Smith and Reynard, 1995, Hardman et al., 2001 and Tamta et al., 2006).***

Inhibition of XO enzyme accounts for the major pharmacological effects of allopurinol which provides an effective therapy for both the primary hyperuricemia of gout and that secondary to hematological disorders or antineoplastic therapy ***(Smalley et al., 2000 and Helms et al., 2006).***

Many previous reports have pointed out the protective effects of allopurinol on various forms of vascular injuries, inflammatory diseases and chronic heart failure, both in experimental animal models and in small scale human clinical trials ***(Harrison, 2004 and Berry and Hare, 2004).***

The present work was done to study the possible protective effect of allopurinol on the histopathological changes induced by L-arginine injections in adult albino rat as an experimental model of acute and chronic pancreatitis.



LITERATURE REVIEW

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An anatomical review of the pancreas

The pancreas is an abdominal gland which lies retroperitoneally in the upper part of the abdomen overlying the spine. In human, it is about 80gm in weight, and about 15 cm in length, and is divided into two major parts, an *exocrine* which accounts for about 80% of the total glandular volume, and an *endocrine* which makes up approximately 2% of the gland. Nerves, blood vessels, and other tissues constitute the remaining portion of the pancreas. Macroscopically, there are four major regions in the pancreas: head, neck, body and tail, based on the anatomical position in the gland ***(Thomson and Shaffer, 2000 and Chowdhury, 2002).***

The head of the pancreas is the broadest part which is moulded in and fills completely the C-shaped concavity of the duodenum. The anterior surface of the head is related to the transverse mesocolon, while the posterior surface is deeply indented by the terminal part of the common bile duct, the inferior vena cava and the renal veins. *The neck* is the narrow band of pancreatic tissue which joins the body with the head, its anterior surface is related to the lesser sac and pylorus, while its posterior surface is related to the portal vein. *The body* of the pancreas extends from the neck to the left, sloping slightly upwards, its anterior surface is related to the lesser sac, while its posterior surface is related to the structures which form the stomach bed. *The tail* of the pancreas is narrow and passes forward and to the left, and it usually reaches the inferior part of the gastric surface of the spleen ***(Bailey et al., 2003 and Sinnatamby, 2001).***

Blood supply, lymphatic drainage and nerve supply of the pancreas:

The *head* receives branches from the superior and inferior pancreatico-duodenal arteries, whereas the *neck, body and tail* of the pancreas receive their blood supply mainly from the splenic artery, The venous blood is drained either directly into the portal vein or indirectly through the splenic and the superior mesenteric veins. *Lymphatics* from the pancreas follow the coarse of the arteries. The head drains from its upper part into the coeliac group, and from its lower part into the superior mesenteric group of pre-aortic lymph nodes To the left of the neck, the pancreas drains into the pancreatico-splenic nodes which accompany the splenic artery ***(Fawcett and Jensh, 2002 and Sinnatamby, 2001).***

The pancreatic acini and the islets of Langerhans are innervated by unmylinated nerve fibers that arise from the coeliac plexus. The nervous connection of the pancreas plays a role in the control of pancreatic secretion, however this nervous control is thought to be of less importance than its regulation by hormones released by the entero-endocrine cells of the duodenal mucosa ***(Schwartz et al., 1994 and Sinnatamby, 2001).***