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Research Article

Modulation of L-arginine-induced acute pancreatitis by meloxicam and/or L-carnitine in rats

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ABSTRACT

Background: Acute pancreatitis (AP) is an inflammatory disease, where oxidative stress, subsequently inflammatory mediators activation play a pivotal role. Currently, no definite treatment exists and therapy is mainly supportive that directed to inhibit local pancreatic injury and systemic inflammatory complications. This study is presented to explore whether anti-inflammatory and/or antioxidant drug could ameliorate L-arginine-induced AP.
Methods: Rats were sub-grouped randomly into five groups. Control group, AP was provoked by a single intraperitoneal injection of L-arginine (250 mg/100g), rat treated with meloxicam (4 mg/kg, IP), animals treated with L-carnitine (500 mg/kg, IP), and rats were treated with both meloxicam and L-carnitine. All treatments were once daily for 7 consecutive days and started 1 hr later after L-arginine administration. Serum and tissues samples were prepared for biochemical analysis. Histopathological examination for the other pancreatic tissues was done.
Results: L-arginine significantly elevated serum activity of amylase and lipase enzymes, while notably reduced serum calcium level. Moreover, L-arginine markedly increased the pancreatic tissues content of tumor necrosis factor-α, malondialdehyde, and nitric oxide. In addition, L-arginine significantly increased pancreatic activity of myeloperoxidase, while markedly depleted glutathione level. Treatment with either meloxicam or L-carnitine significantly attenuated L-arginine-induced biochemical changes. On the other hand, co-administration of both meloxicam and carnitine has an ameliorative effect greater than each drug alone.
Conclusion: Treatment with both meloxicam and L-carnitine is a more effective than each of them alone which is attributed to augmentation their antioxidant, anti-inflammatory effects.

Keywords: Acute pancreatitis, Inflammation, Oxidative stress, Tumor necrosis factor-α

INTRODUCTION

Acute pancreatitis (AP) is an inflammation of the pancreatic gland that ultimately may lead to a severe systemic inflammatory response. AP is evolved by diverse factors but ethanol abuse, and bile duct obstruction still represent the major causes.[1] Although the mechanism of AP development is still divisive, the early event of AP is the dramatic release of ROS with subsequent development of oxidative stress. This condition plays a crucial and decisive role in initiation and prognosis of AP. These effects are contributed to direct oxidative damage to the biomolecules lipids, proteins and DNA and modulation of redox-sensitive transcription factors, such as neuclear factor-κB (NF-κB).[2]

L-carnitine is a powerful antioxidant drug that has potent beneficial effect in several pathological conditions. The protective effect of L-carnitine for tissues is located in its ability to stabilize cell membrane against free radicals and improve the repair of phospholipid bilayer damaged by free radicals.[3]

Meloxicam, selective cyclooxygenase-2 (COX2) inhibitor, is a potent anti-inflammatory drug that belongs to NSAIDs. Action of meloxicam is mediated mainly by downregulating the expression of NF-κB with subsequent reduction of tumor necrosis factor-α (TNF-α) and other inflammatory mediators.[4]

L-arginine model is one of the most widely used experimental models of AP that mimic the human form of the disease and used to study the various biochemical and histological alterations that closely resemble the human phenotype in many facets.[5]

Based on the previous information, this study has been conducted in an attempt to explore the role of meloxicam or/and L-carnitine treatment against L-arginine-induced AP in male Swiss albino rats.

METHODS

Drugs and chemicals

Meloxicam (Amoun CO, Cairo, Egypt), L-carnitine (MEPACO CO, Cairo, Egypt), thiobarbituric acid, Ellman's reagent and 1,1′,3,3′-tetramethoxypropane were obtained from Sigma-Aldrich (St. Louis, MO, USA). Amylase and lipase kits were obtained from Quimica Clinica Aplicada (Amposta, Spain) while calcium kit obtained from Biodiagnostic Company, Egypt. All other chemicals were of the finest analytical grade.

Animals

Male Swiss albino rats weighing 150-200 g were kept in the animal house of the Faculty of Medicine, Assiut University. The animals were housed 1 week to adapt with the environmental conditions. Rats were fed a standard diet and allowed free access to water.

Experimental design

A total of 40 rats were randomly divided into 5 groups, 8 rats in each (n=8).
Group I: Animals, which administered normal saline once daily for 7 consecutive days, were served as control.
Group II: AP was evoked by a single intraperitoneal injection of L-arginine in a dose of 250 mg/100 g body weight.[5]
Group III: Rats were started to be injected with meloxicam in a dose of (4 mg/kg, IP) once daily for 7 consecutive days.[6]
Group IV: Animals were started to receive L-carnitine in a dose of (500 mg/kg, IP) once daily for 7 consecutive days.[7]
Group V: Rats were started to receive both meloxicam and L-carnitine as previously mentioned.

Treatment with meloxicam or/and L-carnitine was started 1 hr following L-arginine injection. 7 days following L-arginine injection, animals were anesthetized with light ether. Blood samples were withdrawn by heart puncture, and serum separation was performed by centrifugation at 2000 g for 10 mins at 4°C. After that the pancreas was cut into small pieces and then homogenized in ice-cold 0.15 M KC1 (w/v) using potter Elvejheim homogenizer (Berlin, Germany) to give a final concentration of 20% (w/v). The extra five pancreata from all groups were kept in 10% formalin and subjected to histological examination.

Evaluation of amylase and lipase activity

Assay of serum amylase activity was done using method described by Klein and Foremann.[8] While lipase activity was determined according to the method depicted by Lott et al.[9]

Determination of plasma calcium level

Plasma calcium concentration was measured according to the method described by Zerwekh and Nicar.[10]

Measurement of TNF-α content

Pancreatic content of TNF-α was determined with enzyme-linked immunosorbent assay kit (Wkea med supplies Corp, Changchun Jilin, China).

Determination of oxidative stress markers in pancreatic tissues

Determination of reduced glutathione (GSH)

GSH determined to utilize Ellman reagent.[11] Equal volumes of pancreatic homogenate and 10% trichloroacetic acid were mixed and centrifuged at 750 g for 5 mins. 0.1 ml of supernatant was mixed with 1.7 ml of 0.1 M potassium phosphate buffer pH 8. Then 0.1 Ellman's reagent was added. The optical density was measured at 412 nm against blank.

Measurement of lipid peroxidation

An aliquot of 0.5 ml of tissue homogenate was added to 3 ml of 1% orthophosphoric acid and 1 ml of 0.6% thiobarbituric acid, incubated in a water bath at 95°C for 45 mins. After cooling, 4 ml of n-butanol was added to each tube and mixed vigorously then centrifuged at 2000 rpm for 10 min. the absorbance was determined in the resultant pink color of n-butanol layer at 535 nm and 520 nm. The difference in optical density of the sample between both wavelengths was used as a measure of malondialdehyde (MDA) content.[12]

Measurement of nitric oxide (NO)

In dry test tube, 0.1 ml sample or standard was added to 1 ml of sulfanilamide, mixed well and allowed to stand for 5 mins. 0.1 ml of N-(1-naphthyl) ethylenediamine was added, mixed well, and allowed to standing for 5 mins. The absorbance was recorded against absorbance of blank at 540 nm.[13]

Assessment of myeloperoxidase (MPO) activity

MPO activity assessed by method of Manktelow and Meyer.[14] In brief, pancreatic MPO was extracted with hexadecyltrimethylammonium bromide. Then, In the presence of hydrogen peroxide, dimethoxybenzidine was oxidized by MPO, and the optical density was measured at 460 nm.

Histopathological examination

Pancreata were kept in 10% formalin prior to staining with hematoxylin and eosin. The tissue sections were then

examined microscopically. The examination was done blind by the histologist.

Statistical analysis

Statistical analysis was done using GraphPad Prism 5.0 software (GraphPad, San Diego, Ca., USA). Data were represented as mean ± standard error. Multiple comparisons were carried out using one-way ANOVA with Tukey-Kramer test as multiple comparison post ANOVA test. $p<0.05$ was selected to refer to statistical significance.

RESULTS

Serum amylase and lipase activity

Injection of L-arginine markedly increased serum amylase and lipase activity compared with control rats. However, treatment with meloxicam or L-carnitine after L-arginine administration significantly decreased serum amylase and lipase activity with respect to L-arginine group. Furthermore, co- administration of the two drugs following L-arginine resulted in significant decrease in serum amylase and lipase activity compared with meloxicam or L-carnitine treated group (Figures 1 and 2).

Serum calcium level

The pancreatic level of calcium was found to be decreased in a significant manner the following administration of L-arginine compared with control animals. Meloxicam or L-carnitine given after L-arginine markedly elevated pancreatic calcium level with respect to L-arginine administered group. Moreover, animals treated with a combination of meloxicam and L-carnitine after L-arginine injection were found to have a great restoration of pancreatic calcium level compared with either meloxicam or L-carnitine treated animals (Figure 3).

Effect of meloxicam or/and L-carnitine on pancreatic TNF-α

Pancreatic tissue content of TNF-α was found to increase in a significant manner following administration of L-arginine compared with control animals. Meloxicam or L-carnitine given after L-arginine markedly reduced pancreatic content of TNF-α with respect to L-arginine administered group. Moreover, rats that received combination of meloxicam and L-carnitine were found to have a huge reduction in pancreatic content of TNF-α compared with either meloxicam or L-carnitine treated animals (Table 1).

Effect of meloxicam or/and L-carnitine on pancreatic oxidative stress parameters

Administration of L-arginine provoked a substantial depletion of GSH content with respect to control rat. Vice versa, MDA

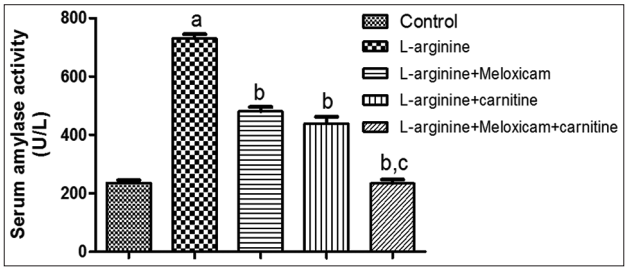

Figure 1: Effect of meloxicam or/and L-carnitine treatment on serum activity of amylase enzyme. Results are expressed as mean ± standard error, (a, b and c) significant difference from control, L-arginine and meloxicam, respectively (n=10) at $p<0.05$.

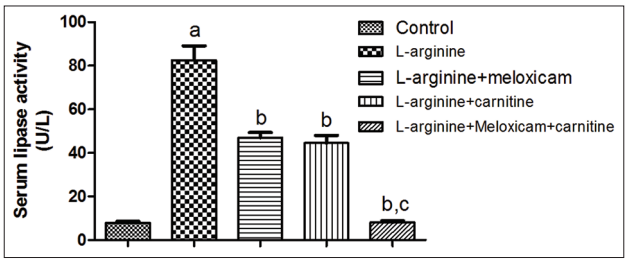

Figure 2: Effect of meloxicam or/and L-carnitine treatment on serum activity of lipase enzyme. Results are expressed as mean±standard error, (a, b and c) significant difference from control, L-arginine, and meloxicam, respectively (n=10) at $p<0.05$.

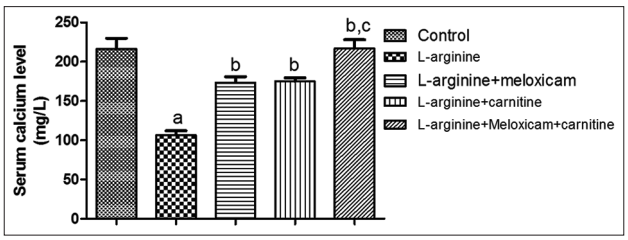

Figure 3: Effect of meloxicam or/and carnitine treatment on serum levels of calcium. Results are expressed as mean±standard error, (a, b and c) significant difference from control, L-arginine and meloxicam, respectively (n=10) at $p<0.05$.

content was found to increase significantly in L-arginine challenged rats compared with control rats. Treatment with meloxicam or L-carnitine after L-arginine administration significantly restored GSH content and notably reduced the MDA content compared with rat subjected to L-arginine injection. Treatment with combination therapy after L-arginine injection resulted in an enormous elevation of GSH content and a huge reduction of MDA content compared with meloxicam or L-carnitine treated rat (Table 1).

Effect of meloxicam or/and L-carnitine on pancreatic MPO activity

Administration of L-arginine evoked a fundamental elevation of pancreatic MPO activity compared with control

Table 1: Effect of meloxicam or/and L-carnitine treatment on pancreatic content of TNF-α, GSH, MDA, NO and MPO activity in rat challenged with L-arginine.

Parameters	Control	L-arginine	L-arginine+ meloxicam	L-arginine+ carnitine	L-arginine and meloxicam+ carnitine
TNF-α (ng/g tissue)	14.93±0.802	52.25±4.203[a]	35.08±3.164[b]	28.35±1.693[b]	15.98±1.008[a,b]
GSH (µmol/g tissue)	2.854±0.213	1.017±0.083[a]	1.619±0.08[b]	1.69±0.156[b]	3.73±0.12[a,b]
MDA (nmol/g tissue)	15.43±1.408	36.70±1.204[a]	26.26±1.193[b]	24.95±1.453[b]	12.43±0.943[a,b]
NO (µmol/g tissue)	1.864±0.15	5.649±0.534[a]	3.801±0.174[b]	3.59±0.256[b]	1.93±0.191[a,b]
MPO (OD/g tissue)	0.102±0.008	0.255±0.013[a]	0.171±0.01	0.159±0.005[b]	0.109±0.009[a,b]

Results are expressed as mean±SE, (a,b and c) significant difference from control, L-arginine and meloxicam, respectively (n=10) at $p<0.05$, TNF-α: Tumor necrosis factor-α, MDA: Malondialdehyde, NO: Nitric oxide, MPO: Myeloperoxidase, SE: Standard error

rats. Treatment with either meloxicam or L-carnitine the following L-arginine administration significantly decreased MPO activity compared to L-arginine challenged animals. Moreover, co-administration of the two drugs resulted in a great reduction of MPO activity with respect to meloxicam or L-carnitine group (Table 1).

Effect of meloxicam or/and L-carnitine on pancreatic NO content

Injection of L-arginine-induced marked elevation in the pancreatic content of NO compared to control group. Treatment with either meloxicam or L-carnitine after L-arginine significantly reduced NO content compared to L-arginine challenged animals. In addition, combination treatment after L-arginine administration resulted in a huge reduction of NO content compared with meloxicam or L-carnitine treated animals (Table 1).

Histological examination

Control rats revealed no histopathological alteration and normal histological structure of the islands of Langerhans cells as endocrine portion as well as the acini and ducts system as exocrine portion (a). Pancreatic tissues of L-arginine treated rats showed ductal cystic dilatation with sever congestion in the blood vessels (b). Meloxicam treated animals showed mild congestion of blood vessels associated with perivascular edema (c). In carnitine treated animals, there was a ductal system associated with mild cystic dilatation (d). Animals treated with both meloxicam and carnitine exhibited no histopathological alteration (e) (Figure 4).

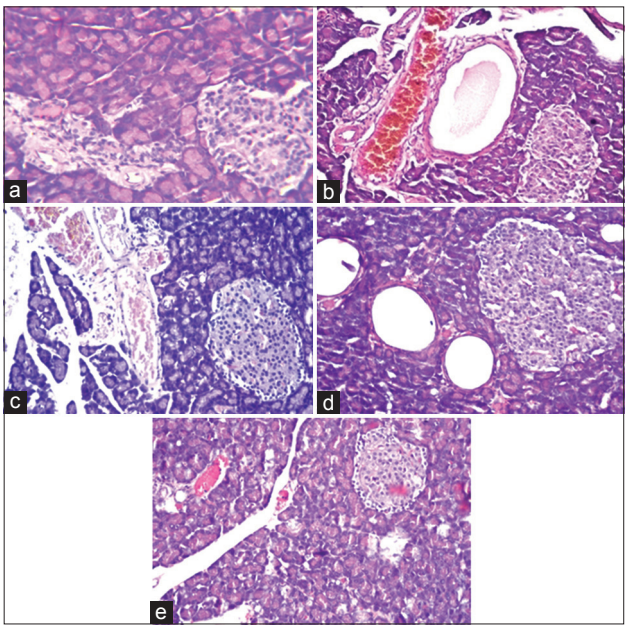

Figure 4: (a) Pancreatic tissue section of control rats showing normal histological structure. (b) Pancreatic section from L-arginine challenged rats showed ductal cystic dilatation with sever congestion in the blood vessels. (c) Pancreatic tissue section from animals treated with meloxicam revealing mild congestion of blood vessels associated with perivascular edema. (d) Pancreatic section from rats treated with L-carnitine exhibiting ductal system associated with mild cystic dilatation. (e) Pancreatic section from animals received both meloxicam and carnitine showing no histopathological alteration (hematoxylin and eosin, ×400).

DISCUSSION

AP is a common disorder with potentially devastating consequences. Although the pathogenesis of AP is unclear, the intrapancreatic activation of digestive enzymes that resulted in autodigestion and tissue necrosis stills the major stimulus of the disease.[15]

The dramatic release of reactive oxygen species (ROS), consequently activation of pro-inflammatory cytokines as TNF-α and infiltration of polymorphnuclear within the pancreas are thought to be early and crucial events in the evolution of AP.[16]

In fact, L-arginine pancreatitis model is one of the most common animal paradigms used to study the biochemical and histological alterations that characterize the disease. The mechanism whereby L-arginine provoked AP involves the production of free radicals that distort the cellular membranes of zymogen granules, thus releasing the digestive enzymes and cellular proteins into the interstitium.[17]

Meloxicam is a member of NSAIDs and selectively inhibits COX-2 enzymes. It can be used effectively for the treatment of many pathological conditions characterized by inflammatory disorders.[18] Carnitine has shown pleiotropic beneficial effects in many toxic and pathological disorders due to its potent antioxidant effect.[3]

There are several previous studies stated that the forerunners for L-arginine model of AP are excess generation of ROS with subsequent activation of pro-inflammatory mediators. This notion warranted our attention to utilize meloxicam and/or L-carnitine in the present work.

The model of AP was well-characterized histopathologically and biochemically. Histopathologically, L-arginine-induced ductal cystic dilatation with sever congestion in the blood vessels. This microscopical result is confirmed by marked elevation of amylase and lipase activity, following L-arginine injection. This might be ascribed to uncontrolled generation of free radicals, which are directly attacked lipids, proteins in the membranes of zymogen granules and cause their dysfunction. Thus, the membrane permeability of zymogen granules is defected with subsequent infiltration of large amount of amylase and lipase into pancreatic tissues with subsequent autodigestion.[19]

Hypocalcemia that has been reported following L-arginine administration is attributed to the enhanced activity of lipase enzyme, which improves the degradation of triglycerides into glycerol and free fatty acid. The latter is coupled with calcium to form a complex thus decreasing the free calcium form.[20]

In the present work, pancreatic tissues content of TNF-α is notably increased following L-arginine administration. This may be contributed to excess generation of ROS that activate NF-κB, with subsequent upregulation of various inflammatory cytokines particularly IL-1β and TNF-α.[21] In this way, L-arginine elevates TNF-α level in pancreatic tissues. In the conducted study, L-arginine markedly increased the pancreatic content of NO compared with the normal rats. Takacs et al.[22] have reported that endogenous NO is an important inflammatory mediator that is crucial for the early evolution of L-arginine pancreatitis. An elevated level of NO is ascribed to induction of inducible NO synthase that evoked by inflammatory cytokines. In addition, NO reacts with superoxide anion to form peroxynitrite that can react directly with lipid, protein and DNA resulting in cellular dysfunction and tissue injury.[23]

The pancreatic MPO activity has been greatly increased after L-arginine injection compared with control rats. This can be attributed to the high generation of ROS that sequestrated polymorph nuclear into the pancreatic tissues. Leukocytes are responsible for MPO production. Therefore MPO activity is a good indicator for leukocytes infiltration.[5]

Depletion of reduced GSH in pancreatic tissue is a hallmark during the initial phase of AP.[24] In this work, L-arginine markedly decreased the pancreatic content of reduced glutathione along with increased MDA level. This may be due to dramatic generation of ROS following L-arginine injection resulted in great depletion and exhaustion of endogenous antioxidant defense mechanism including reduced glutathione.[25] Furthermore, excessive ROS apparently enhances oxidation of cellular membrane biomolecules including polyunsaturated fatty acid resulted in formation of MDA, which is one of the end products of lipid peroxidation.[5]

Regarding such facts, drugs that possess antioxidant and anti-inflammatory actions could interfere with the underlying molecular mechanism of AP in an attempt to achieve improvement or complete curative of this pathological condition.

Treatment with L-carnitine after L-arginine injection significantly decreased and mitigated all the histological alterations. L-carnitine also attenuated all pathological changes in biochemical parameters previously provoked by L-arginine. Both plasma amylase and lipase enzymatic activities were significanly decreased. Additionally, it was shown to restore and correct hypocalcemia associated to AP. L-carnitine effect on serum amylase and lipase activity may be based on its powerful antioxidant effects, consequently stabilization of cell membranes of zymogen granules against free radicals and enhancement the repair of phospholipid bilayer dysfunction caused by free radicals attack.[3,26]

In addition, L-carnitine via ROS scavenging effect inhibits elevation in cytosolic Ca^{2+} intracellularly with subsequent premature activation of trypsinogen that lead to tissue necrosis.[27]

Free fatty acids that generated by the action of lipase enzyme on circulating and tissues triglycerides could improve pancreatic and fat tissue necrosis.[28] Therefore, the protective effects presented by L-carnitine could partially ascribe to its popular ability to transport non-esterified fatty acids into mitochondria to be oxidized through beta-oxidation. This lead to protection of pancreatic tissue against the harmful effects of free fatty acids.

Restoration of hypocalcemic condition may be attributed to stabilization of zymogen granules membrane by scavenging ROS, consequently inhibits release of lipase, which is the restricted cause of hypocalcemia via splitting triglycerides.

Treatment with L-carnitine notably decreased TNF-α compared with animals received L-arginine alone. This effect could be explained by virtue of L-carnitine in correction of redox unbalance that causes not only oxidative damage but also acts as intracellular signal in inflammatory processes, particularly up-regulating pro-inflammatory genes.[29]

Treatment with L-carnitine significantly reduced pancreatic tissues content of NO and MPO activity with respect

to L-arginine-treated rats. This may be attributed to ROS scavenging effect of L-carnitine because ROS sequestrated leukocyte into affected tissues and activated pro-inflammatory cytokines. In addition, leukocytes release MOP enzyme and cytokines that activate iNOS enzyme.[30] Furthermore, L-carnitine plays a protective role in inflammatory conditions via reduction of superoxide anion synthesis that lead to decrease production of another ROS that derived from superoxide radical.[31] So that, L-carnitine treatment following L-arginine markedly increased the pancreatic content of reduced glutathione and notably inhibited lipid peroxidation.

With respect to meloxicam, it was found that treatment with meloxicam resulted in significant reduction of serum amylase and lipase level along with respected restoration of hypocalcemia compared with arginine-treated animals. This may be attributed to early known and well-described role of meloxicam in an inflammatory condition. In the current work, meloxicam significantly reduced pancreatic content of TNF-α. This effect mainly based on downregulation of NF-κB that up-regulates gene of inflammatory mediators, such as TNF-α.[4]

In addition, downregulation of inflammatory mediators, which activates iNOS enzyme, by meloxicam may be responsible for reduction of pancreatic NO content in rats that received meloxicam following arginine compared with arginine-treated animals. Based on the anti-inflammatory effect of meloxicam the pancreatic activity of MPO notably inhibited.[26]

In the present study, the antioxidant effect of meloxicam was manifested by correction of redox imbalance in an endogenous system including induction of GSH and inhibition MDA contents of pancreatic tissue.

Co-administration of both meloxicam and L-carnitine has greater benefits than monotherapy in AP course. This is confirmed by the results that unravel significant difference in the degree of correction of pathological changes between animals subjected to combination therapy and that received monotherapy. These results are a good indicator that combination therapies can affect and target several signaling molecules through different steps during evolution and prognosis of AP.

CONCLUSION

Therapy with meloxicam or L-carnitine alone has limited effects in a rat model of AP, but combination therapy of these agents is more effective through potentiating the effect of each other.

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