SUMMARY

Introduction: The most important factor in the pathogenesis of acute pancreatitis is the stimulation of the trypsinogen and conversion of it to the trypsine. Moreover stimulation of the lipid peroxidation, free oxygen radicals and nuclear factor kappa (NF-κB), tumor necrosis factor-alpha (TNF-α), and various interleukins may play role in the pathogenesis.

Aim: We investigated the roles of the free oxygen radicals, lipid peroxidation, protective enzymes, cytokines and NF-κB on the pathogenesis of the L-arginine induced acute pancreatitis and the roles of the amiphostine, bortezomib, octreotide, and vitamin E and C on the prevention of acute pancreatitis.

Materials and methods: Animal ethic committee approval was received. Study was partially supported by Adnan Menderes University funds. 47 Wistar type adult female rats were enrolled to the study. The rats with mean weight of 246±35 g were divided to 7 groups. Serum saline was given to the first (control) group intraperitoneally (ip), 5 g/kg L-arginine was given to the second group, 5 g/kg L-arginine 30 minutes after i.p. 200 mg/kg vitamin E was given to the third group, 5 g/kg L-arginine 30 minutes after ip. 200 mg/kg vitamin C was given to the fourth group, g/kg L-arginine 30 minutes after ip. 200 mg/kg amiphostine was given to the fifth group, 5 g/kg L-arginine 30 minutes after ip. 1 mg/kg bortezomib was given to the sixth group, sc octreotide was given to the seventh group 30 minutes before 5 g/kg L-arginine and 30, 270 and 510 minutes after 5 g/kg L-arginine. The levels of pancreatic enzymes such as lipase and amylase were evaluated from tail vein spectrophotometrically before and after study. All animals were sacrificed by cervical dislocation 24 hours after last injection. Then pancreas was washed with serum saline and then divided into two parts. One part of them was used for pathological examination and the other part was saved in the -80 ^{0}C until analysis for the examination with spectrophotometrically method of hydrogen peroxide (H_2O_2), total glutatyon (GSH), protective enzymes from free oxygen radicals including catalase, superoxide dismutase (SOD), glutatyon peroxidase (Gpx), malondialdehyde (MDA), marker of lipid peroxidation, and for the examination with ELISA of IL-6, TNF-α and IL-1β. After making homogeneity, they were examined. In the first part of the pancreatic tissue, histopathologically inflammation, edema, necrosis with appropriate scoring systems, and immünohistochemically NFκB staining were examined under light microscopy. Results were compared with the Kruskal-Wallis and Mann-Whitney U tests using SPSS 13.0 and. Values less than $p<0.05$ were accepted as significant.

Results: There was no difference for pancreatic enzymes between before and after study and groups ($p>0.05$). The levels of TNF-α, IL-1β and Gpx were not different between groups ($p>0.05$). L-arginine increased the levels of H_2O_2 ($p<0.005$), MDA ($p<0.05$), and NF-κB ($p<0.005$) compared to the control group. MDA levels in only L-arginine+amiphostine group were not different from the control group ($p>0.05$). When compared with the control group, octreotide ($p<0.005$), vitamin C ($p<0.001$), and bortezomib ($p<0.05$) increased SOD levels. The GSH levels in L-arginine+vitamin C and L-arginine+octreotide groups were not lower than the control group ($p>0.05$). Catalase levels only in L-arginine+vitamin E group was not lower than the control group ($p>0.05$), but the its protective effect in pancreatic tissue was not detected. While bortezomib decreased IL-6 levels ($p<0.05$), it didn't change NF-κB compared to the control group ($p>0.05$). Histopathologically, L-arginine increased the edema ($p<0.001$), inflammation ($p<0.05$), necrosis ($p<0.005$), and the total pathologic score in pancreatic tissue, compared to the control group. Vitamin E and amiphostine did not produce any histopathologic protection, compared to the L-arginine group ($p>0.05$). In L-arginine+vitamin C group, necrosis and cellular infiltration were not different from controls ($p>0.05$). With the bortezomib and octreotide, inflammation, necrosis, and NF-κB staining were not different from the controls ($p>0.05$). Also, inflammation, necrosis was lower than other groups ($p<0.005$ and 0.01, respevtively).

Conclusion: L-argininee leads to edema, cellular inflammation, and necrosis by increasing free oxygen radicals, lipid peroxidation, and NF-κB. Although amiphostine inhibits lipid peroxidation, it had no cytoprotective effect at cellular level. Vitamin C prevented cellular inflammation and necrosis by increasing protective enzymes. Bortezomib decreases cellular inflammation and necrosis by both cytoprotectively and inhibiting the IL-6 and NF-κB. Octreotide prevents pancreatic tissue from cellular inflammation and necrosis by both cytoprotection and inhibition of the NF-κB.