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ORIGINAL ARTICLE

Is there a relationship between beginning time and efficiency of octreotide in the treatment of experimental acute pancreatitis?

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Purpose: The efficacy of octreotide in the treatment of acute pancreatitis is controversial. Octreotide treatment for acute pancreatitis often shows poor correlation between results obtained in experimental studies and results of clinical trials. In a clinical setting, there is always a delay between the onset of the disease and initiation of the octreotide treatment. The aim of this study is to investigate the relationship between the beginning of treatment and alteration in effectiveness of octreotide. **Methods:** Acute pancreatitis was induced by pancreatic duct ligation in 50 rats. The rats were randomly divided into five groups. Octreotide was not used in group 1 (control group). Only single dose (4 μg/kg) octreotide was administered subcutaneously to rats in group 2, having induced pancreatitis. Octreotide treatment was begun at different times (8th, 24th, 48th hour) in three other groups and continued treatment at a dosage of 4 μg/kg t.i.d. The animals were sacrificed at the end of the 72nd hour and blood and tissue samples were collected. **Results:** Leukocyte count and plasma amylase values were less in groups 2 and 3. Hemorrhagic focuses were encountered less at pancreas tissues in group 3. Pancreatic necrosis and alveolar capillary basal membrane damage were lower in groups 3 and 4. No difference was found in fasting blood glucose, calcium and hematocrit. **Conclusion:** Octreotide had benefical effects in acute pancreatitis when octreotide treatment was begun in the first 24 hours.

Key Words: Pancreatitis, Octreotide, Amylase

INTRODUCTION

Treatment and prognosis of acute pancreatitis remain a common problem. Acute pancreatitis induced with various etiologic factors can be recovered from with insignificant symptoms or could progress to severe clinical conditions and, eventually, death [1-5]. Although several treatment protocols have been suggested, their benefits are still limited.

In the early 1980's, with experimental studies conducted, it was supposed that somatostatin and analogues could be used for acute pancreatitis treatment [6,7]. These pharmacologic agents were evaluated in several clinical and experimental studies but contradictory results were

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found [8,9]. Nowadays, while some researchers support the idea that somatostatin and its analogues are effective for the treatment of acute pancreatitis [10-12], some of the clinicians emphasize that these agents have no beneficial effects in acute pancreatitis treatment [13-15].

Multiple therapeutic modalities studied for acute pancreatitis often show a poor correlation between results obtained in experimental studies and results of clinical trials. One of the main reasons for this discrepancy is that in most experimental studies the drugs were administered immediately after induction of pancreatitis, whereas in the clinical setting, there is almost always a delay between the onset of the disease and initiation of the treatment.

Although octreotide, a semisynthetic analogue of somatostatin, has been extensively used in clinical practice and experimental studies, as far as we know there are few studies in the literature demonstrating a relation between beginning time of treatment and alteration of effectiveness of equal doses octreotide.

This experimental study was conducted to evaluate the alteration of effectiveness of octreotide in experimentally induced pancreatitis beginning treatment with octreotide at different times.

METHODS

Median incisions were performed in 50 Sprague-Dawley rats of both sexes with a body weight of 250 to 300 g. Anaesthesia was induced by intramuscular injection of ketamine HCI (25 mg/kg). Acute pancreatitis was induced by pancreatic duct ligation in 50 rats. The rats were randomly divided into five groups of 10 rats each, as follows:

Group 1 (n = 10), octreotide was not used.

Group 2 (n = 10), single dose octreotide was administered subcutaneously to the rats immediately after pancreatic duct ligation at a dosage of 4 μg/kg.

Group 3 (n = 10), initial dose of octreotide was administered subcutaneously to the rats at the 8th hour and continued treatment at a dosage of 4 μg/kg t.i.d.

Group 4 (n = 10), initial dose of octreotide was administered subcutaneously to the rats at the 24th hour and continued treatment at a dosage of 4 μg/kg t.i.d.

Group 5 (n = 10), initial dose of octreotide was administered subcutaneously to the rats at the 48th hour and continued treatment at a dosage of 4 μg/kg t.i.d.

The animals were allowed to have water and a standard rat diet when they awoke. The rats were sacrificed at the end of the 72nd hour. Blood samples (5 mL) were withdrawn from the hearth and 1 g tissue samples were taken from pancreas and lung.

Haematological and biochemical parameters were measured in Olympus AV-2700 (Olympus Co., Tokyo, Japan) and Coulter STKS (Beckman Coulter Inc., Brea, CA, USA). Tissue samples were fixed in a 10% formaldehyde solution. The tissue sections were stained with haematoxylin-eosin and examined by a pathologist who was unaware of treatment and test groups. Histopatologic changes were graded from 0 to 3 points and having added these points, the total score of every group was found and the mean was calculated (0, absent; 1, mild; 2, moderate; 3, severe). Histopathologic changes in the pancreas were evaluated for presence and degree of interstitial edema, neutrophil infiltration, haemorrhagia and necrosis. The presence and degree of interstitial edema, neutrophil infiltration and damage in alveolar capillary membrane were used for evaluation of lung tissue.

SPSS ver. 14.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The haematological and biochemical parameters were expressed as mean ± SD. Statistical comparisons of the data expressed as mean ± SD were analyzed by Mann-Whitney U test. The chi-squared test was used for the analysis of histopathological parameters. Statistical significance was set at $P < 0.05$.

RESULTS

There was no death during the experimental study. Leukocyte count was lower in groups 2 and 3 than the other groups ($P < 0.05$). Plasma amylase values increased in all groups. This increase was significantly low in groups 2 and 3 (Fig. 1A). A significant difference was not observed in fasting blood glucose, calcium and hematocrit (Table 1).

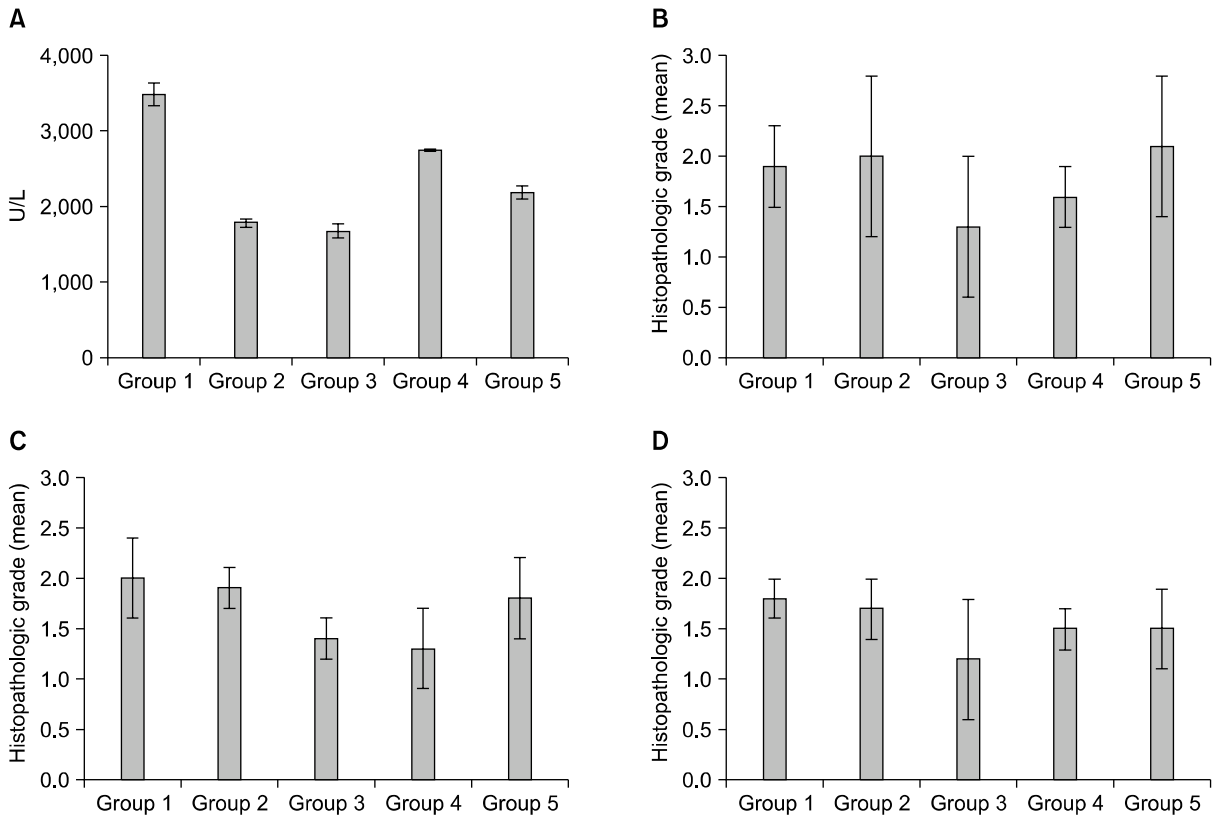

Fig. 1. Amylase levels and degree of histopathological changes that were found to differ between groups. Error bars denote Standard deviation (SD). (A) Amylase levels. (B) Pancreatic haemorrhagia. (C) Pancreatic necrosis. (D) Alveolar capillary basal membrane damage.

Table 1. The levels of hematologic and biochemical parameters

Parameter	Group 1	Group 2	Group 3	Group 4	Group 5
White blood cell	9,420 ± 273	6,620 ± 161[a)]	7,260 ± 190[a)]	9,400 ± 287	8,870 ± 308
Hematocrit	39 ± 5	40 ± 3	37 ± 2	39 ± 3	38 ± 5
Glucose	96 ± 8	89 ± 6	103 ± 11	105 ± 9	96 ± 4
Amylase	3,494 ± 154	1,790 ± 62[a)]	1,681 ± 93[a)]	2,756 ± 22	2,194 ± 85
Ca^{2+}	8,9 ± 1	9,5 ± 1	9 ± 1	10,3 ± 1	10 ± 0

Values are presented as mean ± SD.
[a)]$P < 0.05$, groups 2 and 3 vs. others.

Histopathological changes in the pancreas

Hemorrhagic focuses were less in group 3 than the other groups (Fig. 1B). Pancreatic necrosis in pathological examination was encountered less in groups 3 and 4 (Fig. 1C). There was no statistical difference for interstitial edema and neutrophil infiltration among all the groups (Table 2).

Histopathological changes in the lung

Alveolar capillary basal membrane damage was lower in groups 3 and 4 than the other groups (Fig. 1D). There was no statistical difference among the groups for edema and neutrophil infiltration in pathological examination of lung (Table 3).

Table 2. The degree of histopathological changes in the pancreas

	Group 1	Group 2	Group 3	Group 4	Group 5
Edema	2.5 ± 0.4	2.2 ± 0.6	2.1 ± 0.3	2.4 ± 0.5	2.2 ± 0.3
Neutrophil infiltration	2.2 ± 0.3	2.4 ± 0.5	2.0 ± 0.9	2.2 ± 0.6	2.5 ± 0.4
Haemorrhage	1.9 ± 0.4	2.0 ± 0.8	1.3 ± 0.7[a)]	1.6 ± 0.3	2.1 ± 0.7
Necrosis	2.0 ± 0.4	1.9 ± 0.2	1.4 ± 0.2[b)]	1.3 ± 0.4[b)]	1.8 ± 0.4

Values are presented as mean ± SD.
[a)]$P < 0.05$, group 3 vs. others. [b)]$P < 0.05$, group 3 and 4 vs. others.

Table 3. The degree of histopathological changes in the lungs

	Group 1	Group 2	Group 3	Group 4	Group 5
Edema	2.2 ± 0.5	2.1 ± 0.4	2.1 ± 0.5	1.7 ± 0.6	2.0 ± 0.5
Neutrophil infiltration	2.4 ± 0.4	2.5 ± 0.3	2.2 ± 0.7	1.9 ± 0.4	2.4 ± 0.6
Alveolar-capillary membrane damage	1.8 ± 0.2	1.7 ± 0.3	1.2 ± 0.6[a)]	1.5 ± 0.2[a)]	1.5 ± 0.4

Values are presented as mean ± SD.
[a)]$P < 0.05$, group 3 and 4 vs. others.

DISCUSSION

Acute pancreatitis is still a serious diagnostic and therapeutic problem. Acute pancreatitis can present in a wide clinical spectrum ranging from a mild, self-limiting localized disease to a fatal, widespread multi-organ failure in which mortality ranges from 14 to 30% [16,17]. Clinical features together with elevation of plasma concentrations of pancreatic enzymes are cornerstones of diagnosis. In spite of many experiments, there are no satisfactory methods of the treatment in clinical practice. The major problem is the lack of specific drugs, especially in the early phase of the disease. The initiating pathophysiological process is not known, but autodigestion by pancreatic enzymes may be responsible for disease progression [4]. The main disorder of this disease is necrosis of the pancreatic gland.

Octreotide has a profound inhibitory effect on the endocrine and exocrine secretions of the pancreas, stomach and small intestine [18]. In recent years, a huge number of articles have been published on the treatment of acute pancreatitis in experimental models. However, it is difficult to translate these results into clinical practice. Controversial results are present in clinical studies on the effect of octreotide in the treatment of patients with acute pancreatitis [10,11,13]. In most experimental studies, octreotide was administered immediately after induction of pancreatitis, but in clinical settings there is always a delay between the onset of the disease and initiation of the octreotide treatment. Uhl et al. [13] conducted a randomised, double blind, multicentre trial to look into the efficacy of octreotide. On the basis of this trial, they claimed that octreotide treatment for acute pancreatitis can not be recommended. That the median time elapsing from the onset of symptoms to entry into the study was 44 hours (range, 0 to 145 hours) is a salient point in their study. This inference is totally unacceptable for now.

The question to be answered is - *what is the deadline to begin acute pancreatitis treatment for octreotide to be effective?* There are two studies in the literature partially trying to evaluate this subject.

Kaplan et al. [19] studied the effects of delayed treatment with octreotide on acute experimental pancreatitis. They started octreotide treatment either 4 or 12 hours after onset. The rats were sacrificed at the end of the 36th hour in this study. The authors have not observed any effect of octreotide on amylase levels. They report that octreotide ameliorated pancreatic edema and histopathological injury score. In their study, the deadline to begin octreotide treatment is 12 hours, but sometimes octreotide treatment could begin later; from the onset of the disease in clinical conditions. Octreotide treatment was begun at different

times in our study (0, 8, 24, 48 hours after the operation).

The deadline to begin octreotide treatment is 24 hours in a study by Chen et al. [20]. In this study they used octreotide at different doses in different groups. For this reason, it is difficult to evaluate the alteration of effectiveness of octreotide that was begun at different times.

In many experimental studies, giving octreotide immediately after induction of pancreatitis showed benefical effects on both histopathological and biochemical parameters in experimental pancreatitis. Less pancreatic edema, necrosis and inflammatory cell infiltration, reduction in serum amylase were put forward by these studies [21,22].

In our study plasma amylase levels and leukocyte count were less in groups 2 and 3. Octreotide ameliorated pancreatic necrosis and alveolar capillary basal membrane damage in groups 3 and 4. Control group and group 5 were found to be similar for plasma amylase levels and histopathological damage in pancreas and lung tissues.

In the advanced pancreatitis case; the fact that there exists no benefical effects on inhibition of pancreatic enzymes is obvious as inflamation diffused, permeability increased and necrosis developed. In this case, octreotide is not effective on the course of disease. On the basis of our results we think that if pancreatic enzymes are inactivated at the early phase of pancreatitis without damaging pancreas tissue and other organs via systemic circulation; octreotide treatment can be useful.

In conclusion, octreotide had benefical effects on histopathological injury in induced acute pancreatitis by pancreatic duct ligation, when octreotide treatment was begun in the first 24 hours.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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