Losartan to prevent hyperenzymemia after endoscopic retrograde cholangiopancreatography: A randomized clinical trial

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METHODS: A triple-blind and placebo-controlled randomized clinical trial was performed at two Swedish hospitals in 2006-2008. Patients over 18 years of age undergoing ERCP, excluding those with current pancreatitis, current use of ARB, and severe disease, such as sepsis, liver and renal failure. One oral dose of 50 mg losartan or placebo was given one hour before ERCP. The relative risk of hyperenzymemia 24 h after ERCP was estimated using multivariable logistic regression, and expressed as odds ratio with 95% confidence intervals (CIs), including adjustment for potential remaining confounding.

RESULTS: Among 76 participating patients, 38 were randomized to the losartan and the placebo group, respectively. The incidence rates of hyperenzymemia and acute pancreatitis among all 76 participating patients were 21% and 12%, respectively. Hyperenzymemia was detected in 9 and 7 patients in the losartan and placebo group, respectively. There were no major differences between the comparison groups regarding cannulation difficulty, findings, or proportion of patients requiring drainage of the bile ducts. There were, however, more pancreatic duct injections, a greater extent of pancreatography, and more biliary sphincterotomies in the losartan group than in the placebo group. Losartan was not associated with risk of hyperenzymemia compared to the placebo group after multi-varible logistic regression analysis (odds ratio 1.6, 95%CI 0.3-7.8).

CONCLUSION: In this randomized trial 50 mg losartan given orally had no prophylactic effect on development of hyperenzymemia after ERCP.

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Key words: Renin-angiotensin system; Pancreatitis; Prophylaxis; Placebo-controlled trial
INTRODUCTION

Acute pancreatitis is a serious complication after endoscopic retrograde cholangio-pancreatography (ERCP), affecting 1%-10% of the patients\[^{[1,2]}\]. Elevation of pancreatic enzymes in serum (hyperenzymemia) is linked with pancreatitis, and occurs in 25%-40% of the patients after ERCP\[^{[3,4,5]}\]. Known risk factors for post-ERCP pancreatitis include female sex, previous pancreatitis, and procedure-related factors, including pancreatic duct injection, cannulation difficulties, and use of sphincterotomy\[^{[1,3]}\]. Several agents have been evaluated in the prevention of post-ERCP pancreatitis in clinical trials. Some groups of medications have not been associated with convincing effects, e.g., anti-secretory drugs\[^{[6,7]}\], protease inhibitors\[^{[8,9,10]}\], heparin\[^{[11]}\], and other anti-inflammatory drugs\[^{[12,13]}\]. Other drugs, however, have shown promising effects, e.g., interleukin 10\[^{[14]}\], glyceryl trinitrate\[^{[15]}\], and antibiotics\[^{[16]}\]. To date, however, there is no established medical prophylaxis against pancreatitis after ERCP. There is support for the new hypothesis that angiotensin II type 1 receptor blockers (ARB) prevent the development of pancreatitis or pancreatic hyperenzymemia after ERCP. Acute pancreatitis activates a local pancreatic renin-angiotensin system as well as the circulating renin-angiotensin system\[^{[17,18]}\]. Experimental research has shown that the angiotensin II type receptor and angiotensinogen are highly expressed in inflamed pancreatic tissue, and that administration of angiotensin II increases the secretion of pancreatic enzymes\[^{[19]}\]. This increased secretion can in turn be blocked by the ARB losartan (Cozaar\[^{[3,20]}\]). Moreover, losartan can prevent induced acute pancreatitis in rats\[^{[21]}\]. Furthermore, a recent case-control study by our group indicated a decreased risk of acute pancreatitis among patients treated with ARB\[^{[22]}\]. We have therefore conducted a clinical trial to test whether losartan prevents pancreatic hyperenzymemia after ERCP.

MATERIALS AND METHODS

A triple-blind, placebo-controlled randomized trial was performed at two Swedish hospitals, Karolinska Univer-

sity Hospital and Kalmar County Hospital, during the study period May 1, 2006 through October 31, 2008. There was a temporary intermission in the inclusion of patients during the period October 31, 2007 to May 1, 2008 to allow manufacturing of additional placebo capsules because of a restricted durability. The performing endoscopists recruited study patients. A capsule of 50 mg losartan or an identical capsule of placebo was given orally one hour before the ERCP. The dose was selected to minimize adverse side effects and yet ensure adequate penetration to the pancreatic tissue\[^{[23,24]}\]. The capsules were manufactured by Apoteket AB Produktion och Laboratorier. The primary study outcome was occurrence of hyperenzymemia 24 h after ERCP. Hyperenzymemia was defined as plasma levels of pancreatic amylase or lipase at least three times above the upper reference level. Post-ERCP pancreatitis was a secondary outcome, defined as persistent upper abdominal pain combined with hyperenzymemia 24 h after ERCP.

Patients

Eligible for the study were patients older than 18 years, scheduled for ERCP. The study aimed to investigate first-time ERCP patients, and therefore set an arbitrarily chosen time limit to one year since last ERCP to be included in the study. Other exclusion criteria were: previous ERCP within one year, current elevation of pancreatic amylase or lipase, ongoing acute or chronic pancreatitis, current use of ARB or angiotensin I converting enzyme inhibitor, bilateral renal artery stenosis (or unilateral in patients with a single kidney), known hypersensitivity to ARB, pregnancy, breastfeeding, or predefined severe disease (ongoing sepsis, disseminated intravascular coagulopathy, acute circulatory collapse, severe dehydration, hypovolemia, severe renal insufficiency, or severe liver failure). The participating patients were asked about their medical history and underwent a physical examination. Measurements of blood pressure and heart rate, and assessment of pain on a Visual Analogue Scale were performed at baseline (one hour before the ERCP) and 24 h after the ERCP. Blood pressure and heart rate were also registered hourly until 6 h after the procedure, and later if needed. Blood samples were collected at baseline, and at one, four, and 24 h after the ERCP. In all other respects, the ERCP procedure and ensuing patient care followed the standard clinical routines.

Randomization and blinding

The included patients were randomized to the losartan group or the placebo group by use of consecutive closed study envelopes containing the individual study code, the case report form and the selected capsule. The study coordinator assigned active or placebo drug using computer generated random numbers. The randomization was made in blocks of 10 with equal distribution of active and placebo drugs at the participating centres. The study coordinator, who was not involved either in the patient care or in the analysis of the data, held the key to the
Angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme (ACE) inhibitors are being used to reduce hyperenzymemia after endoscopic retrograde cholangiopancreatography (ERCP). However, the impact of these drugs in reducing hyperenzymemia has not been confirmed by randomized clinical trials. Bexelius et al. conducted a randomized placebo-controlled trial among 76 patients to compare the effects of losartan, an ARB, vs. placebo on the risk of post-ERCP hyperenzymemia. The results showed that losartan significantly reduced the risk of hyperenzymemia compared to placebo. The study was designed to assess the relative risk of hyperenzymemia in patients who received losartan vs. those who received placebo. The study protocol was approved by the regional ethics committee in Stockholm, Sweden, and all participants signed written informed consent before inclusion.

Study participants

Among 291 patients considered for inclusion, 215 were excluded. The reasons for these exclusions are listed in Figure 1. The most common reason for exclusion was recent ERCP (n = 142). Among the remaining 76 patients, 38 were randomized to the losartan group and 38 to the placebo group. Some characteristics of the study participants are presented in Table 1. The distribution of patients between the participating centres was equal in the comparison groups. Men were overrepresented in the losartan group. The distributions by age, BMI, history of pancreatitis, and the indications for the ERCP were equal between the groups, although there were fewer patients with jaundice and cholangitis in the losartan group (Table 1).

Ethics

All participants signed written informed consent before inclusion. The regional ethical committee in Stockholm and the Medical Products Agency in Sweden approved the study. The trial was registered according to regulation formulated by the European Medicines Agency and Good Clinical Practice.

Statistical analysis

The sample size was estimated on the basis of the following assumptions: (1) an incidence of hyperenzymemia of 40%; (2) a reduction of hyperenzymemia to 10% in the losartan group; (3) a significance level (alpha) of 0.05; and (4) a power of 80%. Using two-sample comparison of proportions, the corresponding sample size was 38 patients in each group. We evaluated all patients included in the group to which they were randomized, i.e., according to the analytical rule of intention to treat. To assess the impact of missing outcome data, we analyzed the data using the method of last observation carried forward.[40] The Fisher exact test or $x^2$ test was used for analysis of categorical variables. An analysis of variance or median test was performed for continuous data. To adjust for any imbalance of potentially confounding factors occurring in spite of randomization, we used multivariable logistic regression to estimate the relative risk of hyperenzymemia by calculating odds ratios (OR) with 95% confidence interval (CI). The following variables were adjusted for in the final multivariable model: sex, age (grouped into < or ≥ 65 years), body mass index (BMI, expressed as kg/m$^2$ and categorized as < 20, 20-25, or > 25), history of pancreatitis (yes or no), study center (Karolinska University Hospital or Kalmar County Hospital), and ERCP duration (continuous variable). Other potential confounders, including degree of technical difficulties during ERCP, sphincterotomy, biliary drainage, and time between drug intake and ERCP, were tested in the regression model, but since they did not influence the risk estimates but only diluted the precision of the estimates they were not included in the final model. The statistical analyses were performed with SAS Statistical Package (version 9.0, SAS Institute Inc., Cary, NC, United States).

RESULTS

Study participants and procedures

Among 291 patients considered for inclusion, 215 were excluded. The reasons for these exclusions are listed in Figure 1. The most common reason for exclusion was recent ERCP (n = 142). Among the remaining 76 patients, 38 were randomized to the losartan group and 38 to the placebo group. Some characteristics of the study participants are presented in Table 1. The distribution of patients between the participating centres was equal in the comparison groups. Men were overrepresented in the losartan group. The distributions by age, BMI, history of pancreatitis, and the indications for the ERCP were equal between the groups, although there were fewer patients with jaundice and cholangitis in the losartan group (Table 1). However, there were no statistically significant differences in between the groups. At baseline the mean arterial blood pressure was the same, 100 mm Hg, in the two groups, but 24 h after the ERCP it was lower in the losartan group than in the placebo group (93 mmHg vs 98 mmHg; P < 0.05). As shown in Table 2, there were no major differences between the comparison groups regarding cannulation difficulty, findings, or proportion of patients requiring drainage of the bile ducts. There were,
however, more pancreatic duct injections, a greater extent of pancreatography, and more biliary sphincterotomies in the losartan group than in the placebo group (Table 2). No patient received pancreatic stent. No patients with especially high risk of post-ERCP pancreatitis entered the study, e.g., individuals with sphincter Oddi’s dysfunction, and no high risk procedures, e.g., sphincter Oddi manometry, duct balloon dilatation, or pancreatic sphincterotomy, were performed.

Pancreatic enzyme levels
The incidence rates of hyperenzymemia and acute pancreatitis among all 76 participating patients were 21% and 12%, respectively. In total, 9 patients in the losartan group and 7 patients in the placebo group showed hyperenzymemia 24 h after ERCP (P = 0.51) (Table 3). No decreased risk of hyperenzymemia was found in the losartan group compared to the placebo group in the multivariable adjusted regression model (OR 1.6, 95%CI 0.3–7.8). The median serum amylase concentration at baseline was similar in the two groups (0.44 in the losartan group and 0.46 in the placebo group, P = 0.64). No significant differences in the amylase or lipase values one hour post-ERCP in the comparison groups were seen (data not shown). There was no statistically significant difference in median serum amylase between the groups 24 h after ERCP (0.62 in the losartan group and 0.82 in the placebo group, P = 0.33). Hyperamylasemia occurred in 8 patients in the losartan group and in 4 patients in the placebo group (P = 0.53) (Table 3). Similarly, there was no substantial difference in serum lipase value between the groups either at baseline (0.53 and 0.48 in the losartan and placebo groups, respectively, P = 0.47) or 24 h after ERCP (0.77 and 1.07 in the losartan and placebo groups, respectively, P = 0.62). Eight patients had hyperlipasemia 24 h after ERCP in the losartan group, and 7 in the placebo group (P = 0.89) (Table 3).

The evaluation of the effect of missing outcome data using the enzyme levels 4 h after ERCP in patients with missing 24-h values did not change the main results (data not shown). Acute pancreatitis occurred in 5 patients in the losartan group and 4 in the placebo group (P = 0.57) (Table 3). All cases of pancreatitis were mild as defined according to the Atlanta criteria. Among the cases of

### Table 1 Characteristics of the 76 participating patients and indications for their endoscopic retrograde cholangiopancreatography n (%)

| Characteristic                          | Losartan group | Placebo group |
|----------------------------------------|----------------|---------------|
| Total                                  | 38 (100)       | 38 (100)      |
| Study centre                           |                |               |
| Karolinska                             | 19 (50)        | 19 (50)       |
| Kalmar                                 | 19 (50)        | 19 (50)       |
| Sex                                     |                |               |
| Male                                    | 22 (58)        | 16 (42)       |
| Female                                  | 16 (42)        | 22 (58)       |
| Age, yr                                 |                |               |
| < 65                                    | 13 (34)        | 14 (37)       |
| ≥ 65                                    | 25 (66)        | 24 (63)       |
| Body mass index, kg/m²                 |                |               |
| < 20                                    | 3 (8)          | 2 (5)         |
| 20–25                                   | 14 (37)        | 14 (37)       |
| > 25                                    | 7 (18)         | 9 (24)        |
| Unknown                                 | 14 (37)        | 13 (34)       |
| Previous pancreatitis                  |                |               |
| No                                      | 34 (89)        | 35 (92)       |
| Yes                                     | 4 (11)         | 3 (8)         |
| Indication for ERCP¹                   |                |               |
| Jaundice without cholangitis           | 20 (53)        | 21 (55)       |
| Jaundice with cholangitis              | 7 (18)         | 9 (24)        |
| Suspected tumour in pancreas or bile ducts | 10 (26)    | 13 (34)       |
| Suspected benign disease, i.e., biliary lithiiasis, stricture or other disease | 20 (53) | 16 (42) |

¹Since each procedure could have several indications, the sum of percentages could be > 100. ECRP: Endoscopic retrograde cholangiopancreatography.

### Table 2 Distribution of procedure-related findings at endoscopic retrograde cholangiopancreatography in the 76 participating patients n (%)

| Finding/procedure                          | Losartan group | Placebo group |
|--------------------------------------------|----------------|---------------|
| Total                                      | 38 (100)       | 38 (100)      |
| Cannulation of the common bile duct        |                |               |
| Cannulation difficulty²                    |                |               |
| Easy or medium                             | 27 (71)        | 27 (71)       |
| Difficult or failed                        | 10 (26)        | 9 (24)        |
| Pancreatography                            |                |               |
| Number of pancreatic duct injections³     |                |               |
| None                                       | 21 (55)        | 24 (63)       |
| 1-3                                        | 15 (39)        | 11 (29)       |
| ≥ 4                                        | 1 (3)          | 2 (5)         |
| Extent of pancreatography³                 |                |               |
| None                                       | 21 (55)        | 24 (63)       |
| Main duct                                  | 12 (31)        | 11 (29)       |
| First branch, second branch, and acinarisation | 4 (11)       | 2 (5)         |
| Procedure-related findings in bile ducts² |                |               |
| Normal                                     | 5 (13)         | 3 (8)         |
| Gallstone                                  | 13 (34)        | 14 (37)       |
| Suspected cancer                           | 6 (16)         | 8 (21)        |
| Dilatation, benign or undetermined stricture, or anomaly | 14 (37) | 10 (26) |
| Procedure-related findings in pancreas¹    |                |               |
| Not contrast-filled                        | 21 (55)        | 24 (63)       |
| Normal                                     | 13 (34)        | 10 (26)       |
| Suspected cancer                           | 0 (0)          | 1 (3)         |
| Dilatation                                 | 3 (8)          | 1 (3)         |
| Endoscopic procedure                       |                |               |
| Biliary sphincterotomy                     |                |               |
| No                                         | 11 (29)        | 14 (37)       |
| Yes                                        | 27 (71)        | 24 (63)       |
| Biliary stenting                           |                |               |
| No                                         | 24 (63)        | 23 (61)       |
| Yes                                        | 14 (37)        | 15 (39)       |
| ERCP time, min²                            |                |               |
| < 30                                       | 13 (34)        | 10 (26)       |
| ≥ 30                                       | 22 (58)        | 26 (68)       |
| Time between intake of losartan or placebo capsule and ERCP, min | | |
| < 60                                       | 9 (24)         | 7 (18)        |
| ≥ 60                                       | 29 (76)        | 31 (82)       |

²The endoscopist assessed degree of technical difficulty; ³The total number of participants was 38 patients in each variable, and a sum < 38 indicate missing values between n = 2-5. ECRP: Endoscopic retrograde cholangiopancreatography.
Table 3 Serum pancreatic enzyme levels, abdominal pain, and pancreatitis after endoscopic retrograde cholangiopancreatography among 76 participating patients

| Pancreatic enzyme level in serum | Losartan group | Placebo group | P value |
|---------------------------------|----------------|---------------|---------|
| Amylase (microkat/L), median, (interquartile range) | 0.44 (0.3) | 0.46 (0.4) | 0.64 |
| 4 h after ERCP | 0.75 (2.5) | 0.68 (1.0) | 0.81 |
| 24 h after ERCP | 0.62 (2.3) | 0.82 (1.0) | 0.33 |
| Hyperamylasemiaa 24 h after ERCP | 8 (24) | 4 (13) | 0.53 |
| ERCP, number (%) | | | |
| Missing data | 5 (13) | 6 (16) | |
| Lipase (microkat/L), median, (interquartile range) | 0.53 (0.3) | 0.48 (0.5) | 0.47 |
| 4 h after ERCP | 1.02 (3.9) | 0.76 (1.4) | 0.47 |
| 24 h after ERCP | 0.77 (1.3) | 1.07 (1.5) | 0.62 |
| Hyperlipasemiaa 24 h after ERCP | 8 (21) | 7 (18) | 0.89 |
| ERCP, number (%) | | | |
| Missing data | 5 (13) | 7 (18) | |
| Hyperamylasemiaa 24 h after ERCP | 9 (24) | 7 (18) | 0.51 |
| ERCP, number (%) | | | |
| Missing data | 4 (11) | 3 (8) | |
| Abdominal pain 24 h after ERCP | 8 (23) | 9 (26) | 0.93 |
| ERCP, number (%) | | | |
| Missing data | 3 (8) | 3 (8) | |
| Acute pancreatitis (hyperamylasemia and abdominal pain after 24 h), number (%) | 5 (13) | 4 (11) | 0.57 |
| Missing data | 7 (18) | 4 (11) | |

In all analyses missing values were included as a separate category; P-values refer to overall differences between groups; Defined as 3 times higher than the normal reference value; Occurrence of hyperamylasemia or hyperlipasemia. ECRP: Endoscopic retrograde cholangiopancreatography.

DISCUSSION

This study provided no support for the hypothesis that losartan has a protective effect against the development of pancreatic hyperenzymemia after ERCP. The randomized design, the blinding of all patients, clinical staff and evaluators, the use of identical capsules for losartan and placebo, and the objective outcome measurement, i.e., assessment for predefined pancreatic enzyme levels 24 h after the intervention, are among the strengths of the study. There are, however, several weaknesses to consider. The large number of patients found not to be eligible for inclusion extended the study period. The limited sample size meant that it was not possible to detect weak associations, which meant that type 2 errors could have occurred. The sample size estimation was, however, deliberately carried out with the purpose of detecting a strong decrease in hyperenzymemia only. Despite the randomization, the limited sample size could have introduced confounding if important covariates were not evenly distributed between the comparison groups. The distribution of the evaluated potential confounding factors was, however, fairly equal. Moreover, to avoid confounding due to any remaining imbalances, we analyzed the data using multivariable regression with adjustment for several covariates. Hyperenzymemia was used as a surrogate marker for increased risk of acute post-ERCP pancreatitis. This was justified by the strong link between these conditions; further, hyperenzymemia has previously been used as a marker for pancreatic damage and pancreatitis after ECRP. Since the occurrence of hyperenzymemia is markedly more common than pancreatitis, such a surrogate marker provided an opportunity to have a more limited sample size. If the results of the present study had indicated a prophylactic effect of losartan on hyperenzymemia, we had intended to expand the study to comprise a sufficient number of patients to address the outcome acute pancreatitis. The rate of post-ERCP pancreatitis was somewhat higher than expected, partly due to detection bias. Also, the study is small and therefore the high reported incidence of post-ERCP pancreatitis could be due to chance.

Experimental and clinical findings suggest that ARBs will protect against development of acute pancreatitis, but our study did not support this hypothesis. Apart from a true lack of effect, our negative results could have been due to several other factors: The tested dose (50 mg) of losartan might have been too low to have any preventive effect, and earlier administration of losartan could have been more beneficial, since a peak plasma concentration is obtained 4-6 h after an oral dose. The dose was predefined, however, and chosen on the basis of an experimental report of a protective effect on cerulein induced acute pancreatitis using 0.2 mg/kg in rats. Moreover, losartan did decrease the blood pressure, suggesting that the dosage was at least sufficient to affect peripheral vasoconstriction. To date, the tissue concentration of losartan in the pancreas remains unknown. Thus, the study hypothesis cannot be dismissed on the basis of the present trial only. Before considering another randomized trial, e.g., with a longer pre-treatment latency and a higher dose of ARB, we suggest further observational investigations of the risk of post-ERCP pancreatitis among ARB users.

In conclusion, one oral capsule of 50 mg of the ARB losartan given one hour before ERCP did not prevent pancreatic hyperenzymemia after the ERCP procedure in this randomized, blinded and placebo-controlled clinical trial.

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COMMENTS

Background

This experimental randomized trial based on experimental research, which have
shown beneficial effects on pancreatitis using angiotensin receptor blockers. Also, clinical evidence exists from an epidemiological study showing reduced risk of acute pancreatitis in hypertensive patients in a primary care setting in United Kingdom. Endoscopic retrograde cholangio-pancreatography is usually successful, e.g., removing gallstones and accessing bile ducts for other therapeutic purposes. However, there exist a small risk of the potential lethal complication of acute pancreatitis. This is the reason they are investigating the potential lowering risk of losartan on the risk of development of hyperenzymemia.

**Research frontiers**

Many different approaches both pharmacological and intervention-related have been tried to reduce the incidence of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. Promising results have been seen pharmacologically with drugs, e.g., gabexate and ulinastatin, and with increased use of pancreatic stenting have also been successful in some studies. Still the need for better prophylactic strategies is large to reduce a potential life-threatening complication like pancreatitis.

**Innovations and breakthroughs**

In general, losartan, which belongs to the pharmacological class of angiotensin receptor blockers, are used broadly to treat high blood pressure, and heart failure. Experimentally, a role for angiotensin II receptor blockers (ARB) is suggested in conditions such as inflammation, and cancer. Previously, experimental animal research have tested ARB on pancreatic inflammation with promising results, but the authors aimed to investigate this in humans, with the effect on pancreatic enzymatic secretion, in turn potentially leading to pancreatic inflammation.

**Applications**

This study suggests no benefit of losartan on the development of hyperenzymemia after ERCP. However, due to limited sample size, larger well-designed controlled trials could evaluate this question further to rule out an unseen effect so far.

**Terminology**

Endoscopic retrograde cholangio-pancreatography is an investigation using a flexible endoscope accessing the bile ducts allowing both therapeutic and diagnostic interventions. Losartan is anti-hypertensive drug acting on the renin-angiotensin system, which has effects on blood pressure, inflammation and salt balance.

**Peer review**

This is a well-designed randomized double-blind study, which examines the effect of the well-known anti-hypertensive drugs. Advantages include the strict randomized design, the identical capsules used for placebo and active drugs, objective outcome measurement using pancreatic enzymes, and strict adherence to intention-to-treat principle while analyzing the results. Disadvantages include sample-size, because a larger study would make the results more reliable and also possible to analyze the effect on acute pancreatitis, rather than the proxy variable hyperenzymemia.

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