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BRIEF ARTICLES

Oral allopurinol to prevent hyperamylasemia and acute pancreatitis after endoscopic retrograde cholangiopancreatography

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Abstract

AIM: To assess the efficacy of allopurinol to prevent hyperamylasemia and pancreatitis after endoscopic retrograde cholangiopancreatography (PEP).

METHODS: One hundred and seventy patients were enrolled and randomized to two groups: a study group (n = 85) who received 300 mg of oral allopurinol at 15 h and 3 h before endoscopic retrograde cholangiopancreatography (ERCP) and a control group (n = 85) receiving an oral placebo at the same times. Main Outcome Measurements included serum amylase levels and the number severity of the episodes of pancreatitis. Serum amylase levels were classified as normal (< 150 IU/L) or hyperamylasemia (> 151 IU/L). Episodes of PEP were classified following Ranson's criteria and CT severity index.

RESULTS: Gender distribution was similar between groups. Mean age was 53.5 ± 18.9 years for study group and 52.8 ± 19.8 years for controls. Also, the distribution of benign pathology was similar between groups. Hyperamylasemia was more common in the control group (P = 0.003). Mild PEP developed in two patients from the study group (2.3%) and eight (9.4%) from control group (P = 0.04), seven episodes were observed in high-risk patients of the control group (25%) and one in the allopurinol group (3.3%, P = 0.02). Risk factors for PEP were precut sphincterotomy (P = 0.02), pancreatic duct manipulation (P = 0.002) and multiple procedures (P = 0.000). There were no deaths or side effects.

CONCLUSION: Oral allopurinol before ERCP decreased the incidences of hyperamylasemia and pancreatitis in patients submitted to high-risk procedures.

Key words: Endoscopic retrograde cholangiopancrea tography; Hyperamylasemia; Acute pancreatitis; Oral allopurinol; Risk factors

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INTRODUCTION

Pancreatitis is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP)[1-4], with the reported incidence ranging from 1.8% to 7.2% in most prospective series[5-9]. However, the reported incidence can be up to 30%, depending on the criteria used to diagnose pancreatitis, the type and duration of patient follow-up and the type of case mix[10]. More commonly, hyperamylasemia occurs in up to 30% of patients undergoing ERCP[11].

The generally accepted criteria for the diagnosis of post-ERCP pancreatitis (PEP) were proposed in 1991 during a consensus workshop. These criteria include the new onset of pancreatic-type abdominal pain associated with at least a threefold increase in serum amylase or lipase occurring within 24 h after an ERCP. The pain symptoms need to be severe enough to require admission to a hospital or to extend the length of stay of patients who are already hospitalized[12]. Most of the episodes of acute pancreatitis are catalogued as mild. However, based on the presence of organ failure or local complications, acute severe pancreatitis occurs after 0.3% to 0.6% of ERCP procedures[10,13,14].

Numerous attempts have been made to find a pharmacologic agent that could be used to reduce the incidence and severity of PEP. An ideal agent should be highly effective in reducing PEP, safe for the patient, well tolerated, relatively affordable and not require a prolonged administration time. Unfortunately, nearly all of the agents investigated have fallen short of these goals, but several agents have shown some promise[15,16]. An early step in the pathogenesis of acute pancreatitis is capillary endothelial injury manifested by an increase in capillary permeability[17,18]. Subsequent research has suggested that this capillary injury might be mediated by oxygen-derived free radicals[19-21]. Xanthine oxidase catalyzes the conversion of hypoxanthine to xanthine, which generates an oxygen-derived free radical. This catalyst is commonly derived from a ubiquitous inactive precursor, xanthine dehydrogenase, which is present in the pancreas and the intestinal mucosa. Xanthine dehydrogenase is converted to xanthine oxidase by the proteolytic cleavage of a peptide fragment. These findings have prompted attempts at the prevention of pancreatitis by treatment with free radical scavengers (e.g. superoxide dismutase, dimethyl sulfoxide or catalase), protease inhibitors (e.g. gabexate) or xanthine oxidase inhibitors (e.g. allopurinol)[22-25].

The efficacy of oral allopurinol to reduce PEP has been investigated in an *in vivo* animal model[26]. Pretreatment was not only associated with a significant (sixfold) reduction in the incidence of pancreatitis, but when pancreatitis did occur it was less severe. Other animal models using pretreatment with allopurinol have demonstrated a significant reduction in the progression of histological pancreatic injury and in the severity of experimental pancreatitis in dog and rat models[27-29]. These findings in animals supported the need for human studies on the utility of allopurinol pretreatment to reduce the incidence of hyperamylasemia and PEP. One randomized clinical trial has reported positive clinical results[30], whereas three have reported negative outcomes[31-33]. Given the findings of these published clinical results, the beneficial animal data and the practical benefits of allopurinol's potential use for prevention of hyperamylasemia and PEP, we designed a randomized clinical trial to compare the rates of these symptoms seen with treatment using either allopurinol or a placebo.

MATERIALS AND METHODS

Trial design and patient selection

This was a randomized clinical trial carried out in patients who underwent ERCP within a six-month period (July through December 2007) at the Endoscopy and Gastroenterology Departments of the High Specialty Medical Unit, Specialties Hospital of the Western National Medical Center of the Mexican Institute of Social Security. From the 300 candidates for ERCP, only 170 met the trial criteria. Patients needed to be over 18 years old and undergoing ERCP due to suspected bile duct obstruction with intact papilla of Vater. No patients were enrolled in the study if they had clinically evident acute pancreatitis or hyperamylasemia (> 150 IU/L) before the procedure or if they had ingested nonsteroid anti-inflammatory drugs (NSAIDS) within a week prior to assessment. Patients submitted to diagnostic, therapeutic or failed ERCP 12 mo before the inclusion in the study were not admitted nor were those who had undergone previous endoscopic or surgical sphincterotomy. Patients were also excluded if they were being treated with anticoagulants or platelet antiagregants, such as acetyl salicylic acid and placitaxel or with a prothrombin time with a difference of > 5 s against the blind sample taken no earlier than 72 h before the study. We also eliminated patients who were allergic or hypersensitive to allopurinol or hydrosoluble contrast solutions or those with active hemorrhages of peptic origin. Additional exclusion criteria included a hemoglobin level of less than 8 g/dL; a platelet count of less than 60×10^9/L; relative neutropenia (absolute neutrophil count < 2.0×10^9/L); significant renal dysfunction (serum creatinine level, > 200 μmol/L); decompensated cirrhosis; a known or suspected pregnancy or presence of lactation; current or recent use of allopurinol (within 48 h); current use of drugs with a known interaction with allopurinol, including cyclophosphamide, chlorpropamide, azathioprine/mercaptopurines, or probenecid and an inability to swallow or absorb oral medication.

Main outcome measurements

We included 170 patients in this study. Randomization was performed at the Department of Gastrointestinal Endoscopy by using computer-generated random numbers. Allopurinol and the placebo were similar in presentation and packed in appropriate containers with the identification code. The drug or placebo was only administered after informed consent was obtained. Eighty-five patients were randomly assigned to the study

group receiving 600 mg of allopurinol divided in two oral doses before the procedure (300 mg at 15 h and 300 mg at 3 h before ERCP) and 85 patients were assigned to the control group receiving two doses of an oral placebo at the same time. Blood samples were drawn from all patients to determine serum amylase levels before the procedure and 2 h later and classified as normal level (< 150 IU/L); or hyperamylasemia (> 151 IU/L). If the amylase serum level was > 151 IU/L and there was no evidence of acute pancreatitis (abdominal pain, nausea or vomiting), patients were started on a liquid diet and discharged 8 h to 24 h after the endoscopic procedure. If the serum amylase was above 600 UI/L or three times above the normal value and the patient had a sharp pain irradiating to the back and nausea or vomiting, the diagnosis of PEP was established in the absence of radiological evidence of a pneumoperitoneum or emphysema in the retroperitoneal space through a plain radiologic examination of the abdomen or CT scan. These patients were managed in the hospital with fasting, hydration with crystalloid solutions, antiemetics (metoclopramide) and analgesics. Pancreatitis episodes were classified according to Ranson's prognostic criteria and CT severity index[34].

Details concerning the endoscopic procedure, specifying the difficulty for cannulation, number of pancreatic duct injections, sphincterotomies, characteristics of the bile duct, presence of choledocolithiasis, as well as defining whether the procedure was diagnostic or therapeutic (endoprosthesis placement or stone extraction). Patients were classified as low-risk for the development PEP or those male and older than 50 years old, when the procedure was diagnostic or therapeutic with sphincterotomy, biliary or pancreatic stenting and stone extraction or presence of chronic pancreatitis. Otherwise, patients were considered as high-risk for the development of PEP in the case of female gender and younger than 50 years old, those submitted to pancreatic duct manipulation or precut sphincterotomy, multiple endoscopic procedures, difficult or failed cannulation and patients with suspected sphincter of Oddi dysfunction[10,16]. Other complications such as perforation, bleeding and infection, were recorded.

Statistical analysis

The results are shown as percentages and as means with standard deviations. Statistical inference was tested using chi-squared or Fisher's exact test for qualitative variables, while Student's *t* test was used for quantitative variables. To explore the risk factors, the relative risks and 95% confidence intervals were estimated. $P < 0.05$ was considered statistically significant. Finally, the reduction in absolute risk (ARR), the reduction in relative risk (RRR) and number needed to treat (NNT) were analyzed to estimate factors needed to prevent an episode of pancreatitis.

Ethical considerations

The research protocol was reviewed and approved by the Research and Ethics Committees of our Institution. All patients signed informed consent forms before taking part in the study. The study was financed with funds from the Department of Gastroenterology, Gastrointestinal Endoscopy and the Medical Research Unit in Clinical Epidemiology of the Medical Center.

Table 1 Demographics and ERCP data

	Allopurinol *n* = 85	Placebo *n* = 85	*P*
Age	53.5 ± 18.9	52.8 ± 19.8	0.82
Gender M/F	36/49	34/51	0.86
Diagnosis			
Benign			
Choledocholitiasis	35	35	0.51
Iatrogenic injury of the biliary tract	11	14	0.48
Chronic pancreatitis	3	1	0.31
Chronic hepatopathy	2	2	0.60
Sphincter of oddi dysfunction	2	2	0.60
Mirizzi's syndrome	1	0	0.50
Malignant			
Pancreatic adenocarcinoma	11	12	0.82
Cholangiocarcinoma	4	5	0.50
Periampullary carcinoma	2	2	0.60
Gallbladder cancer	0	1	0.50
Normal cholangiography	8	5	0.48
Failed procedure	6	6	0.61
Total	85	85	

RESULTS

The patients participating in the trail comprised 70 men (41.2%) and 100 women (58.8%). The study group had 36 men and 49 women; in the control group there were 34 men and 51 women. The average age for the study group was 53.5 ± 18.9 years and for the control group it was 52.8 ± 19.8 years. Basal amylase levels were 50.8 ± 19.3 U/dL for the study group and 46.9 ± 16.1 U/dL for the control group.

A benign diagnosis for both groups was reported in 108 patients (63.5%): 54 in the study group and 54 in the control group. Malignant diseases were diagnosed in 17 and 20 cases respectively (21.8%). Normal cholangiography was determined in eight and five cases respectively (7.6%) and difficult or failed ERCP occurred in six patients in each group (7%). The diagnoses reached are shown in Table 1. No significant statistical differences were found between groups, and there were no differences in the procedural details described in Table 2. Twenty-three patients developed hyperamylasemia (> 151 IU/L), five (5.8%) from the study group and eighteen (21.1%) from the control group ($P = 0.003$). Ten patients developed pancreatitis, two from the study group (2.3%) and eight from the control group (9.4%; $P = 0.04$). In all cases amylase levels were above 600 IU/L (range 771 to 8886 IU/L). These patients were classified according to Ranson's criteria at admission and at 48 h by CT Severity index as having mild pancreatitis (less than 3 positive signs and Balthazar's A an B without necrosis, severity index of 0 to 1 points). They were handled conservatively and all did well. All patients were discharged within three days of starting the treatment.

Table 2 Procedural details, endpoints and post-ERCP morbidity *n* (%)

	Allopurinol group *n* = 85	Placebo group *n* = 85	*P*
Procedural details			
Total procedural time (min)	37.8 ± 11.9	38.2 ± 12.4	0.82
Cannulation time (min)	15.4 ± 5.5	15.6 ± 5.6	0.81
Pancreatic cannulation and injection	24 (24.7)	18 (21.1)	0.18
Number of injections	1.23 ± 0.42	1.27 ± 0.44	0.60
Acinarization	9 (10.5)	9 (10.5)	0.58
Invasive diagnostics			
Cytology	15 (17.6)	17 (20)	0.42
Intrabiliary biopsy	2 (2.3)	2 (2.3)	0.69
Therapeutics			
Any Therapeutics	71 (83.5)	74 (87)	0.51
Precut sphincterotomy	15 (17.6)	18 (21.1)	0.56
Biliary sphincterotomy	20 (23.5)	17 (20)	0.57
Stone extraction	29 (34.1)	27 (31.7)	0.74
Biliary stenting	32 (37.6)	37 (43.5)	0.43
Pancreatic stenting	2 (2.3)	3 (3.5)	0.64
End points			
Hyperamylasemia	5 (5.8)	18 (21.1)	0.003
Pancreatitis	2 (2.3)	8 (9.4)	0.049
PEP in low-risk procedures	1/55 (1.8)	1/57 (1.7)	0.70
PEP in high-risk procedures	1/30 (3.3)	7/28 (25)	0.02
ERCP morbidity			
Bleeding	2 (2.3)	2 (2.3)	0.69
Perforation	1 (1.1)	0	0.50

The analysis of the risk factors for the development of PEP revealed that Gender (P = 0.52, RR, 0.83, CI 95% 0.24-3.1), age [younger or older than 50 years old (P = 0.31, RR, 0.38, CI 95% 0.04-3.12)] and etiology (P = 0.18, RR, 0.77, CI 95% 0.46-1.29) were not statistically different between groups. When sphincterotomy or biliary stenting was performed, no risk of developing acute pancreatitis was observed (P = 0.31, RR, 0.38, CI 95% 0.04-3.12). Otherwise, we observed a marked tendency to favor the development of acute pancreatitis if precut sphincterotomy was performed (P = 0.022, RR, 4.9, CI 95% 1.3-18.19), if there was instrumentation of the pancreatic duct (P = 0.002, RR 9.3, CI 95% 1.91-45.4) or if multiple endoscopic procedures such as pre-cut sphincterotomy plus pancreatic duct manipulation plus biliary stenting during the same ERCP were performed, (P = 0.000, RR 14.8, CI 95% 3.0-73.06). PEP was observed in eight patients submitted to high-risk procedures (Table 2), one (3.3%) corresponded in the allopurinol group and seven (25%) patients for the control group (P = 0.02). In contrast, two episodes of PEP were observed in patients submitted to low-risk procedures, one (1.8%) from the allopurinol group and one (1.7%) from the control group (P = 0.70).

We found an ARR of 21.7%, with an RRR of 86.8% and an NNT of 4.6 patients submitted to high-risk ERCP procedures to avoid a clinically evident episode of pancreatitis. Major complications were observed in four patients (two from each group) consisting of mild to moderate bleeding which required blood transfusion and resolved without surgical intervention and one perforation was observed in a patient of the study group treated surgically without complications or mortality. No adverse events were recorded with the use of allopurinol or the placebo.

DISCUSSION

Xanthine oxidase (XO) was first discovered in milk over a century ago and in rat serum nearly 70 years ago[35,36]. This enzyme is now known to be present in many different tissues and in a wide range of species from bacteria to humans[37,38]. It is a cytosolic metalloflavoprotein that is predominantly responsible for the oxidation of endogenous purines and exogenous ethanol[39-41]. Granger and colleagues demonstrated that XO was an important source of the oxidative stress associated with ischemia and reperfusion[38]. This enzyme has since been implicated in the pathogenesis of a wide spectrum of diseases[42], and it is thought to be the most important source of oxygen-derived free radicals and cell damage during reoxygenation of hypoxic tissues and pancreatitis[40-44]. A number of studies in animal models conducted during the past two decades have highlighted the potential benefit of XO inhibition in a range of clinical settings. Thus, clinical studies have shown that it is safe and effective for the treatment of gout and tumor-lysis syndrome (a life-threatening constellation of metabolic abnormalities resulting from spontaneous or treatment-related tumor necrosis or fulminant apoptosis) and to reduce complications such as postoperative arrhythmias, myocardial infarction and associated mortality after cardiovascular surgery[39].

Allopurinol has high oral bioavailability (80%-90%), a rapid onset of action (peak circulating level reached in 0.5-2 h) and a 70% hepatic transformation to a long-lasting active metabolite (oxypurinol, with a half-life of 15 h)[39]. These pharmacokinetic attributes mean a single oral dose of allopurinol before ERCP could conceivably prevent PEP, because the drug targets those changes that contribute to the initial triggering of pancreatitis[42,43]. Allopurinol is also an inexpensive generic drug with an excellent safety record and is not included in the catalog of drugs inducing pancreatitis[45].

Four randomized clinical trials have been published in full to date (Table 3): a negative study from Budzyńska *et al*[31] (n = 300), a positive study from Greece[30] (n = 250), a negative study from the USA[32] (n = 701) and the most recent study published by Romagnuolo *et al*[33], from Canada (n = 586) with negative results. In the present study, we demonstrated that the use of allopurinol led to a significant reduction in the incidence of hyperamylasemia (5.8% *vs* 21.1% in placebo-treated controls, P = 0.003) and acute pancreatitis (2.3% *vs* 9.4%, P = 0.04). According to the particular patient's conditions, type of endoscopic procedure or multiple procedures, patients were divided as low and high risk for the development of PEP. The incidence was similar between patients submitted to low-risk procedures. In contrast, the difference was statistically significant in high-risk procedures, favoring the use of allopurinol (incidence 3.3% in the study group *versus* 25%

Table 3 Summary of randomized trials using allopurinol to prevent post-ERCP pancreatitis

Study (year), SC *vs* MC, country	*n*	Dose, mg	Allopurinol *vs* placebo PEP rates	Percentage high risk[1]	Comment
Budzyńska *et al*[31] (2001) SC, Poland	300	400[2]	12.1% *vs* 7.9%; 12 *vs* 8	0%	3-arm study, with third arm (*n* = 100) given prednisone
Kastinelos *et al*[30] (2005) SC, Greece	250	1200[3]	3.2% *vs* 17.8%; 4 *vs* 21	0%	2 patients with suspected SOD
Mosler *et al*[32] (2005) MC, USA	701	900[4]	13.0% *vs* 12.1%; 46 *vs* 42	70.2%	4% absolute benefit in high-risk patients; 4% absolute harm in average risk
Romagnuolo *et al*[33] (2008) MC, Canada	586	300[5]	5.5% *vs* 4.1%; 16 *vs* 12	11.3%	Harm in average risk patients; benefit in high-risk patients
Current study (2009) SC, Mexico	170	600[6]	2.3% *vs* 9.4%; 2 *vs* 8	34.1%	21.7% absolute benefit in patients with high-risk procedures favoring allopurinol, no difference in low-risk procedures
Raw pooled	2007 (1008 *vs* 999)	-	7.9% *vs* 9.1%; 80 *vs* 91	-	1.2% difference (95% CI, 3.2% to 2.0%)

[1]As defined in this protocol, namely sphincter manometry and/or pancreatic therapy. Other higher-risk cases (e.g. precut sphincterotomy or suspected SOD) were not considered; [2]200 mg 15 h before, 200 mg 3 h before; [3]600 mg 15 h before, 600 mg 3 h before; [4]600 mg 4 h before, 300 mg 1 h before; [5]300 mg 1 h before; [6]300 mg 15 h before, 300 mg 1 h before; SC: Single centre; MC: Multicenter.

in the control group, $P = 0.02$). Fortunately, all episodes of acute pancreatitis were catalogued as mild and there were no deaths.

There was variability in the doses used in the previous studies and in the baseline rates of PEP in the control (placebo) groups (some of which are out of the usual range reported), but these differences do not appear to completely explain the heterogeneity in the results. There remains a possibility for a threshold effect or a minimally effective dose for allopurinol, given that the positive study[30] used the highest dose (1200 mg); however, there does not seem to be a clear dose-response relationship as the larger negative studies[31-33] used different lower doses (300, 400 and 900 mg; Table 3). The four earlier studies all checked formally or informally for interactions, presenting the active treatment and placebo PEP rates in different subgroups. None found significant interactions between diagnostic and therapeutic procedures. The most detailed analyses of this type were found in the studies by Mosler *et al*[32] and Romagnuolo *et al*[33]. Both demonstrated a benefit in the reduction of the episodes of acute pancreatitis as well as the severity when analyzing high-risk patients or those requiring sphincter of Oddi manometry or planned pancreatic therapy. Mosler *et al*[32] demonstrated that allopurinol reduced the incidence of PEP from 27% to 23% in the high-risk group (4% absolute risk reduction) and also reduced harm (8% *versus* 12% PEP) in the non-high-risk group (Table 3). Romagnuolo *et al*[33] found that, for non-high-risk patients, the crude rate of PEP was 5.4% in the allopurinol group and 1.5% in the placebo group ($P = 0.017$ favoring the placebo, indicating harm associated with allopurinol), whereas in the high-risk group the PEP rates were 6.3% in the allopurinol group and 23% in the placebo group ($P = 0.050$ favoring allopurinol). It is also necessary to note that more patients in the allopurinol group (44% *vs* 34% $P = 0.02$) required pancreatic duct injection as well as more injections (two *versus* one, $P = 0.01$). However, confounding was not confirmed statistically, and correcting for pancreatic injection in a stratified model still showed a nonsignificant trend toward harm for allopurinol in the non-high-risk subgroup. If allopurinol is truly harmful for non-high-risk patients undergoing ERCP (the adjusted subgroup OR was not significant), the mechanism responsible is unclear. It could be the result of an idiosyncratic reaction to the medicine itself; one study did suggest that medications with a history of inducing pancreatitis could increase the risk of PEP[46].

Budzyńska *et al*[31], also included primarily non-high-risk patients and showed a higher rate of PEP with allopurinol. In contrast, the patients in the study by Katsinelos *et al*[30] were also primarily non-high-risk patients and yet the study showed a significant benefit for allopurinol. In our results, using 600 mg of allopurinol we observed a significant reduction in the episodes of mild acute pancreatitis (2.3% *vs* 9.4, $P = 0.04$), but the difference was attributed to a beneficial effect of allopurinol in patients submitted to high-risk procedures, since in low-risk procedures the difference was not statistically significant.

The debate still continues. In a recent meta-analysis just published in September, 2008, Bai *et al*[47] concluded that allopurinol may not be useful to prevent PEP. However, they recognized the limitations of their meta-analysis since it was a study-level analysis and the authors denoted the difficulties in stratifying high-risk patients and high-risk procedures because this information was not available in reviewed trials[30-33,47]. To overcome the limitations, they recommended the design of multicenter trials with appropriate numbers of high-risk patients and high-risk procedures.

In conclusion, extensive evidence supports a beneficial effect of allopurinol in the prevention and severity of experimental pancreatitis. Clinical evidence supports a favorable effect of oral allopurinol in the prevention of PEP in patients submitted to high-risk procedures. Our results establish a reduction of the incidence of asymptomatic hyperamylasemia and PEP, particularly in patients submitted to high-risk procedures. More clinical trials with different dosification and patient selection are required to definitively determine any positive or deleterious effect of oral allopurinol in the prevention of PEP.

COMMENTS

Background

Endoscopic retrograde cholangiopancreatography (ERCP) is a widely applied method for the diagnosis and treatment of pancreatobiliary disease. Post-ERCP pancreatitis is the most common postoperative complication of ERCP and its prevention has become an urgent clinical challenge.

Research frontiers

ERCP is an indispensable method for the diagnosis and treatment of pancreatobiliary disease, and pancreatitis is the most common postoperative complication of it. There are some studies on drugs for preventing post-ERCP pancreatitis, but their results remain debatable. Therefore, most endoscopy centers do not give patients a conventional chemoprophylaxis.

Innovations and breakthroughs

This trail revealed that oral allopurinol 300 mg 15 and 3 h (600 mg) before ERCP could reduce pancreatitis and hyperamylasemia.

Applications

Oral allopurinol 300 mg 15 and 3 h (600 mg) before ERCP can prevent post-ERCP pancreatitis. Compared with other drugs, oral allopurinol is inexpensive, convenient and has very few side-effects, and can be used as a protective drug for preventing post-ERCP pancreatitis.

Peer review

This paper is interesting since aiming to demonstrate the effect, and possible effectiveness, of allopurinol on the occurrence of post ERCP acute pancreatitis. The design is well organized and the conclusion is that this drug has a preventive effect on post ERCP - hyperamylasemia and pancreatitis, especially in high risk patients.

REFERENCES

1 **Freeman ML**, DiSario JA, Nelson DB, Fennerty MB, Lee JG, Bjorkman DJ, Overby CS, Aas J, Ryan ME, Bochna GS, Shaw MJ, Snady HW, Erickson RV, Moore JP, Roel JP. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. *Gastrointest Endosc* 2001; **54**: 425-434

2 **Freeman ML**, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, Moore JP, Fennerty MB, Ryan ME, Shaw MJ, Lande JD, Pheley AM. Complications of endoscopic biliary sphincterotomy. *N Engl J Med* 1996; **335**: 909-918

3 **Andriulli A**, Clemente R, Solmi L, Terruzzi V, Suriani R, Sigillito A, Leandro G, Leo P, De Maio G, Perri F. Gabexate or somatostatin administration before ERCP in patients at high risk for post-ERCP pancreatitis: a multicenter, placebo-controlled, randomized clinical trial. *Gastrointest Endosc* 2002; **56**: 488-495

4 **Christoforidis E**, Goulimaris I, Kanellos I, Tsalis K, Demetriades C, Betsis D. Post-ERCP pancreatitis and hyperamylasemia: patient-related and operative risk factors. *Endoscopy* 2002; **34**: 286-292

5 **Masci E**, Toti G, Mariani A, Curioni S, Lomazzi A, Dinelli M, Minoli G, Crosta C, Comin U, Fertitta A, Prada A, Passoni GR, Testoni PA. Complications of diagnostic and therapeutic ERCP: a prospective multicenter study. *Am J Gastroenterol* 2001; **96**: 417-423

6 **Vandervoort J**, Soetikno RM, Tham TC, Wong RC, Ferrari AP Jr, Montes H, Roston AD, Slivka A, Lichtenstein DR, Ruymann FW, Van Dam J, Hughes M, Carr-Locke DL. Risk factors for complications after performance of ERCP. *Gastrointest Endosc* 2002; **56**: 652-656

7 **García Cano Lizcano J**, González Martín JA, Morillas Ariño J, Pérez Sola A. Complications of endoscopic retrograde cholangiopancreatography. A study in a small ERCP unit. *Rev Esp Enferm Dig* 2004; **96**: 163-173

8 **Cheng CL**, Sherman S, Watkins JL, Barnett J, Freeman M, Geenen J, Ryan M, Parker H, Frakes JT, Fogel EL, Silverman WB, Dua KS, Aliperti G, Yakshe P, Uzer M, Jones W, Goff J, Lazzell-Pannell L, Rashdan A, Temkit M, Lehman GA. Risk factors for post-ERCP pancreatitis: a prospective multicenter study. *Am J Gastroenterol* 2006; **101**: 139-147

9 **Williams EJ**, Taylor S, Fairclough P, Hamlyn A, Logan RF, Martin D, Riley SA, Veitch P, Wilkinson ML, Williamson PR, Lombard M. Risk factors for complication following ERCP; results of a large-scale, prospective multicenter study. *Endoscopy* 2007; **39**: 793-801

10 **Freeman ML**, Guda NM. Prevention of post-ERCP pancreatitis: a comprehensive review. *Gastrointest Endosc* 2004; **59**: 845-864

11 **LaFerla G**, Gordon S, Archibald M, Murray WR. Hyperamylasaemia and acute pancreatitis following endoscopic retrograde cholangiopancreatography. *Pancreas* 1986; **1**: 160-163

12 **Cotton PB**, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, Liguory C, Nickl N. Endoscopic sphincterotomy complications and their management: an attempt at consensus. *Gastrointest Endosc* 1991; **37**: 383-393

13 **Vaira D**, D'Anna L, Ainley C, Dowsett J, Williams S, Baillie J, Cairns S, Croker J, Salmon P, Cotton P. Endoscopic sphincterotomy in 1000 consecutive patients. *Lancet* 1989; **2**: 431-434

14 **Barthet M**, Lesavre N, Desjeux A, Gasmi M, Berthezene P, Berdah S, Viviand X, Grimaud JC. Complications of endoscopic sphincterotomy: results from a single tertiary referral center. *Endoscopy* 2002; **34**: 991-997

15 **Rodríguez Muñoz S**. Towards safer ERCP: selection, experience and prophylaxis. *Rev Esp Enferm Dig* 2004; **96**: 155-162

16 **Cooper ST**, Slivka A. Incidence, risk factors, and prevention of post-ERCP pancreatitis. *Gastroenterol Clin North Am* 2007; **36**: 259-276, vii-viii

17 **Broe PJ**, Cameron JL. Experimental gallstone pancreatitis. Pathogenesis and response to different treatment modalities. *Ann Surg* 1982; **195**: 566-573

18 **Sanfey H**, Cameron JL. Increased capillary permeability: an early lesion in acute pancreatitis. *Surgery* 1984; **96**: 485-491

19 **Sanfey H**, Bulkley GB, Cameron JL. The role of oxygen-derived free radicals in the pathogenesis of acute pancreatitis. *Ann Surg* 1984; **200**: 405-413

20 **Schoenberg MH**, Büchler M, Beger HG. Oxygen radicals in experimental acute pancreatitis. *Hepatogastroenterology* 1994; **41**: 313-319

21 **Seo JY**, Kim H, Seo JT, Kim KH. Oxidative stress induced cytokine production in isolated rat pancreatic acinar cells: effects of small-molecule antioxidants. *Pharmacology* 2002; **64**: 63-70

22 **Cavallini G**, Tittobello A, Frulloni L, Masci E, Mariana A, Di Francesco V. Gabexate for the prevention of pancreatic damage related to endoscopic retrograde cholangiopancrea tography. Gabexate in digestive endoscopy--Italian Group. *N Engl J Med* 1996; **335**: 919-923

23 **Masci E**, Cavallini G, Mariani A, Frulloni L, Testoni PA, Curioni S, Tittobello A, Uomo G, Costamagna G, Zambelli S, Macarri G, Innocenti P, Dragonetti C. Comparison of two dosing regimens of gabexate in the prophylaxis of post-ERCP pancreatitis. *Am J Gastroenterol* 2003; **98**: 2182-2186

24 **Sanfey H**, Bulkley GB, Cameron JL. The pathogenesis of acute pancreatitis. The source and role of oxygen-derived free radicals in three different experimental models. *Ann Surg* 1985; **201**: 633-639

25 **Nordback IH**, Cameron JL. The mechanism of conversion of xanthine dehydrogenase to xanthine oxidase in acute pancreatitis in the canine isolated pancreas preparation. *Surgery* 1993; **113**: 90-97

26 **Marks JM**, Dunkin BJ, Shillingstad BL, Youngelman DF, Schweitzer MA, Lash RH, Singh J, Ponsky L, Ponsky JL. Pretreatment with allopurinol diminishes pancreatography-induced pancreatitis in a canine model. *Gastrointest Endosc* 1998; **48**: 180-183

27 **Isik AT**, Mas MR, Yamanel L, Aydin S, Comert B, Akay C,

Erdem G, Mas N. The role of allopurinol in experimental acute necrotizing pancreatitis. *Indian J Med Res* 2006; **124**: 709-714

28 **Shabanov VV**, Milyakova MN, Minyailov NA. Antiradical effect of allopurinol at early stages of experimental acute pancreatitis. *Bull Exp Biol Med* 2006; **142**: 29-31

29 **Comert B**, Isik AT, Aydin S, Bozoglu E, Unal B, Deveci S, Mas N, Cinar E, Mas MR. Combination of allopurinol and hyperbaric oxygen therapy: a new treatment in experimental acute necrotizing pancreatitis? *World J Gastroenterol* 2007; **13**: 6203-6207

30 **Katsinelos P**, Kountouras J, Chatzis J, Christodoulou K, Paroutoglou G, Mimidis K, Beltsis A, Zavos C. High-dose allopurinol for prevention of post-ERCP pancreatitis: a prospective randomized double-blind controlled trial. *Gastrointest Endosc* 2005; **61**: 407-415

31 **Budzyńska A**, Marek T, Nowak A, Kaczor R, Nowakowska-Dulawa E. A prospective, randomized, placebo-controlled trial of prednisone and allopurinol in the prevention of ERCP-induced pancreatitis. *Endoscopy* 2001; **33**: 766-772

32 **Mosler P**, Sherman S, Marks J, Watkins JL, Geenen JE, Jamidar P, Fogel EL, Lazzell-Pannell L, Temkit M, Tarnasky P, Block KP, Frakes JT, Aziz AA, Malik P, Nickl N, Slivka A, Goff J, Lehman GA. Oral allopurinol does not prevent the frequency or the severity of post-ERCP pancreatitis. *Gastrointest Endosc* 2005; **62**: 245-250

33 **Romagnuolo J**, Hilsden R, Sandha GS, Cole M, Bass S, May G, Love J, Bain VG, McKaigney J, Fedorak RN. Allopurinol to prevent pancreatitis after endoscopic retrograde cholang iopancreatography: a randomized placebo-controlled trial. *Clin Gastroenterol Hepatol* 2008; **6**: 465-471; quiz 371

34 **Balthazar EJ**. Acute pancreatitis: assessment of severity with clinical and CT evaluation. *Radiology* 2002; **223**: 603-613

35 **Massey V**, Harris CM. Milk xanthine oxidoreductase: the first one hundred years. *Biochem Soc Trans* 1997; **25**: 750-755

36 **Blauch MB**, Koch F, Hanke M. A study of xanthine oxidase of rat blood. *J Biol Chem* 1939; **130**: 471-486

37 **Borges F**, Fernandes E, Roleira F. Progress towards the discovery of xanthine oxidase inhibitors. *Curr Med Chem* 2002; **9**: 195-217

38 **Parks DA**, Granger DN. Xanthine oxidase: biochemistry, distribution and physiology. *Acta Physiol Scand Suppl* 1986; **548**: 87-99

39 **Pacher P**, Nivorozhkin A, Szabó C. Therapeutic effects of xanthine oxidase inhibitors: renaissance half a century after the discovery of allopurinol. *Pharmacol Rev* 2006; **58**: 87-114

40 **Meneshian A**, Bulkley GB. The physiology of endothelial xanthine oxidase: from urate catabolism to reperfusion injury to inflammatory signal transduction. *Microcirculation* 2002; **9**: 161-175

41 **Parks DA**, Skinner KA, Skinner HB, Tan S. Multiple organ dysfunction syndrome: role of xanthine oxidase and nitric oxide. *Pathophysiology* 1998; **5**: 49-66

42 **Folch E**, Gelpí E, Roselló-Catafau J, Closa D. Free radicals generated by xanthine oxidase mediate pancreatitis-associated organ failure. *Dig Dis Sci* 1998; **43**: 2405-2410

43 **Granell S**, Bulbena O, Genesca M, Sabater L, Sastre J, Gelpi E, Closa D. Mobilization of xanthine oxidase from the gastrointestinal tract in acute pancreatitis. *BMC Gastroenterol* 2004; **4**: 1

44 **Mittal A**, Phillips AR, Loveday B, Windsor JA. The potential role for xanthine oxidase inhibition in major intra-abdominal surgery. *World J Surg* 2008; **32**: 288-295

45 **Badalov N**, Baradarian R, Iswara K, Li J, Steinberg W, Tenner S. Drug-induced acute pancreatitis: an evidence-based review. *Clin Gastroenterol Hepatol* 2007; **5**: 648-661; quiz 644

46 **Perney P**, Berthier E, Pageaux GP, Hillaire-Buys D, Roques V, Fabbro-Peray P, Melki M, Hanslik B, Bauret P, Larrey D, Blayac JP, Blanc F. Are drugs a risk factor of post-ERCP pancreatitis? *Gastrointest Endosc* 2003; **58**: 696-700

47 **Bai Y**, Gao J, Zhang W, Zou D, Li Z. Meta-analysis: allopurinol in the prevention of postendoscopic retrograde cholangiopancreatography pancreatitis. *Aliment Pharmacol Ther* 2008; **28**: 557-564

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