A randomised, double blind, multicentre trial of octreotide in moderate to severe acute pancreatitis

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Abstract

Background—The pharmacological inhibition of exocrine pancreatic secretion with the somatostatin analogue octreotide has been advocated as a specific treatment of acute pancreatitis.

Aim—To investigate the efficacy of octreotide in acute pancreatitis in a randomised, placebo controlled trial.

Methods—302 patients from 32 hospitals, fulfilling the criteria for moderate to severe acute pancreatitis within 96 hours of the onset of symptoms, were randomly assigned to one of three treatment groups: group P (n=103) received placebo, while groups O1 (n=98) and O2 (n=101) received 100 and 200 µg of octreotide, respectively, by subcutaneous injection three times daily for seven days. The primary outcome variable was a score composed of mortality and 15 typical complications of acute pancreatitis.

Results—The three groups were well matched with respect to pretreatment characteristics. An intent to treat analysis of all 302 patients revealed no significant differences among treatment groups with respect to mortality (P: 16%; O1: 15%; O2: 12%), the rate of newly developed complications, the duration of pain, surgical interventions, or the length of the hospital stay. A valid for efficacy analysis (251 patients) also revealed no significant differences.

Conclusions—This trial shows no benefit of octreotide in the treatment of acute pancreatitis.

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Keywords: acute pancreatitis; somatostatin; octreotide; randomised controlled multicentre trial

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Acute pancreatitis is clinically classified into mild and severe forms.[1] The majority of patients suffer from mild acute pancreatitis, a self limiting disease which responds well to conservative treatment. In up to 20% of patients with acute pancreatitis, however, the disease progresses to a severe form involving both pancreatic and extrapancreatic necrosis. While the morbidity and mortality of mild acute pancreatitis are low, patients with severe acute pancreatitis commonly develop systemic complications and have a mortality of 10–50%, despite all currently available treatment strategies.[2–8]

Although the initial steps in the pathogenesis of acute pancreatitis are not fully understood, the term "autodigestion", introduced by Chiari in 1896, summarises the prevailing concept that the acute inflammation is triggered by the activation of digestive enzymes.[9 10] The earliest trial of somatostatin, a hormone which inhibits exocrine pancreatic secretion, as a rational therapeutic approach in human acute pancreatitis, yielded "an impressive clinical improvement".[11] The findings of later, randomised trials of somatostatin in acute pancreatitis were controversial.[12–17] However, a meta-analysis of all adequately designed studies concluded that somatostatin treatment reduced mortality from 14% to 6.2%.[18] In contrast to experimental findings,[19] clinical studies showed that basal exocrine secretion is essentially normal during the acute inflammatory phase of acute pancreatitis.[20 21] These results provoked interest in the synthetic somatostatin analogue octreotide as a potentially useful specific treatment for acute pancreatitis. In an open phase I/II study of patients with moderate and severe acute pancreatitis treated with three different doses of octreotide (100, 200, or 500 µg three times daily), an apparent reduction in the rate of newly developed complications was found which was particularly pronounced in the 200 µg group.[22] We were thus encouraged to evaluate the efficacy of this drug in a randomised, controlled, multicentre trial.

Patients and methods

This report was prepared in accordance with the Consolidated Standards of Reporting Trials (the "CONSORT statement").[23]

STUDY DESIGN AND PROTOCOL

The study protocol was approved by the Ethics Committees of the Universities of Bern (Switzerland) and Ulm and Bremen (Germany). The two treatment groups received octreotide in different doses, 100 µg three times daily (O1) and 200 µg three times daily (O2); the control group received placebo (P). It was intended to enrol 100 patients in each group, as suggested by a power analysis (see below).

Patients with moderate or severe acute pancreatitis were the target group of the study; mild cases were excluded. To be enrolled,

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Abbreviations used in this paper: ARDS, adult respiratory distress syndrome; CRF, case report form; CT, contrast enhanced computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; ITT, intent to treat; O, octreotide; P, placebo; RCT, randomised controlled trial; SIRS, systemic inflammatory response syndrome; VFE, valid for efficacy.

Table 1   Inclusion criteria

Necessary criteria
   First symptoms of acute pancreatitis not more than 96 hours before enrolment
   Serum amylase or lipase increased at least threefold during this period
   Spontaneous upper abdominal pain during this period
   Written informed consent to participate in the study*
Supporting criteria (fulfilment of at least four required)
   Local abdominal resistance
   Subileus/ileus
   Shock: pulse ≥100/min and systolic blood pressure ≤80 mm Hg for more than 10 minutes
   Arterial PO_2 <60 mm Hg
   Leucocyte count >12 g/l
   C-reactive protein >120 mg/l
   Fasting blood glucose >8.4 mmol/l†
   Hypocalcaemia ≤2.0 mmol/l
   Serum creatinine >240 μmol/l
   Characteristic findings of moderate or severe acute pancreatitis on ultrasound or contrast enhanced CT

*If the patient was not competent to give informed consent, the treating physician was allowed to decide in consultation with the patient's family.
†This criterion was not applied in patients with pre-existing diabetes mellitus.

Table 2   Exclusion criteria

Symptoms of acute pancreatitis present for more than 96 hours
Known chronic renal failure
   Serum creatinine continuously >480 μmol/l
   Patient with renal transplant
   Patient undergoing chronic dialysis
Age under 18 years
Pregnancy
Psychosis (except alcoholic delirium)
Previous treatment with aprotinin, glucagon, calcitonin, pirenzepine, atropine, native somatostatin
Second enrolment in the study (new enrolment on relapse not allowed)

Table 3   Optional treatments

Analgesics*
Psychotropics*
Antibiotics*
Treatment* directed at specific complications—for example, insulin, oxygen, mechanical ventilation, H_2 antagonists/proton pump inhibitors
Dialysis or haemofiltration†
Peritoneal lavage†
ERC/ERCP with/without papillotomy†
Interventional and surgical procedures†

*Type and dosages of the drugs were recorded in the case report forms (CRFs).
†The date and other specific information were recorded in the CRFs.
ERC, endoscopic retrograde cholangiography; ERCP, endoscopic retrograde cholangiopancreatography.

patients were required to fulfil four necessary criteria and four of 10 supporting criteria, as defined in a previous multicentre trial (table 1).[8] The necessary and supporting criteria were waived in cases where the diagnosis of severe acute pancreatitis was confirmed by laparotomy within four days of the onset of symptoms. The exclusion criteria of the previous trial were also used in this trial (table 2).[8]

BLINDING AND RANDOMISATION
Each of the participating centres received packages of vials containing either octreotide or placebo. A multiple of six packages (6, 12, 18, etc.) was sent to each centre. Each package contained equal numbers of vials for groups P (n=2), O1 (n=2), and O2 (n=2) in a blinded fashion. The packages were used sequentially as the patients were enrolled in the study. There was thus a strict randomisation in three parallel groups in each hospital, and a strict double blind procedure was guaranteed. The unbroken codes of the individual packages were deposited with the chief investigator in each hospital. A provision was made that the code could be broken in case of severe adverse events after notification of both the principal investigator and trial coordinator.

MEDICATION
The study medication was stored at 2–8°C. The first subcutaneous injection of the study medication was given immediately after enrolment of the patient. Further injections were given at eight hour intervals over the following seven days.

BASAL TREATMENT
The standardised basal treatment was according to generally accepted principles of supportive care in acute pancreatitis,[8] including nothing by mouth diet, nasogastric tube (obligatory in severe acute pancreatitis, optional in moderate acute pancreatitis), central venous catheter, input/output monitoring, and adequate parenteral replacement of fluid and electrolytes. Lipid infusions were permitted, but parenteral hyperalimentation was not. Table 3 summarises further treatments used in some cases; these had to be recorded in the case report forms (CRF).

PRIMARY AND SECONDARY OUTCOME VARIABLES
The efficacy of the treatment was assessed by a score composed of mortality and the occurrence of 15 typical complications (tables 4 and 5). Death was considered to be worse than all other complications together. Therefore, early deaths without complications were assessed

Table 4   Definitions of local, organ, and metabolic complications of severe acute pancreatitis

Local and organ complications	
Shock	Pulse >100/min and systolic blood pressure <80 mm Hg for more than 10 minutes
Sepsis	Leucoctyes >12 g/l or <4 g/l; platelets <100 g/l; body temperature >38.5°C; positive blood culture; metabolic acidosis (base excess greater than −4 mmol/l) (4 of 5 criteria required)
Pulmonary insufficiency	Arterial PO_2 <8 kPa (60 mm Hg) (despite 4 litres O_2/min via nasal tube) or need for mechanical ventilation
Renal insufficiency	Increase in serum creatinine to more than twice the normal value
Peritonitis	Intraoperative finding of suppurative intra-abdominal infection
Haemorrhage	Gastrointestinal and/or intra-abdominal bleeding requiring ≥4 units
Abscess/infected pancreatic necrosis	Pus collection or infected fluid shown by ultrasound or CT guided fine needle aspiration and microbiological culture, or by (re)laparotomy
Fluid collection	Fluid collection with an extent of 5×5 cm or more on sonography or CT
Ileus/subileus	Clinical or radiological signs of intestinal paralysis or obstruction
Metabolic complications	
Hypocalcaemia	Calcium ≤2.0 mmol/l
Coagulopathy	Prothrombin time <70% and/or partial thromboplastin time >45 seconds
Hyperglycaemia	Blood glucose level >8.4 mmol/l
Metabolic acidosis	Base excess greater than −4.0 mmol/l
Jaundice	Total serum bilirubin >20 μmol/l
Encephalopathy	Neuropsychiatric symptoms, abnormal electroencephalogram (except alcoholic delirium)

Table 5 Complication score as primary outcome variable

Organ complication	Points	Metabolic complication	Points
Shock	4	Hypocalcaemia	2
Sepsis	4	Coagulopathy	2
Pulmonary insufficiency	3	Hyperglycaemia	2
Renal insufficiency	3	Metabolic acidosis	2
Peritonitis	3	Jaundice	1
Haemorrhage	3	Encephalopathy	1
Abscess	3		
Pseudocyst	3		
Ileus/subileus	1		
Death	38		

For each complication occurring in a patient the corresponding points were added. The number of points assigned to a complication express the clinical relevance of the complication for acute pancreatitis. Death was assigned 38 points (equal to the sum of all scores + 1), because it is worse than all other complications together. Primary outcome was the sum of points at admission minus the sum of points for complications acquired during treatment. Hence, positive values of the score indicate improvement, negative values deterioration.

Table 6 Secondary outcome variables and clinical and laboratory parameters monitored for safety reasons

Secondary outcome variables
    Total duration of pain until the patient became pain free
    Apache II score
Clinical and laboratory parameters
    Blood pressure, pulse, temperature
    Leucocytes, haematocrit, haemoglobin, platelets
    Partial thromboplastin time, prothrombin time
    Calcium
    Glucose
    Total bilirubin
    Creatinine
    Aspartate aminotransferase
    Lactate dehydrogenase
    Amylase
    Lipase
    C-reactive protein
    Arterial P_{O_2}, base excess

adequately. The chief investigator in each hospital was advised to look for these complications each day during the treatment phase (day 0 to day 7) and in the follow up period on days 8–11, 12–14, and 15–21, and on the day of discharge. The severity of acute pancreatitis during the study period was graded according to a scoring system defined in a previous study on the basis of these complications.[8] The clinical change in each patient was calculated as the score given on enrolment in the trial, minus the total score for newly developed complications during hospitalisation. A zero or negative calculated value thus indicates clinical deterioration, while a positive value indicates clinical improvement.

The duration of pain and the Apache II scores over the study period were used as secondary outcome variables. Other parameters were monitored for safety reasons (table 6) daily from day 0 to day 7, and thereafter at the same intervals as those used to assess efficacy.

The preparation, randomisation, and delivery of the study medication, as well as the monitoring of the study centres by checking the information in the CRFs, were carried out by Novartis (formerly Sandoz), Nuremberg (Germany). The study headquarters was located in the Department of Visceral and Transplantation Surgery of the University of Bern (Switzerland) and was responsible for medical problems, data checking, and data entry. Checking of the data for plausibility, and all statistical analyses, were performed by the Department of Biometry and Medical Documentation of the University of Ulm (Germany), after the code was broken.

POWER ANALYSIS AND STATISTICS
In the multicentre study with the use of gabexate mesilate in moderate to severe acute pancreatitis, the percentage of patients with one or more newly developed complications in the placebo group was 63%.[8] In the present octreotide study, conducted in patients with disease of the same degree of severity, we hypothesised that octreotide treatment would reduce the complication rate from 63% to 35%. A power analysis indicated that 100 patients would have to be enrolled in each of the three groups to detect such a reduction at

Table 7 Characteristics of the 302 patients in the intent to treat analysis

Characteristics	Total (n=302)	Placebo (n=103)	O1 (n=98)	O2 (n=101)
Sex (M/F)	198/104	62/41	70/28	66/35
Age				
Mean	50	53.5	49.4	49.9
Range	18–93	19–93	18–88	21–87
Aetiology				
Alcohol	126 (42%)	42 (41%)	41 (42%)	43 (43%)
Gallstones	111 (37%)	38 (37%)	35 (36%)	38 (38%)
Alcohol + gallstones	4 (1%)	0	2 (2%)	2 (2%)
Alcohol + others	2 (0.7%)	0	1 (1%)	1 (1%)
Others	59 (20%)	23 (22%)	19 (19%)	17 (17%)
Duration of pain (hours)*	44 (0–145)	46 (2–103)	44 (7–145)	44 (0–105)
Severity of disease†				
Ranson score	3 (0–9)	3 (1–8)	3 (0–8)	3 (0–9)
Apache II score	8 (0–37)	7 (0–28)	7 (0–22)	9 (0–37)
Complication score	6 (1–30)	6 (1–20)	6 (1–27)	7 (1–30)
C-reactive protein	148 (0–777)	150 (0–438)	141 (2–777)	146 (1–510)
CT findings‡				
Normal pancreas	1 (0.3%)	1 (1%)	0	0
Oedema	22 (7%)	10 (10%)	3 (3%)	9 (9%)
Oedema + exudate	133 (44%)	48 (47%)	49 (50%)	36 (36%)
Necrosis <30%	70 (23%)	25 (24%)	17 (17%)	28 (28%)
Necrosis <50%	26 (9%)	4 (4%)	13 (13%)	9 (9%)
Necrosis >50%	12 (4%)	2 (2%)	5 (5%)	5 (5%)
Not performed	38 (13%)	13 (13%)	11 (11%)	14 (14%)
Total	302 (100%)	103 (100%)	98 (100%)	101 (100%)

*Until enrolment; median values (range).
†Median values (range).
‡CT findings within 96 hours after onset of symptoms.

Table 8   Characteristics of the 251 patients in the valid for efficacy analysis

Characteristics	Total (n=251)	Placebo (n=90)	O1 (n=78)	O2 (n=83)
Sex (M/F)	169/82	54/36	58/20	57/26
Age				
Mean	50.6	54.3	48.5	48.7
Range	18–93	19–93	18–84	21–80
Aetiology				
Alcohol	103 (41%)	33 (37%)	33 (42%)	37 (45%)
Gallstones	96 (38%)	37 (41%)	29 (37%)	30 (36%)
Alcohol + gallstones	2 (0.8%)	0	0	2 (2%)
Alcohol + others	2 (0.8%)	0	1 (1%)	1 (1%)
Others	48 (19%)	20 (22%)	15 (19%)	13 (16%)
Duration of pain (hours)*	44 (4–96)	46 (5–96)	44 (7–96)	44 (4–96)
Severity of disease†				
Ranson score	3 (0–9)	4 (1–8)	3 (1–8)	3 (0–9)
Apache II score	7 (0–37)	7 (0–28)	7 (0–22)	9 (0–37)
Complication score	6 (1–27)	6 (1–20)	6 (1–27)	6 (1–27)
C-reactive protein	145 (0–777)	154 (0–438)	134 (2–777)	146 (1–510)
CT findings‡				
Normal pancreas	1 (0.4%)	1 (1%)	0	0
Oedema	19 (8%)	9 (10%)	2 (3%)	8 (10%)
Oedema + exudate	115 (46%)	44 (49%)	42 (54%)	29 (35%)
Necrosis <30%	60 (24%)	22 (24%)	15 (19%)	23 (28%)
Necrosis <50%	19 (8%)	2 (2%)	10 (13%)	7 (8%)
Necrosis >50%	9 (4%)	2 (2%)	3 (4%)	4 (5%)
Not performed	28 (11%)	10 (11%)	6 (8%)	12 (14%)
Total	251 (100%)	90 (100%)	78 (100%)	83 (100%)

*Until enrolment; median values (range).
†Median values (range).
‡CT findings within 96 hours of onset of symptoms.

the one sided 5% significance level with a power of 98.8%. If the power is reduced to 80% a decrease in the complication rate from 63% to 45% can be detected under the same conditions.

Two orthogonal tests were applied to the primary and secondary outcome variables: the two octreotide groups, taken together, were tested against placebo (O1, O2 versus P), and high dose octreotide was tested against low dose octreotide (O2 versus O1). A χ^2 or Fisher's exact test was applied for qualitative variables, and a Wilcoxon U or Kruskal-Wallis H test for quantitative variables.

The study was designed for one single outcome variable. However, the restriction to one outcome variable is only relevant if the study delivers a significant result. If several outcome variables are tested, but none of these tests is significant, this gives even more evidence that octreotide is not helpful in moderate to severe acute pancreatitis than one test on the primary outcome variable. In the case of non-significance the problem is not to control type 1 error, but to minimise type 2 error. The latter is true if no significance is achieved despite testing several outcome variables.

Results

PATIENT CHARACTERISTICS

Thirty one centres in Germany and one in Switzerland participated in this trial; 302 patients with moderate to severe acute pancreatitis were enrolled from November 1993 to March 1996. The mean age was 50 years (range 18–93); there were 198 men and 104 women (table 7). The aetiology of acute pancreatitis was alcohol abuse in 126 patients (42%), gallstones in 111 (37%), alcohol abuse and gallstones in four, alcohol and other causes in two, and other aetiologies in 59 (20%). The median time elapsing from the onset of symptoms to entry into the study was 44 hours (range 0–145), and the patients fulfilled a median of five supporting criteria (range 3–10) on enrolment. The median Ranson, Apache II, and complication scores were 3 (range 0–9), 8 (range 0–37), and 6 (range 1–30) points, respectively. Contrast enhanced computed tomography (CT) was performed within 96 hours in 264 (87%) of the 302 patients; pancreatic oedema with exudate, and varying extents of pancreatic and peripancreatic necrosis, were found in 133 (44%) and 108 (36%) patients, respectively.

The intent to treat (ITT) analysis included all 302 patients enrolled in the study. A total of 103 patients were treated with placebo (P), 98 with octreotide 100 μg three times daily (O1), and 101 with octreotide 200 μg three times daily (O2). Table 7 gives the patient characteristics in the three treatment groups. Fifty one patients were excluded from the valid for efficacy (VFE) analysis for various reasons:
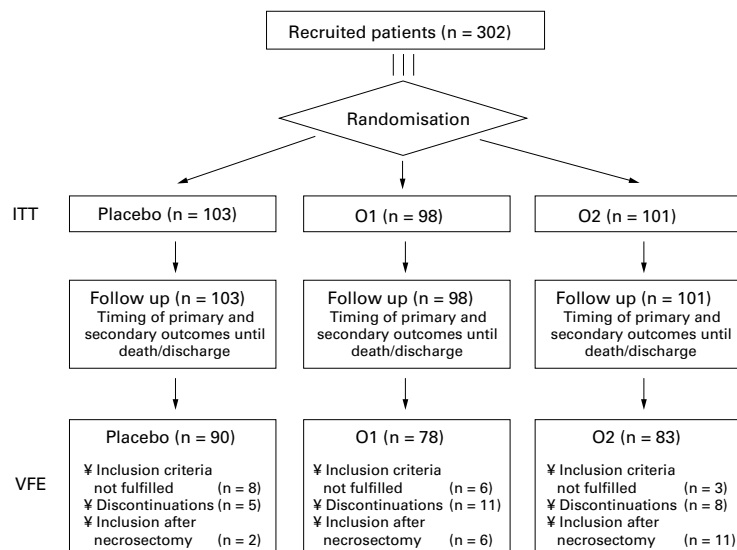

Figure 1   Flow chart of the allocation of patients to the study groups. ITT, intent to treat analysis; VFE, valid for efficacy analysis. Some patients were excluded for more than one reason.

Table 9   Primary and secondary outcome variables in the intent to treat analysis

Outcome variables	Total (n=302)	Treatment groups		
		Placebo (n=103)	O1 (n=98)	O2 (n=101)
Death	43 (14%)	16 (16%)	15 (15%)	12 (12%)
Death ≤14 days	17	3	8	6
Death >14/≤30 days	9	3	3	3
Death >30 days	17	10	4	3
Patients with newly developed complications	220 (73%)	73 (71%)	74 (76%)	73 (72%)
Duration of pain (days)*	6 (0–209)	6 (0–209)	6 (0–105)	7 (1–156)
Hospital stay (days)*	21 (0–210)	21 (2–210)	21 (0–112)	22 (2–163)

*Median values (range).

Table 10   Complications at inclusion of the patients and newly developed complications in the intent to treat analysis

	Number of patients with complications at inclusion (n=302)	Number of patients with newly developed complications		
		Placebo (n=103)	O1 (n=98)	O2 (n=101)
Local and organ complications				
Shock	42	8	2	4
Sepsis	14	4	4	5
Pulmonary failure	98	20	13	17
Renal insufficiency	25	5	7	5
Peritonitis	13	2	1	7
Haemorrhage	4	7	3	4
Abscess/infected pancreatic necrosis	6	8	8	7
Fluid collection	144	7	3	5
Ileus/subileus	281	2	1	0
Metabolic complications				
Hypocalcaemia	108	32	31	26
Coagulopathy	58	34	32	26
Hyperglycaemia	191	14	15	18
Metabolic acidosis	55	11	11	10
Jaundice	167	15	14	19
Encephalopathy	20	3	2	9
Death	43	16	15	12

Table 11   Primary and secondary outcome variables in the valid for efficacy analysis

Outcome variables	Total (n=251)	Treatment groups		
		Placebo (n=90)	O1 (n=78)	O2 (n=83)
Death	27 (11%)	13 (14%)	7 (9%)	7 (8%)
Death ≤14 days	4	1	2	1
Death >14/≤30 days	8	3	2	3
Death >30 days	15	9	3	3
Patients with newly developed complications	180 (73%)	61 (68%)	59 (76%)	60 (72%)
Duration of pain (days)*	6 (0–209)	6 (0–209)	6 (0–105)	7 (1–89)
Hospital stay (days)*	21 (5–210)	22 (7–210)	21 (5–105)	20 (7–163)

*Median values (range).

the frequency of necrosectomy at enrolment in the study (p=0.023); however, even though this p value rose above the 5% significance level after adjustment for multiple testing with the Bonferroni-Holm correction, all patients with initial laparotomy and necrosectomy were excluded from the VFE analysis. Additionally, the influence of the centres on mortality was estimated with a logistic regression calculation. Neither the centres nor the treatment groups were significantly different in mortality according to either the ITT (p=0.22 and p=0.85, respectively) or VFE (both p=0.54) analyses.

PRIMARY OUTCOME VARIABLES

In the ITT analysis, 14% (43/302) of the patients died, with a mortality of 16% (16/103), 15% (15/98), and 12% (12/101), in group P, O1, and O2, respectively (p=0.71). The three groups also did not differ in early and late mortality (table 9). Nearly three quarters of the patients developed new complications in the course of the study (P: n=73, 71%, O1: n=74, 76%; O2: n=73, 72%); there was no significant difference among the three groups in the overall morbidity or in the frequency of each of the 15 specified complications (table 10). The median difference between the complication scores at inclusion and over the course of treatment (newly developed complications only) was 3 in the placebo group and 3 in the two octreotide groups combined (p=0.12). The comparison of O2 with O1 revealed a median difference of complication scores of 4 in the high dose octreotide group, as opposed to 3 in the low dose octreotide group (p=0.059; fig 2). The VFE analysis yielded a mortality of 11% (27/251), distributed as 14% (13/90) in group P, 9% (7/78) in O1, and 8% (7/83) in O2 (p=0.37). The other figures were similar to those found in the ITT analysis (table 11).

SECONDARY OUTCOME VARIABLES

The median duration of pain was six days in both P and O1, and seven days in O2, according to either the ITT analysis or the VFE analysis (tables 9 and 11). There were no differences in the Apache II score (fig 3) or in the laboratory parameters listed in table 6.

Surgical intervention for necrosectomy was necessary in 46 patients during the course of the study, 19 (18%) in P, 13 (13%) in O1, and 14 (14%) in O2. Other pancreatitis related operations (for example, relaparotomy for abscess, symptomatic postacute pseudocysts, etc., and cholecystectomy) were performed in 34 patients (33%) in P, 34 (35%) in O1, and 42 (42%) in O2. The rates of surgical intervention were similar in the VFE patient population.

The median length of hospital stay was 21 days (range 0–210) in both the ITT and the VFE analyses and did not differ significantly among treatment groups (tables 9 and 11).

Discussion

The idea that the pharmacological inhibition of exocrine pancreatic secretion might serve as a specific treatment for acute pancreatitis has been a subject of controversy for more than

unfulfilled inclusion criteria (n=17), discontinuation or incorrect use of study medications (n=14), withdrawal of consent (n=10), and previous laparotomy with necrosectomy (n=19) (fig 1). Table 8 summarises the characteristics of the remaining 251 patients considered in the VFE evaluation (90 in P, 78 in O1, and 83 in O2).

COMPARABILITY OF GROUPS

There were no demographic differences between treatment groups in the categorical variables sex, aetiology, severity of disease, and presence of pre-existing and accompanying diseases (tables 7 and 8). Twenty three variables were used to assess the comparability of groups in the ITT and VFE analyses; there was therefore an expectation of 1.15 falsely significant tests at the 5% significance level. The only indication of a non-comparability of groups was a nominally significant difference in
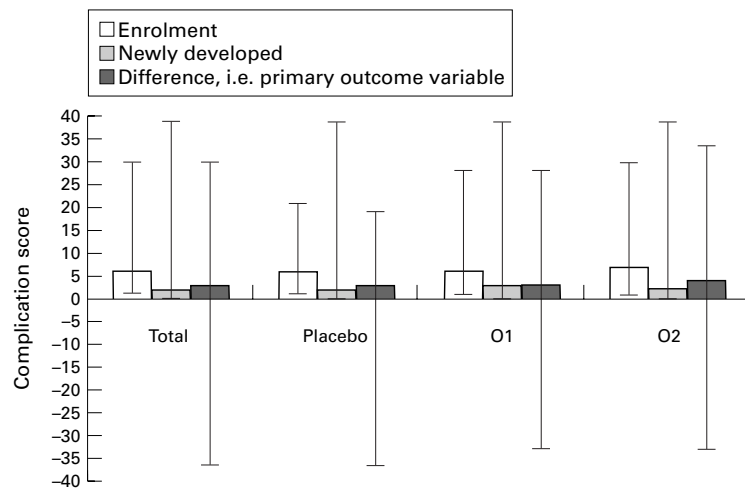
Figure 2   Scores for complications on enrolment, newly developed complications, and their difference in the intent to treat patient group. Results expressed as medians and ranges. The difference in complication scores (enrolment minus new complications) was computed for each patient. The median of the individual differences was then calculated.
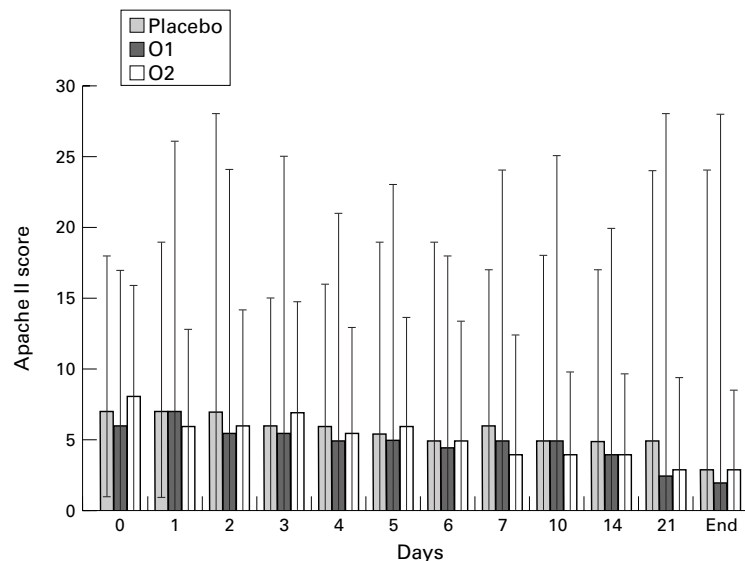

Figure 3   Course of the Apache II score in the intent to treat patient group. Results are expressed as medians and ranges.

occur as a result of infection of pancreatic necrosis.[26]

Although the initiating pathophysiological processes are not known, the disease is thought to result from destruction of the pancreas and peripancreatic fatty tissue by digestive enzymes which are produced in the acinar cells and activated intracellularly or extracellularly.[9 10] Two treatment options might be of value to limit the "autodigestive" local damage and to interfere with SIRS in the early phase of acute pancreatitis: inhibition of the activated enzymes with protease inhibitors; or inhibition of exocrine secretion to "put the gland to rest" and prevent the further release and activation of digestive enzymes. Protease inhibitors (such as aprotinin and gabexate mesilate), hormones (such as calcitonin and glucagon), and atropine have all been clinically tested as possible specific treatments for acute pancreatitis, so far without success.[6–8]

Somatostatin and its analogue octreotide have been tested in several experimental models of acute pancreatitis, with contradictory results, sometimes negative,[27–31] and sometimes positive.[32–37] The first clinical study of somatostatin treatment, published in 1980, revealed "an impressive improvement" in all 14 patients treated with a continuous intravenous infusion of somatostatin.[11] This encouraging result provided the motivation for further trials, none of which showed a significant benefit on the prognosis of patients with acute pancreatitis.[12–17] In 1991, Carballo and colleagues[18] published a meta-analysis of six randomised clinical trials involving somatostatin. The individual trials had not revealed any statistically significant benefit; in the meta-analysis, however, the 207 patients in the somatostatin group had a significantly lower mortality than the 207 patients in the placebo group (6.2% versus 14%, p<0.01). A possible explanation for the apparent lack of effect in the individual clinical studies was suggested by the finding that, in various animal models of acute pancreatitis, the basal and stimulated pancreatic exocrine secretion are reduced or even nearly abolished.[19] Yet this has been found not to be the case in human acute pancreatitis, where the initial interdigestive exocrine pancreatic secretion remains in the normal range or is even increased.[20 21]

Octreotide, a long acting octapeptide analogue of the native hormone somatostatin, became clinically available in 1982.[38] It has proved to be a powerful inhibitor of basal and stimulated exocrine pancreatic secretion in healthy volunteers, and, unlike somatostatin, can be given subcutaneously.[39] The results of a phase I/II study with three different octreotide dosages suggested a possible benefit in acute pancreatitis.[22] The patients receiving 200 μg of octreotide three times daily had fewer complications than those receiving 100 μg three times daily, or than historical controls.

While our trial was being conducted, other clinical studies of somatostatin or octreotide treatment in acute pancreatitis were published, with conflicting results (table 12).[40–46] These studies, however, are open to criticism: they either were not randomised, controlled

three decades. Activated pancreatic enzymes seem to be involved in the generation and progression of this "autodigestive" acute inflammatory disease, and it was therefore hypothesised that the administration of somatostatin or its analogue octreotide might help prevent progression of the disease and its complications. Nonetheless, the present randomised, controlled, multicentre study, whose size and design give it the power to detect a major clinical benefit if present, found no evidence for any positive effect of octreotide treatment on the course and outcome of patients with moderate to severe acute pancreatitis.

The morbidity and mortality of severe acute pancreatitis are still distressingly high.[2–5] Its natural course has two phases. The first phase (during the first two weeks after onset) is characterised by a systemic inflammatory response syndrome (SIRS) due to the liberation of vasoactive and toxic mediators by the necrotising process.[24 25] In the second phase (during the third week and beyond), septic complications

Table 12 Prospective clinical studies using somatostatin or its analogue octreotide in human acute pancreatitis

Reference	Study design	Drug/dosage	Number of patients	Complications		Mortality	
				Controls	Treatment	Controls	Treatment
Gjorup and colleagues[40]	RCT, multicentre	Somatostatin 250 µg/h for 3 days	63	30% (9/30)	42% (14/33)	3% (1/30)	3% (1/33)
Luengo and colleagues[41]	RCT	Somatostatin 250 µg/h for 48 h	100	NA	NA	2% (1/50)	2% (1/50)
Beechey-Newman[42]	Open	Octreotide 0.5 µg/kg/h for 10 days	19	NA	NA	0%	0%
O'Hair and colleagues[43]	RCT	Octreotide 100 µg t.i.d. s.c. until discharge	180	10% (9/90)	3% (3/90)	0%	1% (1/90)
Paran and colleagues[44]	Open	Octreotide 100 µg t.i.d. s.c. for 14 days	38	74% (14/19) 63% (12/19)	26% (5/19)[†] 37% (7/19)[‡]	31% (6/19)	10.5% (2/19)
Fiedler and colleagues[45]	Case controlled	Octreotide 100 µg t.i.d. i.v. for 10 days	93	87% (47/59) 40% (21/59)	51% (26/39)[§] 18% (7/39)[¶]	61% (33/54)	26% (10/39)[*]
McKay and colleagues[46]	RCT, multicentre	Octreotide 40 µg/h i.v. for 5 days	58	37% (11/30)	53% (15/28)	20% (6/30)	18% (5/28)
Present study	RCT, multicentre	Octreotide 100 µg t.i.d. s.c. for 7 days	302	71% (73/103)	76% (74/98)	16% (16/103)	15% (15/98)
		Octreotide 200 µg t.i.d. s.c. for 7 days		71% (73/103)	72% (73/101)	16% (16/103)	12% (12/101)

RCT, randomised controlled trial; NA, not assessed.
*p<0.05; †sepsis, p=0.004; ‡ARDS, p=0.1; §shock, p<0.05; ¶ARDS, p<0.05.

trials,[42 44 45] included mainly patients with mild acute pancreatitis,[40–43] or contained only a small number of patients.[40–42 44–46] The present multicentre trial sought to overcome all these problems by including a sufficiently large number of patients with an adequate level of disease severity, and randomising them to either octreotide or placebo treatment within 96 hours of the onset of symptoms. This period was chosen so that the patients in the study would all be in the early phase of the disease. From early surgical interventions in severely ill patients, and from serial measurements of C-reactive protein, it has been shown that pancreatic necrosis develops early in the course of the disease (within 96 hours), regardless of the underlying aetiology.[47 48] It therefore seemed reasonable to evaluate the possible benefit of octreotide within this early, "vulnerable" period. The severity of acute pancreatitis among the patients in our study can be seen from the median Ranson and Apache II scores (3 and 8, respectively), from the overall mortality rate (14%), and from the fact that 80% of the patients had initial CT findings consistent with severe acute pancreatitis of Ranson grade C or worse.[49] However, octreotide was not found to be beneficial to our patients, either in the intent to treat (n=302) or in the valid for efficacy (n=251) analysis.

In other clinical circumstances, octreotide has been found beneficial if given prophylactically before invasive pancreatic procedures are performed, such as ERCP,[50] elective pancreatic surgery,[51–54] and pancreatic transplantation.[55] However, for the great majority of patients with acute pancreatitis, prophylactic treatment is not possible; octreotide therapy may well come too late, because of the unavoidable interval between the onset of symptoms and hospitalisation. This problem is likely to impair the usefulness of any drug, not just octreotide, used to interfere with the early phase of acute pancreatitis.

In conclusion, octreotide treatment for acute pancreatitis cannot be recommended on the basis of our results. The early phase of severe acute pancreatitis with SIRS can be managed successfully today with maximal intensive care support, without any specific medication directed against the pathophysiological process of acute pancreatitis. In the late phase, however, septic complications frequently occur and are the most important risk factor for death. Preventing infection of pancreatic necrosis thus seems to be the most promising approach to the treatment of this disease at present.[26 56–59]

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