GASTROINTESTINAL FISTULAE

Role of somatostatin-14 and its analogues in the management of gastrointestinal fistulae: clinical data

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Summary: Somatostatin-14 and its analogue octreotide both exert inhibitory effects on gastrointestinal secretions and may therefore be beneficial in the treatment of gastrointestinal fistulae. There are no studies that have compared these two drugs directly and hence this paper aims to review studies that are available for each drug. There are only six controlled studies that have examined the effects of somatostatin-14 and octreotide on fistula output reduction, three for each drug. All studies compared conservative therapy and the drug in combination with conservative therapy. Of the somatostatin-14 studies, two showed a significant effect on output ($p<0.05$) and the other demonstrated an output reduction on day 1 that was twice that in the control group (NS). Of the octreotide studies, one showed a significant effect ($p<0.01$) and the other two showed no effect of the drug on output. No study with either drug has demonstrated an increase in the number of patients that have achieved closure. However, a positive effect on the time to achieve closure has been found. Of the five controlled studies with somatostatin-14, all showed a significant reduction in time to closure. Of the two controlled studies with octreotide, one showed a significant reduction ($p=0.002$) and the other showed no difference. Due to the limited number of trials, a definitive evaluation of the efficacies of somatostatin-14 and octreotide in the treatment of gastrointestinal fistulae is not possible. However, currently available information seems to suggest a considerable benefit of somatostatin-14 when administered in association with standard conservative treatment, but this needs to be confirmed in a large prospective controlled study.

Gastrointestinal fistulae most commonly develop after surgery although conditions such as inflammatory bowel disease (IBD) and pancreatitis can lead to spontaneous fistula formation.[1] The development of a fistula is a serious complication as it causes the diversion or loss of gastrointestinal contents, digestive secretions, water, electrolytes, and nutrients, resulting in malnutrition and possibly death.

Gastrointestinal fistulae present a considerable surgical challenge. Since the 1970s, the mainstay of fistula treatment has been artificial nutrition to stabilise the patient and induce gastrointestinal tract rest, and antibiotics to control infection. Before the introduction of artificial nutrition, mortality rate among patients with external gastrointestinal fistulae was very high (48%).[2] The introduction of total parenteral nutrition (TPN) reduced mortality and has been suggested to increase closures rates[3] to approximately 60%,[4] but time to achieve fistula closure remained long, and was associated with considerable morbidity. Fistulae patients receiving oral or enteral nutrition are treated in the same way as patients with high output jejunostomy; restricted oral fluids, glucose-saline solutions sipped, and administration of drugs that either reduce gastrointestinal motility (loperamide or codeine phosphate) or secretions (H_2 antagonists or proton pump inhibitors).[5]

More recently, the pharmacological agents somatostatin-14 and its analogue octreotide have been used in addition to artificial nutrition, due to their inhibitory effects on gastrointestinal secretions.[6] However, despite numerous case series and small uncontrolled studies, there is still a lack of large, double blind, randomised, controlled studies. In this paper, we analyse the available data, classified according to evidence based medicine (EBM) scores,[7] and endeavour to reach a conclusion about the potential role of these drugs in the management of gastrointestinal fistulae.

MANAGEMENT

Diagnosis

External gastrointestinal fistulae are easily recognisable—the presence of drainage fluid makes it possible to diagnose the complication and analysis of its contents may help to establish the site of the fistula. However, undrained internal fistulae are more difficult to diagnose. Generally, the patient will complain of pain and intestinal obstruction, and eventually a septic state will result. Diagnosis of a fistula should be followed by rapid patient assessment, including medical history and thorough examination. The output volume of the fistula should be determined, and biochemical evaluation (amylase and bilirubin content) of the fistula fluid performed. Further tests, such as the methylene blue test, microbiological evaluation, and various radiographic evaluations (computed tomography (CT) scan, *x* ray, magnetic resonance imaging (MRI) or ultrasonography) or endoscopies can also be highly informative.

Goals of treatment

The main goal of fistula treatment is to achieve closure (cicatrisation) in the shortest possible time (fig 1). This can generally be achieved by patient management to reduce the loss of fluids and nutrients, and by reducing the output of the fistula (for example, with pharmacotherapy). Minimising the cicatrisation time should reduce the risk of infection and shorten hospital stay, hence improving the quality of life for the patient and reducing treatment and hospital costs (fig 1).

Conservative treatment

Once a fistula has been diagnosed, immediate conservative treatment should involve monitoring and control of fluid,

Abbreviations: CT, computed tomography; EBM, evidence based medicine; IBD, inflammatory bowel disease; MRI, magnetic resonance imaging; SSTR, somatostatin receptor; TPN, total parenteral nutrition.

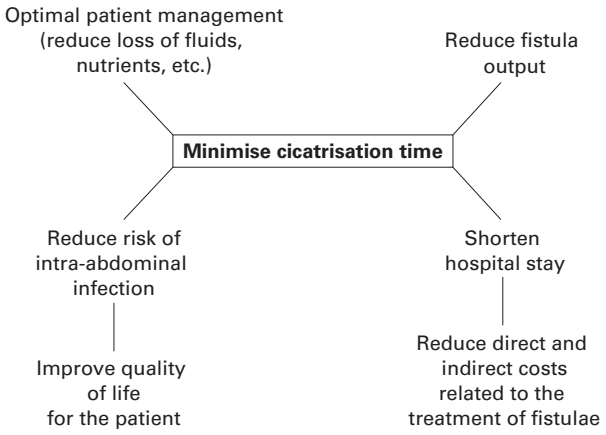

Figure 1 The goals of treatment for patients with gastrointestinal fistulae.

electrolyte and acid-base imbalances, as well as nutritional state, fever, shock, and sepsis. Fluid and nutrition levels can be effectively controlled using artificial nutrition—enteral nutrition, parenteral nutrition, or TPN. This initiates gastrointestinal tract rest which may reduce fistula output by decreasing the production of gastrointestinal and pancreatic secretions thereby promoting conditions favourable for spontaneous closure.[8] Discussions persist as to the optimal means of providing adjuvant nutritional support. There is an increasing tendency to manage patients with enteral rather than parenteral nutrition. Generally, patients considered to have inadequate gastrointestinal function are given TPN while those deemed to have a functioning gastrointestinal tract receive enteral nutrition. TPN substantially improves the prognosis of gastrointestinal fistulae by increasing the rate of spontaneous closure and improving the nutritional status of patients requiring repeat operations.

Prevention or early detection and treatment of bacterial infections with appropriate antibiotics are critical, although surgical and/or interventional drainage of abscesses may be necessary to control intra-abdominal sepsis.[8] Adequate drainage of the fistula must be established and maintained to avoid major complications, such as sepsis. Adequate drainage also allows[9]:

- a more exact guide to volume and electrolyte replacement;
- evaluation of the progress of therapy;
- protection of the skin, as the fistula fluid can be corrosive. Disadvantages of conservative medical therapy include[8]:
- high morbidity and mortality associated with prolonged hospitalisation and long duration of treatment (4–6 weeks increasing to 11–20 weeks for pancreatic fistulae);
- an unsatisfactory closure rate (24–72% increasing to 61–75% for pancreatic fistulae);
- high cost;
- complications of long term TPN (sepsis, central venous thrombosis, and liver disturbances);
- complexity of wound care and personal hygiene;
- psychological effect on self image and self esteem;
- reduced quality of life;
- delay in return to social and work activities;
- anxiety about future operative procedures and possible death.

Specific therapy

Once the patient has been stabilised, specific therapy can be added if necessary. Generally, surgery is indicated in patients with fistulae that fail to close spontaneously after a 30–60 day period of sepsis free parenteral nutrition,[10 11] although in some cases surgery can be avoided for at least three months (see González-Pinto and Moreno-González, this supplement, page iv22). Timing ultimately depends on individual practice and varies between hospitals. Other specific therapies may involve endoscopic or transcutaneous methods of intervention, or drugs that reduce gastrointestinal secretions (for example, somatostatin-14 or its analogue octreotide). Other substances that inhibit pancreatic secretions (for example, glucagon and calcitonin) have also been investigated, although these drugs have little if any effect on fistula output.[12] This paper will concentrate on the role of pharmacological therapy using somatostatin-14 or octreotide.

SOMATOSTATIN-14 AND ITS ANALOGUES

Somatostatin-14 is a tetradecapeptide that is found naturally in large amounts in the gastrointestinal tract and the pancreas. It is also found in the central nervous and the peripheral nervous systems.[6] The biological effects of somatostatin-14 and its analogues on gastrointestinal functions are summarised in table 1.

Somatostatin-14 and its analogues are not intended as a replacement for conservative treatment. Instead, when used in combination, somatostatin-14 and TPN appear to exert a synergistic effect on the reduction of gastrointestinal secretions and improve fistula closure rates.[13] Unlike TPN, somatostatin-14 totally inhibits basal exocrine gastrointestinal secretions and suppresses the possibility of exogenous stimuli.[13] The dual therapy combines the effects of TPN on protein synthesis induction with total inhibition of fistula losses by somatostatin-14, which is the primary condition for spontaneous closure.[13]

Because of the short half-life of somatostatin-14 (1–2 minutes[14]), which necessitates continuous intravenous infusion, several analogues have been developed for the treatment of a variety of disorders—octreotide, lanreotide, and vapreotide. Of these, the octapeptide octreotide is the only analogue that has been widely used in the treatment of gastrointestinal fistulae. The main biological effects of octreotide in the gut are similar to those of somatostatin-14 (table 1). Octreotide has a half life of 113 minutes[15] which allows intermittent (three times daily) subcutaneous dosing schedules for the treatment of fistulae. However, this regimen may cause fluctuations in enzyme concentrations between doses. For example, in a study on a single patient, octreotide treatment (100 μg three times daily) significantly reduced pancreatic secretory volume and protein output compared with baseline levels ($p<0.001$) (fig 2).[16] After the first octreotide injection, pancreatic secretory volume decreased markedly and remained low for the duration of the treatment period (fig 2). However, enzyme concentrations of the pancreatic secretions, although markedly reduced by each injection of octreotide, began to rise approximately four hours after each injection (fig 2). Concentrations in pancreatic secretions peaked approximately six hours after each administration of octreotide to concentrations above basal levels (fig

Table 1 Biological effects of somatostatin-14 and its analogues on gastrointestinal functions[6]

Inhibition of:
• hormone secretion (gastrin, cholecystokinin, secretin, insulin, glucagon and vasoactive intestinal peptide)
• exocrine secretory responses (gastric acid secretion and exocrine pancreatic secretion)
• motor activity (gastric emptying and gall bladder contraction)
• nutrient absorption
• splanchnic/portal venous blood flow
Stimulation of:
• water and electrolyte absorption

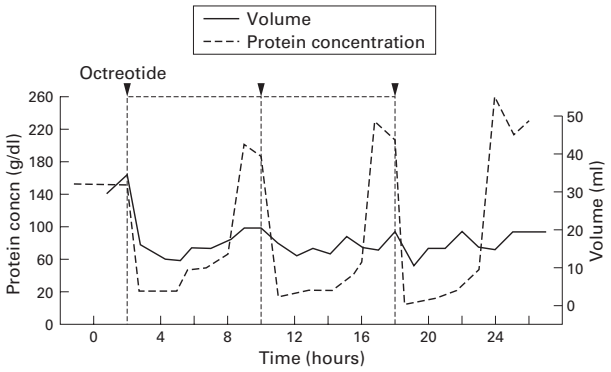

Figure 2 Volume and protein concentration of pancreatic secretions following octreotide (100 μg three times daily) administration.[16] Reproduced with permission from Jenkins et al.[16]

2). This rebound effect on enzyme concentration may be deleterious to the fistula tract and delay healing.

There is evidence to suggest that the higher the fistula output, the more effective octreotide is in reducing the volume of output. A study by Paran and colleagues[17] demonstrated that the reduction rate of secretions in high output intestinal fistulae (>500 ml/day) was higher than that in the low output fistulae (63±8% *v* 39±4%; p<0.05).

Furthermore, the effects of octreotide have been reported to diminish with repeat applications. In a study of six healthy volunteers, the initial potent inhibition of exocrine pancreatic secretion by octreotide (100 μg three times daily) diminished considerably after several days of application (fig 3).[18] Although the reason for this is not understood, it is probably due to downregulation of somatostatin receptors.[19]

In addition, the affinity of octreotide for the different somatostatin receptors is variable (table 2).[20] Octreotide binds with similar affinity to somatostatin-14 to somatostatin receptors (SSTR) 2 and SSTR 5, with moderate affinity to SSTR 3, but not to SSTR 1 or SSTR 4. Therefore, cells that express SSTR 1 or SSTR 4 may respond poorly or not at all to octreotide.[21] Thus the spectrum of biological activity and efficacy of octreotide may not necessarily be the same as that of somatostatin-14.

At present, the distribution and location of the five SSTRs is not known. However, in competitive displacement studies of somatostatin-14 and octreotide in normal and neoplastic human gastric and colonic tissues, octreotide did not displace somatostatin-14 at any concentration tested.[22] This may suggest that the receptor subtype(s) in these tissues is predominantly SSTR 1 or 4.

CLINICAL STUDIES

To date, there are only six randomised controlled clinical studies of somatostatin-14 (two studies) or octreotide (four studies) in the treatment of gastrointestinal fistulae, and no study has directly compared the two drugs. There are three parameters that are important in determining the efficacy of gastrointestinal fistula treatments, namely the effects of the drugs on:

- fistula output volume;
- fistula closure rates (percentage of patients whose fistulae close);
- time to closure.

Somatostatin-14 and octreotide have also been used, with varying success, in the prevention of complications following pancreatic surgery (for a comprehensive review, see Gouillat and Gigot in this supplement, page iv32). They may also be used to stabilise fistula patients prior to surgery in cases where reoperation is necessary (for example, there is an obstacle downstream of the fistula or a discontinuity between the fistula and the digestive tract). This approach may also simplify surgery which is obviously beneficial to the patient.

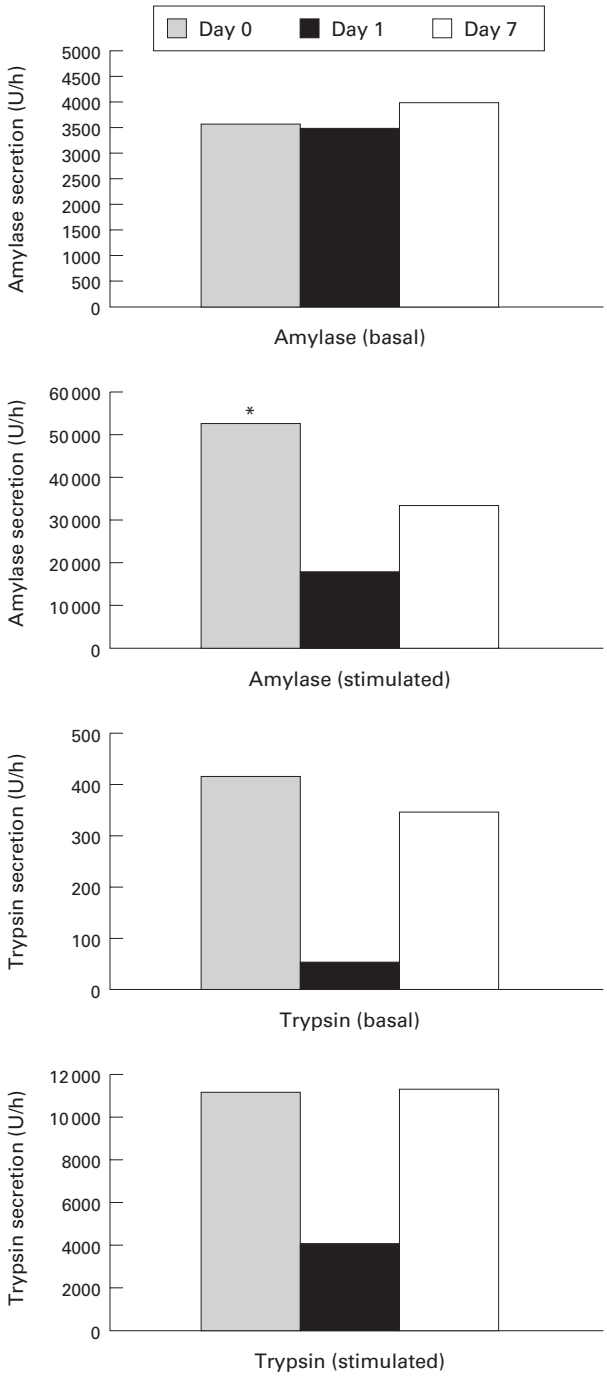

Figure 3 Effect of octreotide on exocrine pancreatic secretions diminishes after several days.[18] Basal, baseline pancreatic secretion, collection period 30 minutes; stimulated, pancreatic secretion during continuous infusion of secretin (1 U/kg body weight) and ceruletide (80 ng/kg body weight), collection period 60 minutes. *p<0.05 versus day 0.

Effects of somatostatin-14 and octreotide on fistula output volume

A drug that reduces fistula output is likely to be highly beneficial to the patient and improve the poor prognosis of high output fistulae. Table 3 summarises the main somatostatin-14 and octreotide trials that have studied their effect on output volume. They are listed in approximate order of clinical evidence, starting with randomised, blinded, controlled studies, then controlled case series, and finally uncontrolled studies.

Table 2 Binding affinities of somatostatin-14 and octreotide to somatostatin receptor subtypes SSTR 1 to SSTR 5[20]

	Receptor subtype				
	SSTR 1	*SSTR 2*	*SSTR 3*	*SSTR 4*	*SSTR 5*
Somatostatin-14	+ +	+ +	+ +	+ +	+ +
Octreotide	—	+ +	+	—	+ +

+ +, high affinity; +, moderate affinity; —, does not bind

Randomised controlled studies (level Ib EBM)

Somatostatin-14. The only prospective, randomised, controlled, multicentre, single blind trial which analysed the effect of somatostatin-14 on gastrointestinal fistula output, performed by Torres and colleagues,[23] showed a significant positive effect. The control group (n=20) was treated with TPN alone for 15 days. After this time, if the decrease in fistula output was less than 30%, patients were given additional somatostatin-14. The somatostatin-14 group (n=20) received TPN alone for 2–3 days, followed by somatostatin-14 (250 μg/h) plus TPN for up to 20 days. After this time if the fistula had not healed the use of somatostatin-14 was reviewed. All fistulae were demonstrated radiographically and were single tract with no distal obstruction. Patients with sepsis, gross early anastomosis leakage (>1000 ml/48 hours), intra-abdominal foreign bodies, and neoplasm infiltrated fistula sites were excluded from the study. Demographic criteria were comparable between the TPN and somatostatin-14+TPN groups except for patient age (50 *v* 62 years, respectively; $p<0.05$) and pretrial fistula output (202 *v* 370 ml/24 hours; $p<0.05$).

As can be seen in fig 4, somatostatin-14 significantly reduced the time to achieve 50%, 75%, and 100% reductions in fistula output, despite patients in the somatostatin-14 group having poorer prognostic factors.

These results appear promising, however in criticism, this study was single, rather than double blinded, and pancreatic and small bowel fistulae were considered together rather than separately. Furthermore, it has been suggested that the timing of somatostatin-14 treatment is an important factor for

Table 3 Studies on the effects of somatostatin-14 and octreotide on fistula output

Study	Patient population	Evidence level[1]	Dose of S/O	Treatment	n	Pretreatment fistula output (ml/day)*	% Output reduction after 1 day	Significant effect on output?
Torres *et al* 1992[23]	All PO: 7 panc, 5 duodenum, 7 jejunum, 18 ileum, 3 ileocolic	Ib	250 µg/h	TPN S+TPN	20 20	ND	ND ND	p<0.05
Nubiola-Calonge *et al* 1987[20]	All PO: 2 duodenal, 9 jejunal, 3 ileal	Ib	75–100 µg tid	(Pl,O,O)[2]+PN (O,Pl,O)[2]+PN	6 8	692 (230)	9 53	p<0.01
Scott *et al* 1993[28]	All PO, ext: 2 gastric and small bowel, 4 duodenal, 2 panc, 11 small bowel	Ib	100 µg tid	Pl[3,4] O[3,4]	8 11	401 (149)	ND ND	NS
Sancho *et al* 1995[24]	All PO, ext: 1 stomach, 5 panc, 11 duodenum, 5 jejunum, 9 ileum	Ib	100 µg tid	Pl+TPN O+TPN	17 14	729 (267)	32 34	NS
Pederzoli *et al* 1986[12]	All ext, panc, HO, PO	IIa	250 µg/h for 3–4 days, then 125 µg/h	TPN S+TPN	18 8	ND	39.4 82.3	NS
Planas *et al* 1990[29]	All PO, EC (small intestine)	IIa	3.5 µg/kg bolus, 3.5 µg/kg/h	TPN S+TPN	46 15	ND	ND ND	p<0.05
Hild *et al* 1986[31]	All PO, ext: 9 gastric/duodenum, 8 jejunum, 4 ileal, 11 panc, 3 bile duct	IIb	250 µg/h	S+PN	35	ND	64–88	NS
Ysebaert *et al* 1994[30]	All PO, ext: 6 panc, 5 duodenum, 3 jejunum, 9 ileum	IIb	250 µg/h	S+TPN	23	ND	69	p<0.001
di Costanzo *et al* 1987[13]	All ext: 1 oesoph, 2 stomach, 9 duodenum, 3 biliary tract, 5 panc, 8 jejunum, 7 ileum, 2 colon	IIb	250 µg/h	S+TPN	37	677.7 (100.9)	70	p<0.001
Nubiola *et al* 1989[34]	All PO, EC: 11 LO, 11 HO, 5 in large abdominal wall defects	IIb	100 µg tid	O+PN	27	ND	55	NS
Barnes *et al* 1993[32]	All ext, panc: 8 HO, 4 LO	III	50 µg bid up to 200 µg tid	O[4]	12	360 (347)	69	p<0.05
Lansden *et al* 1989[33]	All ext, panc: 3 LO, 2 HO	III	50 µg bid up to 150 µg tid	O[4]	5		52	NS
Tulassay *et al* 1993[35]	All HO, PO, ext, panc	III	100 µg bid	O+TPN	16	380 (190)	55 (26–69)	NS

EC, enterocutaneous; ext, external; HO, high output; LO, low output; ND, no data; O, octreotide; oesoph, oesophageal; panc, pancreatic; Pl, placebo; PO, postoperative; PN, parenteral nutrition; S, somatostatin-14.

[1]Evidence level[7] Ia, meta-analysis of randomised controlled trials (RCTs); Ib, RCT; IIa, non-randomised controlled study; IIb, quasi-experimental study; III, non-experimental descriptive studies; IV, expert committee reports; opinions or clinical experience of respected authorities.
[2]Patients received octreotide for two days, TPN for two days, and then octreotide until closure or operation, or TPN for two days, octreotide for two days, and then octreotide until closure or operation.
[3]Only 12 days of octreotide or placebo.
[4]Conservative treatment not mentioned.
*Mean (SEM).

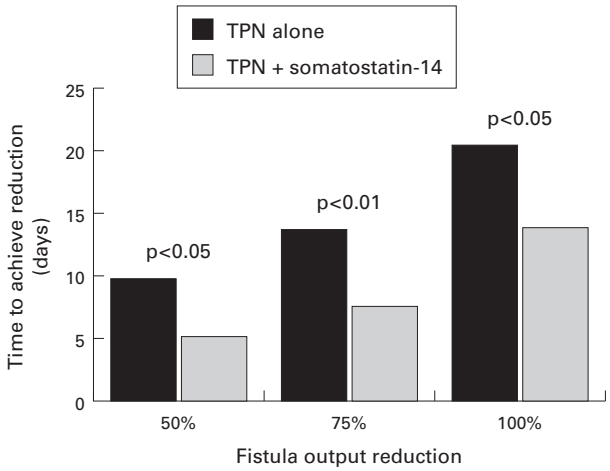

Figure 4 Time to achieve fistula output reductions of 50%, 75%, and 100% in patients treated with total parenteral nutrition (TPN), alone or in combination with somatostatin-14.[23] Reproduced from Torres and colleagues.[23]

efficacy of treatment[24] and information on delay and latency times was not provided.

During the trial, four patients were transferred from the TPN to the somatostatin-14 group after 15 days of TPN treatment. Transfer of these patients, who presumably represented the most severe clinical cases, may ultimately have prevented the study from demonstrating clear superiority of somatostatin-14 by artificially elevating the success rate in the TPN treatment group.[25 26] In total, 33/40 (83%) of the fistulae were reported to have closed spontaneously, which included 17/20 (85%) patients who received somatostatin-14 plus TPN. No mention was made of the remaining seven fistulae, which failed to close spontaneously. While closure time was reduced significantly, no significant increase in spontaneous closures was noted. However, in order to demonstrate a significant increase in closure rate, a study population in excess of 390 patients would be required, which would be difficult to obtain, even in a multicentre trial, due to the low frequency of postoperative fistulae.[26]

Octreotide. As with somatostatin-14, experience with octreotide in the treatment of postoperative gastrointestinal fistulae is limited. There are two randomised, double blind, placebo controlled trials[27 28] and one blind crossover trial[27] that have examined the effect of octreotide on fistula output. However, only one of these three studies showed a beneficial effect of octreotide in reducing fistula output.[27] In this small study, 14 patients with postoperative small bowel fistulae, who had received at least seven days of conventional treatment (parenteral nutrition, cimetidine, and nasogastric suction), were randomised to two days of octreotide followed by two days of placebo or two days of placebo followed by two days of octreotide. After this time, all patients were treated with octreotide until closure or reoperation.

As shown in fig 5, output in the group that received octreotide on days 1 and 2 fell from 638 ml/day on day 0 to 228 ml/day on day 2, while those receiving placebo during this time did not experience a fall in output.[27] During days 3 and 4, patients then receiving octreotide exhibited a reduction in output while the output of those receiving placebo increased.

However, despite the positive results of the study of Nubiola-Calonge and colleagues,[27] two later studies demonstrated a lack of effect of octreotide. A study by Scott and colleagues[28] included 19 patients with postoperative enterocutaneous fistulae, of which 11 received octreotide and eight were given placebo for 12 days. Fistula output during the seven days before commencing octreotide or placebo was similar in both groups. During the treatment phase, median fistula output actually tended to be greater for patients receiving octreotide than for those given placebo.

In a further study,[24] 31 patients with postoperative gastrointestinal or pancreatic fistulae were recruited from five centres and randomised to receive TPN plus octreotide (100 μg three times daily) (n=14) or placebo (n=17) within eight days of fistula onset. Unlike the somatostatin-14 trial, none of the patients received TPN prior to recruitment and all patients were included, irrespective of sepsis. Figure 6 shows fistula output of the two groups as mean percentage of basal values, and the effect of octreotide was no different from that of placebo. As the reduction in output was similar in both groups, it is likely that the predominant contribution to the effect was made by TPN treatment rather than octreotide. In conclusion, the authors stated that the results of the study did not support the use of octreotide in the treatment of enterocutaneous fistulae within eight days of onset.

Controlled studies (level IIa EBM)

Somatostatin-14. Early data on the efficacy of somatostatin-14 in the treatment of gastrointestinal fistulae were published by Pederzoli and colleagues.[12] Forty five patients with external pancreatic fistulae not contaminated by intestinal secretion and with an output >200 ml/day were administered TPN, alone (n=18) or in combination with calcitonin (n=7), glucagon (n=12), or somatostatin-14 (n=8). These results showed

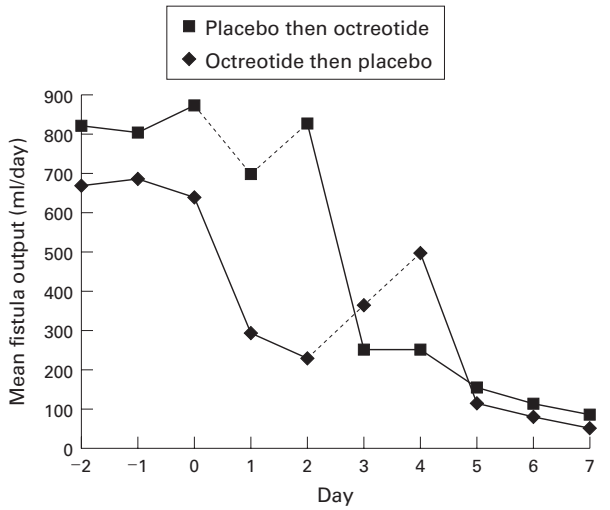

Figure 5 Effect of octreotide on fistula output in a crossover study. Patients received either: placebo (broken line) then octreotide (solid line) or octreotide (solid line) then placebo (broken line). After four days all patients received octreotide (solid line) until closure of the fistula or operation.[27]

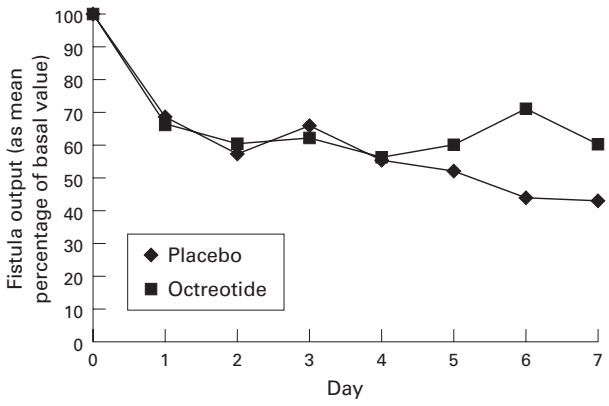

Figure 6 Fistula output in patients administered either octreotide or placebo.[24]

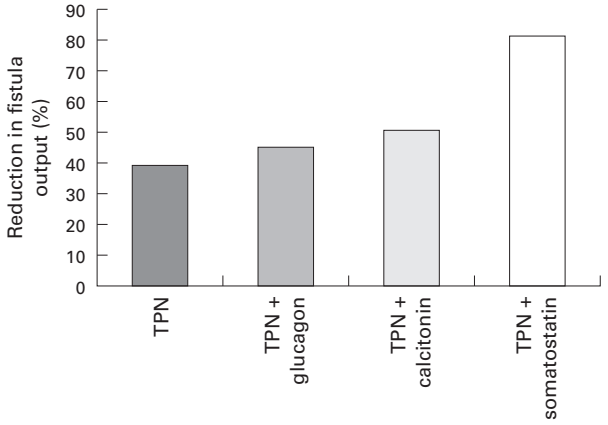

Figure 7 Effects of total parenteral nutrition (TPN) alone or in combination with glucagon, calcitonin, or somatostatin-14 on reduction in fistula output.[12]

that somatostatin-14 produced an immediate (within 24 hours) reduction in output of 82.3% whereas the other three treatments produced output reductions of only 40–50% (NS) (fig 7).

In a later study by Planas and colleagues,[29] patients with fistulae of the small intestine received somatostatin-14+TPN (n=15) or TPN alone (n=46). The output reduction in the somatostatin-14 group during the first two days was reported to be significantly greater than that in the TPN group ($p<0.05$).

Retrospective studies (level IIb EBM) and case studies (level III EBM)

Of the uncontrolled studies detailed in table 3, two of three of the level IIb EBM somatostatin-14 trials showed a significant reduction in fistula output on day 1 compared with baseline[13 30] (fig 8). The study by Ysebaert and colleagues[30] included 23 patients with external fistulae, and somatostatin-14 produced a reduction in output of 69% on day 1 ($p<0.001$). In the study by di Costanzo and colleagues,[13] a mean output reduction of 70% on day 1 was found in 37 patients with external fistulae. The third uncontrolled somatostatin-14 study showed a similar reduction in fistula output, although this was not significant—pancreatic fistulae, 64%; common bile duct fistulae, 88%; other gastrointestinal fistulae, 78%[31] (fig 8).

Of the four studies with octreotide, only one (level III EBM) showed a significant reduction in fistula output on day 1 (69%; $p<0.05$) in 12 patients with external pancreatic fistulae.[32] The other three trials showed non-significant reductions of 52% (n=5; level III EBM),[33] 55% (n=27; level IIb EBM),[34] and 55% (n=16; prospective, open, uncontrolled trial)[35] (fig 8).

Overall effect on fistula output volume

Reducing fistula output rapidly and consistently is obviously beneficial to the patient as it reduces nutritional and other losses and encourages faster healing. Although it must be remembered that all of the published studies are small, and many of them are uncontrolled, of the four evidence level Ib studies, 1/1 was positive for somatostatin-14 and 1/3 was positive for octreotide. Of the seven lower evidence level studies, somatostatin-14 produced a fistula output reduction of 64–88% on the first day (2/3 studies significant) and octreotide produced a reduction of 52–69% (1/4 studies significant). Overall, there are a greater number of studies that show a beneficial effect for somatostatin-14 than for octreotide.

Effects of somatostatin-14 and octreotide on fistula closure rates

No studies, using either somatostatin-14 or octreotide, have shown an increased rate of closure in patients administered these drugs (table 4). This is not unexpected as the majority of fistula patients, when given adequate conservative treatment with TPN, antibiotics, etc., will achieve spontaneous fistula closure, although this may take several weeks or even months. Conversely, patients with a distal obstruction, uncontrolled sepsis, or malignancy in the fistula bed are unlikely to

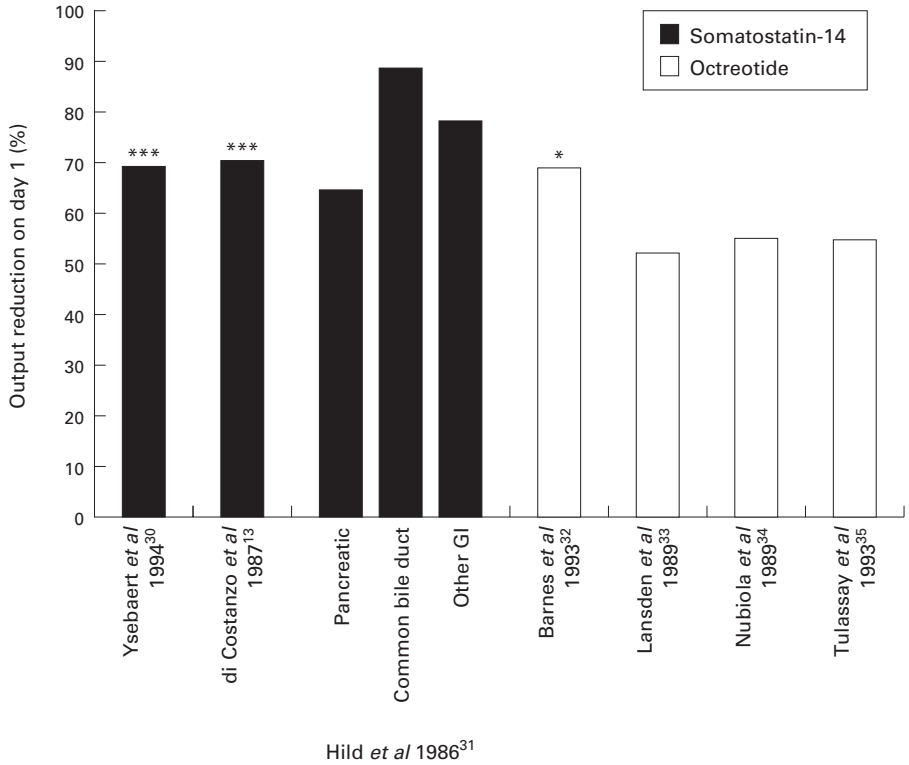

Figure 8 Effects of somatostatin-14 and octreotide on first day fistula output. *p<0.05, ***p<0.001.

Table 4 Studies on the effects of somatostatin-14 and octreotide on fistula closure rates and times

Study	Patient population	Evidence level[1]	Dose of S/O	Treatment	n	Closure (%)	Mortality (%)	TPN/PN (+placebo)	Time to closure (days)		Significant effect on closure time?
									TPN/PN prior to S/O+TPN/PN	S/O+TPN/PN	
Torres *et al* 1992[23]	All PO: 7 panc, 5 duodenum, 7 jejunum, 18 ileum, 3 ileocolic	Ib	250 µg/h	TPN	20	81	0	20.4 (3.0)			p<0.05
				S+TPN	20	85	0		2–3	13.9 (1.8)	
Isenmann *et al* 1994[37]	All PO, ext: 20 panc, 21 small intestine, 4 biliary tract	Ib	250 µg/h, up to 500 µg/h	TPN	20	19[2]	ND	19			p=0.013
				S+TPN	25	78[2]	ND		7	12.5	
Sancho *et al* 1995[24]	All PO, ext: 1 stomach, 5 panc, 11 duodenum, 5 jejunum, 9 ileum	Ib	100 µg tid	Pl+TPN	17	35[3]	12	12 (7)			NS
				O+TPN	14	57[3]	14		0	7 (3)	
Nubiola-Calonge *et al* 1987[27]	All PO: 2 duodenal, 9 jejunal, 3 ileal	Ib	75–100 µg tid	(Pl,O,O)[4]+PN	6	78	ND	NA	⩾7	4.5 (2–10)[5]	NA
				(O,Pl,O)[4]+PN	8						
Hernández-Aranda *et al* 1996[38]	All PO, ext. Mainly small intestine, HO	Ib	100 µg tid	TPN	45	56	31	27 (15)			p=0.002
				O+TPN	40	65	25		ND	18 (11)	
Pederzoli *et al* 1986[12]	All ext, panc, HO, PO	IIa	250 µg/h for 3–4 days, then 125 µg/h	TPN	18	94	ND	31.8 (21.1)			p=0.000028
				S+TPN	8	88			ND	6.6 (3.0)	
Planas *et al* 1990[29]	All PO, EC (small intestine)	IIa	3.5 µg/kg bolus, 3.5 µg/kg/h	TPN	46	30	28	29.7 (18.0)			p<0.05
				S+TPN	15	53	13		ND	11.1 (1.6)	
Spiliotis *et al* 1990[39]	All PO, HO, ext: 16 gastroduodenal, 15 small bowel, 6 choledochoduodenostomy, 11 panc	IIa	250 µg/h	TPN[6]	30	67	10	27.4 (8.7)			p<0.01[7]
				S+TPN	18	78	6		15.3 (6–25)	6.1 (3.1)	
Hild *et al* 1986[31]	All PO, ext: 9 gastric/duodenum, 8 jejunum, 4 ileal, 11 panc, 3 bile duct	IIb	250 µg/h	S+PN	35	80	ND	NA	18	11.3	NA
Saari *et al* 1989[40]	All panc	IIb	250 µg bolus, then 250 µg/h	S+TPN	19[8]	68	ND	NA	10 (0–40)	7 (2–14)	NA
Ysebaert *et al* 1994[30]	All PO, ext: 6 panc, 5 duodenum, 3 jejunum, 9 ileum	IIb	250 µg/h	S+TPN	23	83	ND	NA	ND	11.0 (7.9)	NA
di Costanzo *et al* 1987[13]	All ext: 1 oesoph, 2 stomach, 9 duodenum, 3 biliary tract, 5 panc, 8 jejunum, 7 ileum, 2 colon	IIb	250 µg/h	S+TPN	37	82	13	NA	21.2 (3.8) (1–123)	5.4 (0.7) (1–14)	NA
Nubiola *et al* 1989[34]	All PO, EC: 11 LO, 11 HO, 5 in large abdominal wall defects	IIb	100 µg tid	O+PN	27	78	7	NA	25 (2–98)	5.8 (2.7)	NA
Barnes *et al* 1993[32]	All ext, panc: 8 HO, 4 LO	III	50 µg bid up to 200 µg tid	O[9]	12	58	ND	NA	1 w–11 m	3 d–7 m	NA
Lansden *et al* 1989[33]	All ext, panc: 3 LO, 2 HO	III	50 µg bid up to 150 µg tid	O[9]	5	100	ND	NA	28–132	24 (7–44)	NA
Spiliotis *et al* 1994[41]	All PO, ext, panc	III	100 µg tid	O[10]+TPN	25	76	ND	NA	ND	14.1 (2.3	NA
Segal *et al* 1993[42]	All HO, ext, panc	III	100 µg tid	O (+TPN[11])	8	88	0	NA	ND	23 (5) (14–54)	NA
Tulassay *et al* 1993[35]	All HO, PO, ext, panc	III	100 µg bid	O+PN	16	88	ND	NA	17 (4–35)	8 (3–15)	NA

EC, enterocutaneous; ext, external; HO, high output; LO, low output; NA, not applicable; ND, no data; O, octreotide; oesoph, oesophageal; panc, pancreatic; Pl, placebo; PO, postoperative; PN, parenteral nutrition; S, somatostatin-14.
[1]Evidence level[7] Ia, meta-analysis of randomised controlled trials (RCTs); Ib, RCT; IIa, non-randomised controlled study; IIb, quasi-experimental study; III, non-experimental descriptive studies; IV, expert committee reports; opinions or clinical experience of respected authorities. [2]On day 14. [3]Within 20 days. [4]Patients received octreotide for two days, TPN for two days, and then octreotide until closure or operation, or TPN for two days, octreotide for two days, and then octreotide until closure or operation. [5]After continuous octreotide. [6]Historical controls. [7]The total time to closure in the somatostatin-14 group (18.2 (6.3 days)) was significantly less than that in the TPN group (27.4 (8.7 days)) (p<0.01). [8]19 fistulae in 18 patients. [9]Conservative treatment not mentioned. [10]Only 10 days of octreotide. [11]6/8 received TPN, 2/8 received a fat free polymeric enteral diet.

achieve spontaneous closure. Although somatostatin-14 is an active pharmacological agent, it cannot be expected to correct a mechanical problem.[36] Therefore, it is unlikely to increase the number of patients whose fistulae close. However, reducing the time taken to achieve closure in those patients that are likely to close spontaneously is more important, and this is examined in detail below.

Effects of somatostatin-14 and octreotide on fistula closure times

Randomised controlled studies (level Ib EBM)

Somatostatin-14. The somatostatin-14 study by Torres and colleagues[23] not only showed a significant positive effect on fistula output but also a significantly reduced time to closure. As shown in fig 4, mean time to closure was 13.86±1.84 days in the somatostatin-14 group compared with 20.4±2.98 days in the TPN group ($p<0.05$). This reduces the required period of TPN treatment which in turn decreases morbidity and costs. Furthermore, the number of complications (pneumonia, pneumothorax, wound or skin problems, or catheter, abdominal, or urinary sepsis) was significantly lower in the somatostatin-14+TPN group than in the group that received TPN alone (35% *v* 69%, respectively; $p<0.05$). During the study, four patients were transferred from the TPN alone to the TPN+somatostatin-14 group but if these patients had remained in their original group, the study may have achieved a higher level of significance.[26] The authors concluded that somatostatin-14 in combination with TPN accelerates spontaneous closure of postoperative gastrointestinal fistulae and significantly reduces the required period of TPN treatment, with consequential reduction of morbidity.

A further randomised study of 45 patients with postoperative external upper gastrointestinal fistulae also showed a reduction in closure time with somatostatin-14.[37] If treatment with TPN alone for seven days proved unsuccessful, patients were randomised to receive TPN alone (n=20) or somatostatin-14 plus TPN (n=25). In the TPN group, if 14 days continued TPN treatment was unsuccessful, somatostatin-14 could be administered to the patient if deemed necessary. After a maximum of 30 days of treatment, the observed fistula closure rate was clearly in favour of somatostatin-14 (fig 9).

Octreotide

Two comparative studies have examined reduction in closure time by octreotide.[24 38] In a study by Sancho and colleagues,[24] closure within 20 days was observed in 8/14 (57%) fistulae in patients given octreotide compared with 6/17 (35%) in those receiving placebo ($p=0.4$). For the eight closures in the octreotide group, mean time to closure was 7±3 days whereas in the placebo group mean time to closure was 12±7 days ($p=0.16$).

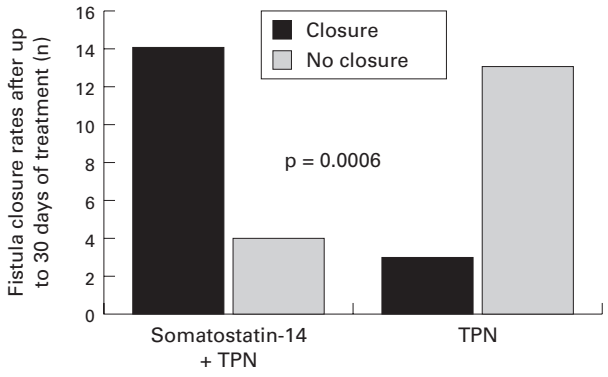

Figure 9 Effect of somatostatin-14 on the rate of fistula closure over 30 days of treatment, in patients receiving total parenteral nutrition (TPN).[37] p=0.0006. Source: Isenmann et al.[37]

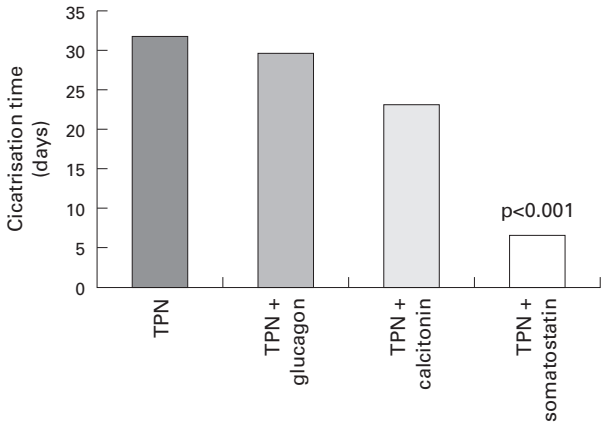

Figure 10 Effects of total parenteral nutrition (TPN) alone or in combination with glucagon, calcitonin, or somatostatin-14 on cicatrisation time.[12] p<0.001.

In the study by Hernández-Aranda and colleagues,[38] 99 patients were given conservative treatment or additional octreotide. In the group that received octreotide, fistula closure time was reduced from 27±15 days to 18±11 days ($p=0.002$), and duration of nutritional support requirement was also reduced, from 29±17 days to 22±15 days ($p=0.04$). However, hospital stay was not significantly reduced (35±21 days *v* 31±19 days). Although this study shows promising results it should be mentioned that the fistula closure rate in the control group (56%) was very low compared with other trials. Also, study design limitations, such as analysis of data from fistulae of mixed aetiology and lack of information regarding prior treatment, prevent a clear comparison.

Controlled studies (level IIa EBM)

Somatostatin-14. A trial by Pederzoli and colleagues[12] also showed a significantly reduced cicatrisation time with somatostatin-14 in patients with external pancreatic fistulae. Mean time to closure in the somatostatin-14 group was only 6.57±2.99 days, significantly shorter than that in the other groups (23–32 days; $p<0.001$) (fig 10).

Figure 11 shows the percentage of closure observed in each group with respect to time. In the group treated with somatostatin-14 plus TPN, 87% of fistulae closed within 12

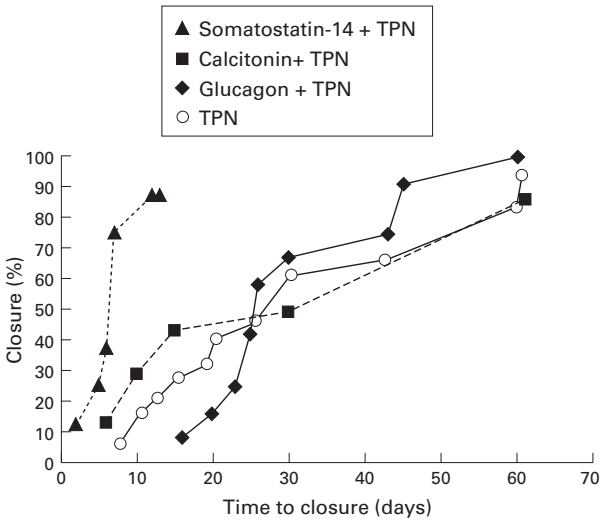

Figure 11 Percentage and time of closure of fistulae treated with four different treatment schedules: somatostatin-14+total parenteral nutrition (TPN), calcitonin+TPN, glucagon+TPN, and TPN alone.[12] Reprinted with permission from J Am Coll Surg 1986;***163***:428–32.

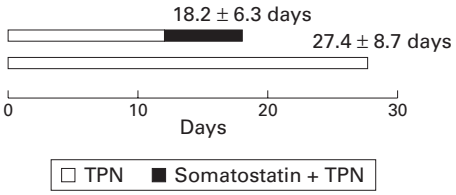

Figure 12 Time to closure in the trial of Spiliotis and colleagues.[39]

days. However, in the other groups, to achieve a comparable percentage of closure took much longer. The observed probability of closure of the fistulae treated with somatostatin-14 plus TPN was significantly different from that of all other treatments ($p<0.000028$). This study also showed an estimated economic saving of approximately $2100 per patient in 1986 due to shorter hospitalisation.

A further controlled study of 61 patients with postoperative enterocutaneous fistulae of the small intestine divided patients into groups: TPN (n=46) or TPN plus somatostatin-14 (n=15).[29] Again, a significant difference was found in the time taken to close the fistulae in the two groups: 29.7±18 days in the TPN group versus 11.1±1.6 days in the somatostatin-14 group ($p<0.05$).

In a further trial of somatostatin-14 in patients with postoperative enterocutaneous fistulae, 30 patients were treated with somatostatin-14, TPN, skin care, and infection control. These were compared with 18 historical controls that had received TPN, skin care, and infection control.[39] Figure 12 shows time to closure. In the somatostatin-14 group, closure was achieved after 18.2±6.3 days, during the last 6.1±3.1 of which patients also received somatostatin-14. However, patients in the TPN group required significantly longer (27.4±8.7 days).

Uncontrolled studies

Of the uncontrolled trials detailed in table 4, times for closure were 5–11 days for somatostatin-14[13 30 31 40] and 6–24 days for octreotide,[33–35 41 42] although in one octreotide study times taken to closure were 3–6 days in three patients, 1.5–3 months in six patients, and seven months in two patients.[32] However, in the majority of the studies, patients received TPN alone for varying times before addition of the drug, from seven days up to 11 months, and some studies did not specify the duration of TPN therapy prior to addition of the drug.

Overall effect on closure time

Due to the limited number of randomised controlled trials on the use of somatostatin-14 and octreotide in the treatment of fistulae, it is not possible to draw any firm conclusions regarding their efficacy in reducing closure time. Furthermore, the majority of the trials included patients with different types of fistulae. However, of the controlled trials, 5/5 using somatostatin-14 showed a significant beneficial effect on closure time[12 23 29 37 39] whereas 1/2 octreotide trials showed a significant advantage.[38] Therefore, overall, there are more studies supporting the positive effect of somatostatin-14 on closure time.

Mortality rates

Of the trials that recorded mortality rates, only the study by Planas and colleagues[29] showed a reduced mortality rate in the treatment group—13% in the somatostatin-14 group versus 28% in the placebo group. There were no deaths in the somatostatin-14 or TPN groups in the study of Torres and colleagues,[23] and there were equal numbers of deaths in each arm of the study of Spiliotis and colleagues[39] (6% in the somatostatin-14 group *v* 10% in the TPN group). Of the octreotide studies, mortality rates were similar in the octreotide and TPN groups—14% versus 12%[24] and 25% versus 31%,[38] respectively.

Safety profiles

Both somatostatin-14 and octreotide are associated with favourable safety profiles. The incidence of adverse events was low in all studies. In patients receiving somatostatin-14, there were a few reports of blood sugar variations, nausea/vomiting, hot flushes, tachycardia, and diarrhoea.[37 39] In patients receiving octreotide, there were occasional reports of local pain at the injection site,[24] allergic reaction,[27 34] diarrhoea, and transient hyperglycaemia.[33]

CONCLUSION

A definitive evaluation of the efficacies of somatostatin-14 and octreotide in the treatment of fistulae is not possible. Although there are a large number of case reports and small patient series, there are only a few controlled studies comparing these drugs with placebo (both arms receiving conservative treatment). Furthermore, even controlled studies generally had heterogeneous and small patient collectives.

The information currently available seems to suggest a beneficial effect of somatostatin-14 when administered in association with standard conservative treatment, although current data are insufficient to draw firm conclusions. However, outcomes with respect to reduction in time to spontaneous closure are particularly promising and certainly warrant further investigation in well controlled blinded studies.

Octreotide has been shown to decrease fistula output in two studies[27 32] although in others it has been shown to exert no effect.[24 28] Possible explanations for the apparent reduced efficacy of octreotide include: a rebound effect between doses, lack of affinity for some of the somatostatin receptors, and downregulation of the receptors, resulting in a diminished effect after several days of treatment. However, despite these potential disadvantages of octreotide, some results with this drug are promising, and it has certain advantages over somatostatin-14. The main advantage of octreotide over somatostatin-14 is that it can be administered by intermittent subcutaneous injection. This also means that it can be used occasionally for outpatient management.

The dose of somatostatin-14 used for digestive fistulae is an initial bolus of 250 μg plus a continuous intravenous infusion of 250 μg/h until closure, followed by 3 mg/day (125 μg/h) for 48 hours to protect against fistula recurrence. It is important that continuous infusion of somatostatin-14 is not interrupted, and nursing staff therefore have to be extremely vigilant. If continuous infusion is interrupted, a rebound effect may be seen, during which time gastrointestinal secretions can increase, and this may lead to reduced efficacy. However, this can be avoided if the infusion is reinstated as soon as possible, together with another bolus of 250 μg. Although somatostatin-14 administration is more complex than that for octreotide, continuous administration may be advantageous in fistula patients, as fluctuations in output volume and/or concentration can generally be avoided.

Although somatostatin-14 is a relatively expensive treatment, it may help to reduce morbidity, duration of hospital stay, and hospital costs. Therefore, treatment with somatostatin-14 promises to be cost effective. However, this needs to be confirmed in a pharmacoeconomic study.

In conclusion, current data are encouraging, especially for somatostatin-14, and prospective controlled studies with this drug are therefore warranted to confirm the results already obtained. Overall, there are more studies supporting the use of somatostatin-14 in the treatment of postoperative fistulae than there are for its analogue octreotide. However, these results need to be confirmed in a large randomised controlled trial.

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