Gastrointestinal fistulae most commonly develop after surgery although conditions such as inflammatory bowel disease (IBD) and pancreatitis can lead to spontaneous fistula formation. 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%). The introduction of total parenteral nutrition (TPN) reduced mortality and has been suggested to increase closures rates to approximately 60%, 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 (H₂ antagonists or proton pump inhibitors).

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. 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, and endeavour to reach a conclusion about the potential role of these drugs in the management of gastrointestinal fistulae.

**GASTROINTESTINAL FISTULAE**

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

U Hesse, D Ysebaert, B de Hemptinne

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 on day 1 that was twice that in the control group (NS). Of the octreotide studies, one showed a significant effect (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.

**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 (cicatrization) 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 cicatrization 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,
allows. The age of the fistula must be established and maintained to avoid complications of long-term TPN (sepsis, thrombosis, and liver disturbances). Reduction of fistula output: Somatostatin-14 totally inhibits basal exocrine gastrointestinal secretions and suppresses the possibility of exogenous stimuli. The dual therapy combines the effects of TPN on protein synthesis induction with total inhibition of fistula output.

**Optimal patient management**

- Reduce loss of fluids, nutrients, etc.
- Reduce fistula output
- Minimise cicatrisation time
- Reduce risk of intra-abdominal infection
- Improve quality of life for the patient
- Shorten hospital stay
- Reduce direct and indirect costs related to the treatment of fistulae

**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. 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. Adequate drainage of the fistula must be established and maintained to avoid major complications, such as sepsis. Adequate drainage also allows:

- 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:
- 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, although in some cases surgery can be avoided for at least three months (see González-Pinto and Moreno-González, this supplement, page iiv22). 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. 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. 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.

**Table 1: Biological effects of somatostatin-14 and its analogues on gastrointestinal functions**

<table>
<thead>
<tr>
<th>Inhibition of:</th>
<th>Stimulation of:</th>
</tr>
</thead>
<tbody>
<tr>
<td>hormone secretion (gastrin, cholecystokinin, secretin, insulin, glucagon and vasoactive intestinal peptide)</td>
<td>water and electrolyte absorption</td>
</tr>
<tr>
<td>exocrine secretory responses (gastric acid secretion and exocrine pancreatic secretion)</td>
<td></td>
</tr>
</tbody>
</table>
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 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% ± 39% vs 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).

Although the reason for this is not understood, it is probably due to downregulation of somatostatin receptors.

In addition, the affinity of octreotide for the different somatostatin receptors is variable (table 2). 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. 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. This may suggest that the receptor subtype(s) in these tissues is predominantly SSTR 1 or 4.

**CLINICAL STUDIES**

The 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.

**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.
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, 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 fistulas 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 2. Binding affinities of somatostatin-14 and octreotide to somatostatin receptor subtypes SSTR 1 to SSTR 5

<table>
<thead>
<tr>
<th>Receptor subtype</th>
<th>SSTR 1</th>
<th>SSTR 2</th>
<th>SSTR 3</th>
<th>SSTR 4</th>
<th>SSTR 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatostatin-14</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Octreotide</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
</tr>
</tbody>
</table>

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

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

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

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.

Evidence level: Ia, meta-analysis of randomised controlled trials (RCTs); Ib, RCT; Ila, non-randomised controlled study; Iib, quasi-experimental study; III, non-experimental descriptive studies; IV, expert committee reports, opinions or clinical experience of respected authorities.

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.

Only 12 days of octreotide or placebo.

Conservative treatment not mentioned.

Mean (SEM).
Somatostatin-14 in the management of gastrointestinal fistulae

epitome of treatment 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. 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.

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 and one blind crossover trial 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. 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 period did not experience a fall in output. 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-Calange and colleagues, two later studies demonstrated a lack of effect of octreotide. A study by Scott and colleagues 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, 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) or placebo 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. 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
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. The other three trials showed non-significant reductions of 52% (n=5; level III EBM), 55% (n=27; level IIb EBM), 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
Table 4  Studies on the effects of somatostatin-14 and octreotide on fistula closure rates and times

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

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.

<sup>1</sup>Evidence level: Ia, meta-analysis of randomised controlled trials (RCTs); Ib, RCT; Iib, non-randomised controlled study; Ila, quasi-experimental study; IIa, non-experimental descriptive studies; IV, expert committee reports, opinions or clinical experience of respected authorities. 2On day 14. 3Within 20 days. 4Patients 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. After continuous octreotide. 5Historical controls. 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). 6TPN fistulae in 18 patients. 7Conservative treatment not mentioned. 8Only 10 days of octreotide. 96/8 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. 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 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, pleural, or urinary sepsis) was significantly lower in the somatostatin-14+TPN group than in the group that received TPN alone (35% vs 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. 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. 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 fistula closure within 20 days was observed in 8/14 (57%) fistulae 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 vs 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.

**Octreotide**

Two comparative studies have examined reduction in closure time by octreotide. In a study by Sancho and colleagues, 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=0.16). 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).

In the study by Hernández-Aranda and colleagues, 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 vs 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 Ila EBM)**

**Somatostatin-14.** A trial by Pederzoli and colleagues 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 days.
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<0.0000028). 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). 13 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±6.6 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. This study showed an estimated economic saving of approximately $2100 per patient in 1986 due to shorter hospitalisation.

Uncontrolled studies
Of the uncontrolled trials detailed in table 4, times for closure were 5–11 days for somatostatin-14,14 16 40 and 6–24 days for octreotide.13 15 19 46 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.29 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.29 35 37 39 whereas 1/2 octreotide trials showed a significant advantage.39 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 colleagues28 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,29 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%, and 25% versus 31%, respectively.

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 31 although in others it has been shown to exert no effect.28 29 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 reinstalled 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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