Addition of somatostatin-14 to a standard Total Parenteral Nutrition-mixture in the treatment of fistulae : a clinical, double-blind, randomised, cross-over study

G. Roeyen[1,2], T. Chapelle[1], H. De Bosscher[2], E. Mattheeussen[2], C. Wouters[2], M. Ruppert[2], D. Ysebaert[1,2]

(1) Department of Hepatobiliary, Endocrine and Transplantation Surgery ; (2) Nutrition Team, University Hospital of Antwerp, Edegem (Antwerp), Belgium.

Abstract

Background / study aims : **Somatostatin and total parenteral nutrition (TPN) are routinely used in the treatment of pancreatic and enterocutaneous fistulae. The objective of this clinical randomised cross-over study was to investigate the serum levels of somatostatin infused alongside TPN by a separate intravenous line, and when it had been added to the TPN mixture.**

Patients / methods : **The subjects were recruited by the treating physicians and the nutrition nurses. From the patients who started the study, no one dropped out. Ten patients were treated with a standard TPN mixture and somatostatin 6 mg/day. Patients were randomised to two possible regimens : 'somatostatin plus TPN - somatostatin separately – somatostatin plus TPN' or 'somatostatin separately – somatostatin plus TPN – somatostatin separately'. Each regimen consisted of 3 × 3 days of therapy, during which, serum levels of somatostatin were measured daily. Pre- and post-treatment samples were also analysed.**

Results : **When somatostatin was infused separately, the mean serum level was 884.8 pg/ml (SD : 557.3 ; range : 54-1900). When added to TPN, the mean serum level was 807.5 pg/ml (SD: 505.8 ; range 162-2279) (p value of difference = 0,473). The mean pre-treatment level was 17.1 pg/ml (SD : 7.5 ; range : 8-33), and post-treatment was 32.8 pg/ml (SD : 26.5 ; range : 16-97).**

Conclusions : **These results demonstrate that serum levels of somatostatin are similar in both treatment regimens and therefore may be added to a TPN mixture.**

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Key words : Nutrition ; total parenteral nutrition ; somatostatin ; fistula ; TPN.

Introduction

Somatostatin-14 is a natural hormone, routinely used in the treatment of pancreatic and enterocutaneous fistulae. Until now, the standard treatment for such fistulae consisted of total parenteral nutrition (TPN) and a separate continuous infusion of somatostatin. However, if somatostatin could be added to the TPN mixture, then only one intravenous line would be necessary for the administration of both drugs. This would require less manipulation by the nursing staff and would reduce the risk of administration errors.

In this study, the serum levels of somatostatin were compared when somatostatin was infused separately alongside TPN, and when it had been added to the TPN mixture.

Materials and methods

Ten patients with pancreatic or enterocutaneous fistulae, were enrolled in this clinical cross-over study. The caustic nature of these fistulae was proven by biochemical analysis (amylase and lipase content) of their output. The study was approved by the Ethical Committee of our hospital (University Hospital Antwerp, Belgium), and the patients' written consent was obtained.

The study medications were somatostatin-14 (Somatostatin-ucb®, UCB Pharma SA, Brussels, Belgium) 6 mg/day and a standard TPN-mixture (Kabiven® 14, Fresenius Kabi AG, Bad Homburg, Germany). This commercially available mixture supplies daily 13.5 grams of nitrogen, 250 grams of glucose, 100 grams of lipids and electrolytes. Before the clinical study, a stability evaluation of the addition of somatostatin to the TPN mixture was performed. Samples were drawn from the mixture immediately after the addition of somatostatin, and then 4 hours and 24 hours after preparation.

Patients were randomised to two possible treatment regimens, for a study period of 9 days. In treatment regimen A, somatostatin was administered separately from the TPN during the first 3 days ; the following 3 days, somatostatin was added to the TPN ; followed by another 3-day period of separate infusion. In treatment regimen B, it was the reverse arrangement : during the first 3 days, somatostatin was added to the TPN, followed by 3 days of separate infusion, followed by another 3 days of somatostatin added to the TPN. If clinically necessary (e.g., fistula not healed at the end of the study period), the somatostatin infusion was continued after the study period.

The primary endpoint of the study was the serum level of somatostatin in patients treated with either regimen A

Correspondence and requests for reprints : G. Roeyen, M.D., Department of Hepatobiliary, Endocrine and Transplantation Surgery, University Hospital of Antwerp, Wilrijkstraat 10, 2650 Edegem (Antwerpen), Belgium. E-mail : geert.roeyen@uza.be.

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or regimen B. Serum somatostatin levels were determined daily, as were control samples before and after treatment. Pre-treatment, a control sample was drawn before administration of somatostatin or its analogues. During somatostatin therapy, serum samples were drawn every morning at 8.00 AM. After fistula closure, or after stopping somatostatin administration another post treatment sample was drawn. When fistula output could be measured, the clinical effect of somatostatin administration was also evaluated as a secondary endpoint.

The somatostatin levels were measured by radioimmunoassay (1).

Statistical analysis was performed with SPSS software package. Descriptive results are presented as mean, standard deviation and range.

Area under the curve was calculated by a graphical approach of the evolution of the serum level over time. For a three day period, an addition was made of the separate areas of each day. For comparison of the area under the curve for the consecutive 3-day-periods of individual patients, the non parametric Friedman test for K-related samples was performed.

Because of the limited number of patients and the wide variation of the values, non parametric tests were used for comparison between both ways of administration. Mann-Whitney U test was used for comparison in unpaired observations.

Results

Patients

Ten patients were enrolled in this study, 6 male and 4 female. Mean age was 58,3 years (range : 33-69 years). In 8 of those 10 patients the fistula output could be measured. Mean baseline fistula output was 293 cc (range : 30-1285 cc). In the other 2 patients the fistula drained in granulation tissue (a laparostoma) and the output could therefore not be measured properly. Patient characteristics are summarised in table 1.

Somatostatin availability

Stability evaluation confirmed that the addition of somatostatin to TPN results in a stable mixture for a 48-hour period at 4°C.

In healthy volunteers, endogenous somatostatin normally ranks below 110 pg/ml. Samples drawn at start-point and at, 4 hours and 24 hours after preparation of the ‘all in one’ mixture demonstrated a somatostatin availability of more than 100 000 pg/ml.

Serum levels of somatostatin

The individual and mean serum levels of somatostatin following drug administration are illustrated in Figure 1. The mean serum level of somatostatin before treatment was 17.1 pg/ml (SD : 7.6 ; range : 8-33), and after treatment 32.8 pg/ml (SD : 26,4 ; range : 16-97). When somatostatin was infused separately from the TPN mixture, the mean serum level was 884.8 pg/ml (SD : 557.3 ; range : 54-1900). When somatostatin was added to the mixture and it was infused ‘all in one’, the mean serum somatostatin level was 807 pg/ml (SD : 505.8 ; range : 162-2279) (p value of difference = 0,473) (Table 2).

The area under the curve (AUC) was also calculated for each patient and for each 3-day segment of administration (Fig. 2). Mean area under the curve per three day administration period ranked in treatment regimen A from 2484 to 2603 and 2780 (p value = 0,819) and in treatment regimen B from 2358 to 2455 and 2024 (p value = 0,091), showing no difference between the three periods within the same regimen. Comparison between both treatment regimens is shown in table 3. There are no differences in AUC between both treatment regimens for each three day segment of administration.

Clinical effect of somatostatin

Somatostatin treatment was considered successful (fistula closure) in five of the eight patients with a measurable output. In the two remaining patients, the output could not be measured because the fistula drained in granulation tissue. In those patients in whom the fistula didn’t close, one patient died from her oncological disease with a still-producing fistula, and two patients underwent additional surgery for their active fistulae.

Discussion

Somatostatin-14 is a natural hormone, secreted by the delta cells of the pancreatic islets. It is a profound

Table 1. — **Patients and clinical characteristics**

	regimen A			regimen B			p-value
	mean	standard deviation	range	mean	standard deviation	range	
Age	60,0	7,9	50-69	56,6	14,1	33-68	0,916
Weight	70,8	9,6	60-80	64,8	5,9	58-72	0,327
Pre-treatment somatostatin level	18,4	4,3	16-26	15,8	10,3	8-33	0,195
Post-treatment somatostatin level	31,0	14,4	16-50	34,2	35,1	16-97	0,537
Fistula output	514	527	150-1285	103	86	30-200	0,078

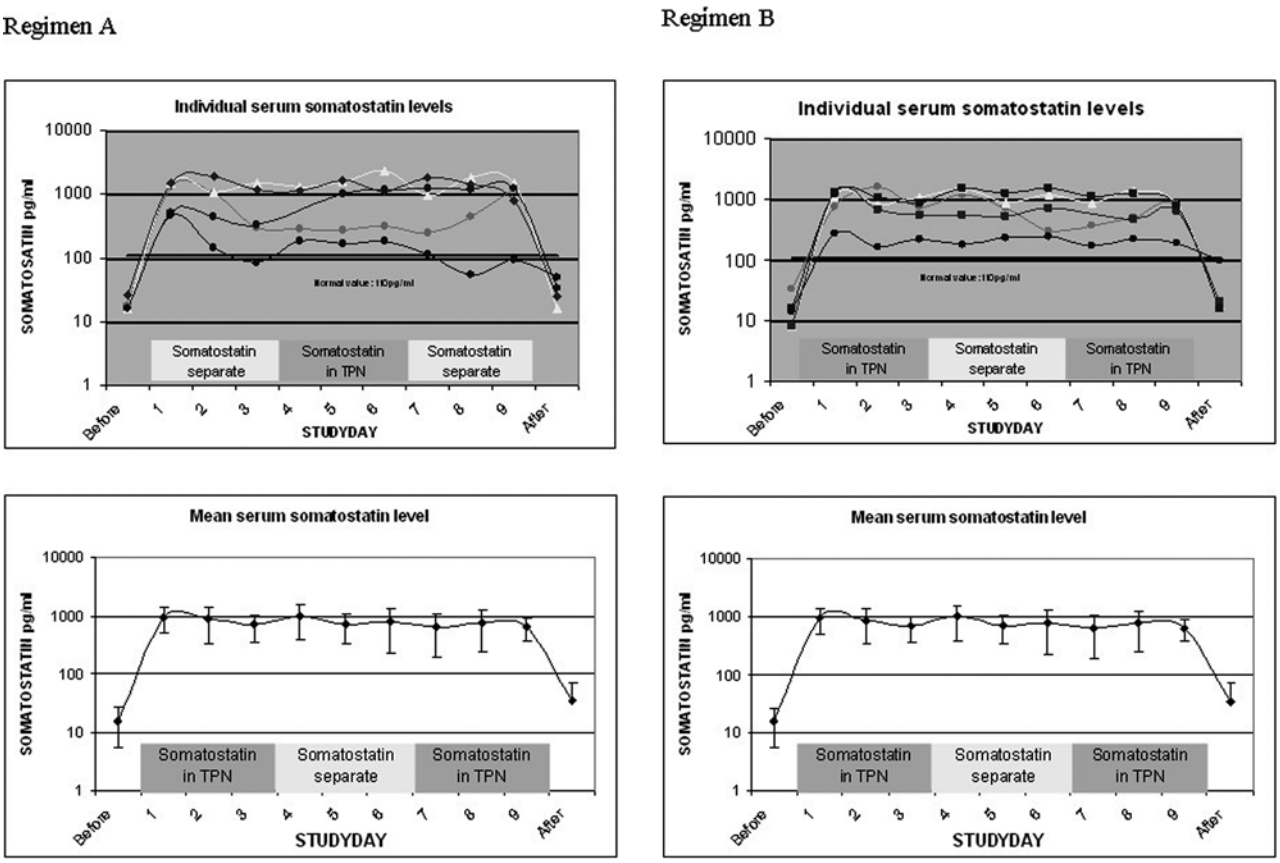


Fig. 1. — Individual and mean serum somatostatin levels (with standard deviation)

Table 2. — **Comparison of mean serum somatostatin level when somatostatin has been infused separately to serum somatostatin levels when somatostatin had been added to a standard TPN-mixture**

Somatostatin serum levels	mean	standard deviation	range	p value of difference
Pre-treatment	17	7	8-33	
Somatostatin added to TPN	807	505	162-2279	0,473
Somatostatin separately	884	557	54-1900	
Post-treatment	33	26	16-97	

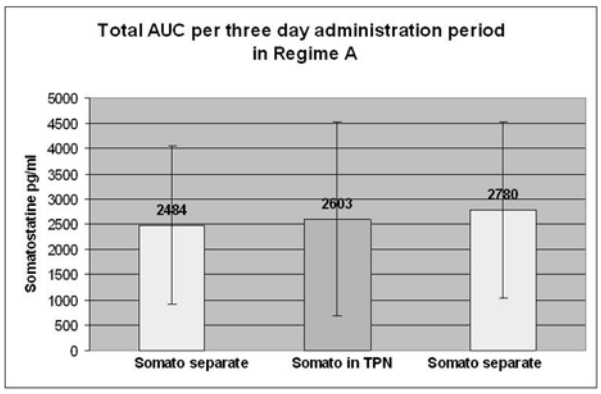
Table 3. — **Comparison of AUC per three day period between both treatment regimens**

	regimen A			regimen B			p-value
	mean	standard deviation	range	mean	standard deviation	range	
AUC during treatment period 1 (3 days)	884	566	231-1536	836	355	217-1066	0,754
AUC during treatment period 2 (3 days)	917	662	180-1714	832	479	216-1418	0,917
AUC during treatment period 3 (3 days)	939	571	87-1438	673	363	193-1059	0,251

inhibitor of pancreatic exocrine function. Besides this effect, somatostatin-14 inhibits insulin and glucagon secretion, gastric duodenal and gallbladder motility and secretion of intestinal and gastric juices (2). Therefore, intravenous somatostatin-14 is in our centre routinely administered with TPN for the treatment of pancreatic and enterocutaneous fistulae (3,4,5,6). The native hormone was used instead of the octreotide acetate because it has an action mechanism on all 5 known somatostatin receptors, whereas the synthetic analogue only acts on receptor 2 and 5.

Because of its short half-life (3 minutes), somatostatin-14 has to be administered by a continuous infusion. Interruption of this infusion may lead to a rebound phenomenon on fistula output. Until now, standard administration of this drug was through a separate intravenous line from the TPN mixture. The reason for this separation lies in the possible interactions between

Regimen A



Regimen B

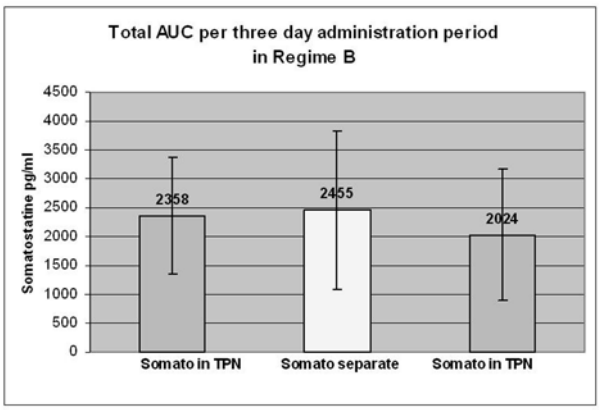


Fig. 2. — Mean area under the curve per three day administration period (with standard deviation).

somatostatin and the components of TPN (carbohydrates, lipids, amino acids, vitamins and oligoelements). If somatostatin and TPN could be administered through the same line, a supplementary intravenous line could be omitted, and this would result in less manipulation, reduced workload for nursing staff, and fewer interruptions of this continuous infusion.

In this study, we conclude that the mixture of somatostatin and TPN remains stable at 4°C during a 48-hour period, and that somatostatin is still fully available after 24 hours. We also demonstrate that addition of somatostatin to a standard TPN mixture ('all in one' bag) results in somatostatin serum levels and area under the curve values that are similar to those obtained when somatostatin is administered separately.

Therefore, somatostatin may be added to a TPN mixture, and only one intravenous line is needed for the administration of both drugs.

This study needs to be confirmed in a larger population. The beneficial effect of somatostatin added to a TPN mixture on fistula closure has also to be compared with the classical route of administration (somatostatin infused separately).

Addendum

Stability testing of the somatostatin addition has been expanded to other commercially available TPN confirming stable mixtures for 72 hours storage at 4°C and thereafter an additional 24 hours storage at 21°C (during infusion). During the whole period the somatostatin was available at more than 100 000 pg/ml. The somatostatin had been added to the following mixtures : Kabiven 11, Structokabiven 12 (with and without electrolytes) and to Oliclinomel N6, Oliclinomel N7 (with and without electrolytes), Oliclinomel N8 (without electrolytes). The stability of these TPN mixtures with the somatostatin added has been performed by their manufacturers : Fresenius Kabi AG, Homburg, Germany and Baxter R&D Europe, Nivelles, Belgium. The stability of the somatostatin 14 in these mixtures has been tested by UCB Pharma, Brussels, Belgium.

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