

Effects of somatostatin on intestinal calcium absorption in man with primary hyperparathyroidism

par L. MONNIER, G. SAUTOT, C. COLETTE, J. GUERIS *, J. MIROUZE

Clinique des Maladies métaboliques, Hôpital Saint-Éloi, 34059 Montpellier Cedex
** Laboratoire de Radioimmunologie, Hôpital Lariboisière, Paris.*

Summary. Eight patients suffering from primary hyperparathyroidism were studied in basal conditions, i. e. during a saline infusion and under somatostatin administration (a 250 µg bolus injection followed by continuous infusion of 500 µg per hour over 240 min). The calcium metabolism was estimated from (i) concentrations of plasma calcium, phosphorus, 25-hydroxyvitamin D (25-OH-D), iPTH and (ii) intestinal calcium absorption determined by a double radiotracer technique using oral ⁴⁷Ca and IV ⁴⁵Ca. The results show that somatostatin produced no significant change in calcium, phosphorus, 25-OH-D or iPTH levels. On the contrary, the fractional absorption of calcium (FA Ca), expressed as a percentage of the total oral dose and measured at 30 minute intervals over 240 min, was significantly depressed with somatostatin during the first 2 hours. Beyond the second hour FA Ca remained slightly depressed with somatostatin, but was not significantly different from the basal conditions. From the present results, we conclude that somatostatin slows down calcium absorption, while the total amount of calcium absorbed at the completion of the absorption process is not significantly diminished. Furthermore, as 25-OH-D and iPTH remained unchanged, somatostatin seems to have no effect on the hormonal control of calcium absorption. Therefore, we suggest that somatostatin has only a mechanical effect on calcium absorption, slowing down the intestinal transit.

Introduction.

Somatostatin, a recently discovered hormone, is widely distributed in the body. It has several target tissues and may function either as a neurotransmitter, a neurohormone, a parahormone (paracrine hormone) or perhaps as a classical hormone. Somatostatin exerts a potent inhibitory effect on many polypeptide secretions, such as insulin, glucagon and growth hormone, both in physiologic and pathologic situations. However, in some circumstances, it is only active in patients with hormonal hypersecretions. For instance, somatostatin has no effect on basal ACTH or plasma ACTH responses to metopyrone and insulin-induced hypoglycaemia in normal man, but it does inhibit ACTH hypersecretion due to lack of cortisol feedback. The data concerning the effects of somatostatin on calcium homeostasis in normal subjects are controversial (Evensen, Hanssen and Berstad, 1978 ; Scholz and Schwille, 1978). In the present study, we have investigated the effect of somatostatin on patients suffering from primary hyperparathyroidism, i. e. exhibiting PTH hypersecretion and therefore high plasma calcium levels and increased calcium absorption (Reeve, Hesp and Veall, 1979).

Material and methods.

Eight patients suffering from primary hyperparathyroidism were investigated once informed consent had been obtained. In all cases, hyperparathyroidism was due to parathyroid adenoma and the patients were treated surgically by simple nodulectomy.

During the preoperative period, all the patients were investigated twice on separate days. All the studies began at 8.00 a. m. after an overnight fast.

The first investigation was carried out under basal conditions, i. e. during a saline infusion. In the second study, the patients received 250 μg of cyclic somatostatin (supplied by the medical research center of Clin Midy Lab., France) as an intravenous bolus given at 8 : 00 a. m., immediately followed by the constant infusion of somatostatin (500 $\mu\text{g}/\text{hr}$) over 240 min.

During both studies, the intestinal absorption of calcium was determined using a double radiotracer technique (Birge *et al.*, 1969 ; Monnier *et al.*, 1978) whose principle was based on the simultaneous and bolus administration of an oral (^{47}Ca) and intravenous (^{45}Ca) dose of radiocalcium. The doses were given at 8 : 00 a. m. and plasma radioactivities of both tracers were monitored up to the sixth hour by serial blood sampling at 30 min intervals. According to the impulse analysis method (Shiple and Clark, 1972), the transfer pattern of oral calcium from the gut lumen to the plasma, i. e. the transit time curve of oral calcium, was calculated from the time courses of plasma ^{47}Ca and ^{45}Ca activities, using a mathematical procedure of inverse convolution (Shiple and Clark, 1972).

Four main parameters were obtained from the transit time curves : (i) the amount of calcium absorbed at the completion of the absorption process, i. e. the fractional absorption (FA Ca) expressed as a percentage of the total dose (p. 100 of TD) and calculated from the total area under the transit time curve, (ii) the peak absorption rate (p. 100 of TD/min), (iii) the time of the peak absorption rate (min), and (iv) the mean transit time (min) across the intestinal barrier. Finally, the time course of cumulative fractional absorption (p. 100 of TD) was obtained from calculations of the area under the transit time curve at different times.

In addition, during the second study, somatostatin effects on calcium homeostasis were evaluated by measuring : (i) plasma calcium and phosphorus levels, (ii) plasma immunoreactive PTH, and (iii) plasma 25-hydroxyvitamin D (25-OH-D). One baseline sample was collected at 8 : 00 a. m. prior to somatostatin administration. Additional blood was sampled at 30-min intervals over the entire period of somatostatin infusion, i. e. for 4 hrs.

Analytical methods. — Plasma calcium and phosphorus were respectively determined by atomic absorption spectrophotometry and by a modification of the Fiske-Subbarow procedure (Fiske and Subbarow, 1925).

Plasma immunoreactive levels of parathormone (iPTH) were determined by an heterogeneous immunological system : labelled porcine PTH and antiporcine PTH antibodies supplied by C. Arnaud (Gueris, 1974).

Plasma 25-OH-D was determined by a competitive binding assay as previously described by Preece *et al.* (1974).

Statistical analysis. — All results were given as the mean \pm standard error (SEM). The data were compared using the Wilcoxon ranking test which does not require normal distribution and large sample sizes.

Results.

The time courses of cumulative fractional absorption of calcium (fig. 1) illustrate clearly that the intestinal calcium absorption was significantly depressed during the first 2 hrs under somatostatin infusion as compared to the control studies. Beyond the second hour, cumulative fractional calcium absorption remained slightly diminished under somatostatin, but the difference was not significant as compared to the studies under saline infusion (fig. 1). Therefore, fractional absorption at the completion of the absorption process, i. e. at the sixth hour (FA Ca), was not statistically different whether the patients were infused with somatostatin or saline (table 1).

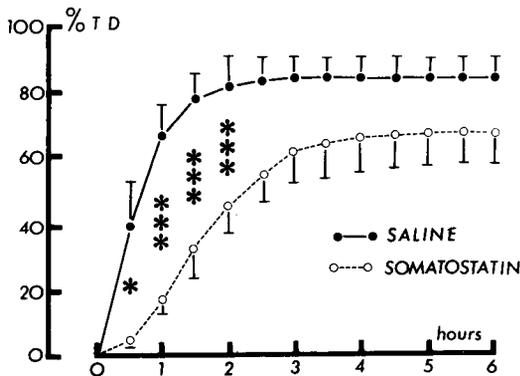


FIG. 1. — Effect of somatostatin on the cumulative fractional absorption of calcium (p. 100 of total dose). Somatostatin was given as a 250 μ g bolus at time 0 and infused continuously (500 μ g/hr) from time 0 for 4 hrs. * $P < 0.05$, *** $P < 0.01$.

TABLE 1

Effects of somatostatin on the parameters of calcium absorption in 8 patients suffering from primary hyperparathyroidism

| Conditions | Under saline infusion | | Under somatostatin infusion |
|---|-----------------------|----------------------------|-----------------------------|
| No. Tested | 8 | | 8 |
| Fractional absorption of Ca (p. 100 of total dose)..... | 86.7 \pm 6.2 | | 64.1 \pm 9.4 |
| Peak absorption rate (p. 100 of TD/min) .. | 2.6 \pm 0.8 | | 1.2 \pm 0.5 |
| Time of peak absorption (min) | 35.8 \pm 8.9 | $\leftarrow * \rightarrow$ | 83.3 \pm 21.2 |
| Mean transit time (min) | 48.8 \pm 11.6 | $\leftarrow * \rightarrow$ | 88.7 \pm 15.6 |

All results given are the mean \pm SEM. Statistical differences are only indicated when significant * $P < 0.05$.

As shown on table 1, the somatostatin infusion resulted in slower intestinal transit time. The time of peak absorption was significantly delayed and the mean transit time was longer than under saline.

As indicated on figure 2, plasma concentrations of calcium, phosphorus and 25-OH-D remained unchanged during the entire period of somatostatin infusion. In two patients whose plasma samples were assayed for iPTH, there was no significant change in that parameter after somatostatin infusion.

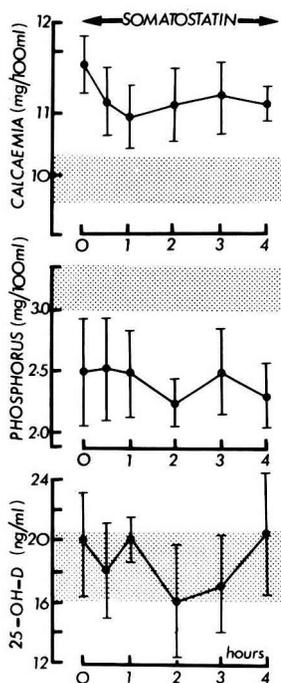


FIG. 2. — Effects of somatostatin on plasma concentrations of calcium, phosphorus, and 25-OH-D. Somatostatin was given as a 250 μ g bolus at time 0 and infused continuously (500 μ g/hr) from time 0 for 4 hrs. The shaded area corresponds to the normal range.

Discussion.

The present results show that cyclic somatostatin infused intravenously reduces the intestinal calcium absorption. However, as in other studies (Evensen, Hanssen and Berstad, 1978 ; Scholz and Schwille, 1978), the absorption rate was only depressed during the first 2 hours. This effect could be due either to unspecific actions or to a direct inhibition of the active calcium transport across the intestinal barrier (Holdsworth, 1975), the latter being mainly regulated by the active metabolites of vitamin D derived from the sequential hydroxylation of vitamin D₃ by the liver (Blunt, De Luca and Schnoes, 1968) and the kidney (Norman, 1974). Renal hydroxylation which results in the production of the 1,25 (OH)₂ vitamin D₃ is also controlled by calcium (Bikle and Rasmussen, 1975), phosphorus (Gray *et al.*, 1977) and PTH (De Luca, 1978). As shown by our results, plasma concentrations of calcium, phosphorus, PTH and 25-OH-D remained unchanged when somatostatin was infused to hyperparathyroid patients. Furthermore, other authors (Defos *et al.*, 1976 ; Metz *et al.*, 1978) have shown that

somatostatin infusion does not reduce basal PTH levels either in normal subjects or in patients with hypercalcaemia, and fails to prevent PTH increase when the hormonal secretion is stimulated by pharmacological agents (Metz *et al.*, 1978). It therefore seems unlikely that somatostatin impairs calcium absorption by interfering with active calcium transport and its regulation mechanism.

On the contrary, our findings that somatostatin produces a delay in absorption, rather than a reduction of net absorption, would suggest that somatostatin acts through a non-specific mechanism. This hypothesis is supported by the fact that somatostatin reduces splanchnic blood flow and slows down gastric and duodenal emptying by inhibiting the motility of the gastroduodenal tract (Schrumpf, Stadaas and Hanssen, 1976 ; Transy *et al.*, 1978).

We conclude from the present study that somatostatin has no specific effect on calcium metabolism, even in patients suffering from primary hyperparathyroidism. Although somatostatin infusion slows down the intestinal absorption of calcium, it cannot be considered a useful agent in the management of hypercalcaemia in primary hyperparathyroidism.

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Résumé. Huit malades atteints d'hyperparathyroïdisme primaire sont étudiés à l'état de base, pendant une perfusion de salé isotonique et sous somatostatine (injection en giclée de 250 µg suivie par une perfusion de 500 µg horaire pendant 240 min). Le métabolisme calcique est évalué à partir : (i) des concentrations plasmatiques en calcium, phosphore, 25 hydroxyvitamine D (25-OH-D), i PTH et (ii) de l'absorption intestinale du calcium, déterminée par une méthode de double marquage isotopique utilisant du ⁴⁷Ca par la bouche et du ⁴⁵Ca par voie IV. Les résultats montrent que la somatostatine n'entraîne aucune modification de la calcémie, de la phosphorémie, de la 25-OH-D et de la i PTH. A l'inverse, l'absorption fractionnelle du calcium (FA Ca) exprimée en pourcentage de la dose totale ingérée et mesurée, toutes les 30 min pendant 240 min est significativement diminuée par la somatostatine pendant les deux premières heures. Au-delà de la deuxième heure, la FA Ca reste modérément diminuée par la somatostatine, mais la baisse n'est pas significative par rapport aux conditions basales. A partir de ces résultats, on peut conclure que la somatostatine ralentit l'absorption calcique mais la quantité totale absorbée à la fin du processus d'absorption n'est pas diminuée de manière significative. De plus, étant donné que la 25-OH-D et la i PTH restent inchangées, la somatostatine ne semble pas avoir d'effet sur le contrôle hormonal de l'absorption. De ce fait, il semble que la somatostatine agisse sur l'absorption calcique par un effet purement mécanique, en ralentissant le transit intestinal.

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