Aliment Pharmacol Ther 2001; 15: 857–864.

Bolus somatostatin but not octreotide reduces hepatic sinusoidal pressure by a NO-independent mechanism in chronic liver disease

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Accepted for publication 19 January 2001

SUMMARY

Background: Evidence exists that somatostatin and octreotide might have different effects on hepatic haemodynamics.

Aim: The investigation of the effects of somatostatin and its octapeptide analogue, octreotide, on sinusoidal pressure measured by the wedged hepatic venous pressure in patients with cirrhosis or chronic hepatitis and the correlation with the levels of hepatic vein NO.

Methods: Patients were randomly assigned to receive an injection of either 250 μg somatostatin ($n = 14$: cirrhosis six, chronic hepatitis eight) or an injection of 125 μg octreotide ($n = 19$: cirrhosis nine, chronic hepatitis 10) during hepatic vein catheterization. Baseline wedged hepatic venous pressure was measured, followed by measurements at 2, 5, 10 and 15 min after the injection of the drug. Nitrites/nitrates of the hepatic vein were measured before the injection and after 15 min.

Results: Both agents showed a similar qualitative but a different quantitative haemodynamic profile. No change in the wedged hepatic venous pressure was observed during the first 2 min after the injection of both drugs. This was followed by a decrease: 18% at 5 min (N.S.), 23% at 10 min ($P < 0.01$) and 24% at 15 min ($P < 0.01$) for somatostatin. Octreotide induced a relatively smaller decrease in the wedged hepatic venous pressure: 8% at 5 min (N.S.), 20% at 10 min ($P < 0.01$) and 16% at 15 min (N.S.). Further analysis of the sub-groups of cirrhotic and chronic hepatitis patients revealed a different effect. In the sub-group of cirrhotic patients, somatostatin caused a maximum decrease of 34% at 15 min post-injection ($P < 0.01$), but octreotide failed to produce a significant change on the wedged hepatic venous pressure. In contrast, no change was observed in chronic hepatitis patients with either drug. No change in the hepatic vein concentration of NO after treatment was observed with either somatostatin or octreotide. Moreover, no correlation of the levels of NO with the wedged hepatic venous pressure values was found.

Conclusions: This study shows that somatostatin is more effective than octreotide in acutely reducing the wedged hepatic venous pressure after bolus injection and the observed change is probably mediated by a NO-independent mechanism.

INTRODUCTION

Portal hypertension is the main complication of liver cirrhosis and chronic hepatitis. This syndrome is responsible for the frequently fatal complication of massive gastrointestinal bleeding from ruptured oesophageal varices. Portal pressure may increase because of an increase in either portal blood flow, or intrahepatic vascular resistance, or a combination of both. It is well-established that, although the primary factor leading to portal hypertension is an increased resistance to portal blood flow, an increased portal venous inflow contri-

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butes equally and becomes especially important in advanced stages.[1]

Many pharmacological attempts to treat portal hypertension have aimed to correct the increased portal blood inflow with splanchnic vasoconstrictors. Somatostatin and its cyclic octapeptide analogue, octreotide, have been shown to produce an immediate reduction in portal pressure and collateral blood flow.[2–7] Their immediate effect, together with the relatively high safety of both agents has provided the rational for their use in the treatment of acute variceal bleeding. The beneficial effects of somatostatin and octreotide are largely attributed to splanchnic vasoconstriction.[8–10] However, the exact mechanism of action remains unknown. Although a direct effect on splanchnic vasculature cannot be excluded, indirect methods of action are under investigation. A reduction in circulating vasodilators such as glucagon has been suggested as a possible method of action of these drugs.[9, 10] Recent studies have focused on somatostatin-induced changes in the equilibrium of paracrine vasoactive factors such as NO and endothelin.[11–13]

The present study was designed to compare the efficacy of both drugs in reducing sinusoidal pressure as measured by the wedged hepatic venous pressure, as well as to clarify whether the induced effects are accompanied by changes in the local concentration of NO.

MATERIALS AND METHODS

Patients

A total of 33 patients investigated for portal hypertension were included in the study. Twenty-one (63.6%) patients were male and 12 (36.4%) were female, with a mean age of 59.4 years (range 36–75 years). All patients had biopsy-proven chronic liver disease. Fifteen patients had cirrhosis (10 viral, three alcoholic, one primary biliary cirrhosis, one primary sclerosing cholangitis) and 18 patients had chronic viral hepatitis (10 hepatitis C virus, six hepatitis B virus, two with both hepatitis C virus and hepatitis B virus). The modified Child–Pugh classification was used to assess the severity of disease in cirrhotic patients (10 patients were Child–Pugh class A and five were Child–Pugh class B).[14] All cirrhotic patients had oesophageal varices but no previous bleeding episodes. Patients with ascites or evidence of hepatic encephalopathy were excluded from the study. Furthermore, none of the patients included in the study had previously received any pharmacological treatment for portal hypertension. Clinical data for the patients studied are given in Table 1. All patients gave their consent to participate in the study.

Materials

HEPES was purchased from MERCK (Darmstadt Germany). Nitrate reductase (from Aspergilus species), lactate dehydrogenase, pyruvic acid (sodium salt), NADPH (reduced form, tetrasodium salt), FAD (disodium salt), N-(1-naphthyl)ethyl-enediamine and sulfanilamide were purchased from SIGMA (Munchen, Germany).

Haemodynamic study

Under local anaesthesia, a venous catheter introducer was placed in the right jugular vein and a balloon-tipped catheter was advanced under fluoroscopy into the main right hepatic vein for the measurement of the wedged hepatic venous pressure, according to standard techniques. Patients were randomly assigned to receive a bolus injection of either 250 μg somatostatin (14 patients) or 125 μg octreotide (19 patients) in a peripheral vein. Wedged hepatic venous pressure was recorded before and at 2, 5, 10 and 15 min after bolus administration of the drugs.

Blood samples

Blood was drawn directly from the hepatic vein before and 15 min after bolus injection of somatostatin or

Table 1. Clinical and haemodynamic characteristics of patients included in the study

	Somatostatin 250 μg	Octreotide 125 μg
n	14	19
Age	63.5 ± 2.6	56.6 ± 2.1
Sex (male/female)	8/6	13/6
Disease		
Cirrhosis	6	9
CH	8	10
Etiology		
Viral	12	16
Alcoholic	1	2
Other	1	1
Oesophageal varices	6	9
Child–Pugh score (A/B/C)	4/2/0	6/3/0
Mean WHVP (mmHg)	14.4 ± 1.5	14.7 ± 1.2

CH, chronic hepatitis; WHVP, wedged hepatic venous pressure.

octreotide. Blood samples were collected in silicon-coated glass tubes and immediately centrifuged after clotting (1500 ***g***, 10 min, room temperature). Serum was collected and stored at – 70 °C until tested. Storage period did not exceed 6 months in any case.

Nitric oxide measurement

Total serum nitrite (NO_3^-) plus nitrate (NO_2^-) concentration represent an index of nitric oxide (NO) production. In order to determine local production of NO, total NO_2^-/NO_3^- of the above serum samples were assayed using a modification of the Griess reaction as previously described.[15] Briefly, 100 μL of serum sample were incubated for 30 min at 37 °C in the presence of 0.2 U/mL Aspergilus nitrate reductase, 5 μM FAD and 0.1 mM NADPH in 50 mM HEPES buffer (total volume 500 μL) for the conversion of nitrate to nitrite. Following the incubation, 5 μL of lactate dehydrogenase (1500 U/mL) and 50 μL of 100 mM pyruvic acid were added to each tube to oxidize any unreacted NADPH (reduced pyridine nucleotides strongly inhibit the Griess reaction). Samples were then incubated for an additional 10 min at 37 °C. Finally, 1 mL of pre-mixed Griess reagent was added to each tube. After a 10-min incubation time at room temperature, the absorbance of each sample was determined at 543 nm with a Hitachi U-2000 Spectrophotometer.

Data analysis

The results are reported as mean ± S.E.M. Student's *t*-test for paired data was used to evaluate the effect of bolus injections of somatostatin and octreotide within each group. Comparisons among groups were performed by the Student's *t*-test for unpaired data. Linear regression with Pearson's correlation was used for comparisons between wedged hepatic venous pressure values and nitrates/nitrites. All statistical comparisons were performed by the SPSS for Windows statistical software (SPSS Inc., Chicago, Illinois). Significance was established at $P < 0.05$.

RESULTS

Baseline data

No statistically significant difference was observed between the patients receiving somatostatin or octreotide in relation to age, sex, aetiology or severity of liver disease (Table 1). Five patients of the somatostatin group were unable to complete measurements for reasons unrelated to drug side-effects, hence the difference in the number of patients in the two groups. There was no significant difference in wedged hepatic venous pressure baseline values between patients receiving somatostatin or octreotide. Cirrhotic patients had significantly higher wedged hepatic venous pressure compared to patients with chronic hepatitis (17.6 ± 1.3 vs. 12.1 ± 0.9 mmHg, respectively, $P = 0.001$).

Effect of bolus injection of somatostatin

The bolus injection of 250 μg somatostatin resulted in a marked decrease in the wedged hepatic venous pressure when patients with either cirrhosis or chronic hepatitis were grouped together. More specifically, although no change was observed 2 min after treatment, wedged hepatic venous pressure was consequently decreased by 18 ± 6% at 5 min (N.S.), 23 ± 7% at 10 min ($P < 0.01$) and 24 ± 7% at 15 min ($P < 0.01$). However, when the two groups were separately analysed a different effect was observed. In the sub-group of patients with chronic hepatitis, no significant change was observed (Figure 1, Table 2). On the other hand, in the sub-group of patients with cirrhosis, somatostatin produced a decrease in wedged hepatic venous pressure by 14 ± 9% at 2 min (N.S.), 29 ± 9% at 5 min ($P < 0.05$), 32 ± 6% at 10 min ($P < 0.01$) and 34 ± 7% at 15 min ($P < 0.01$, Figure 2 and Table 3).

Effect of bolus injection of octreotide

The bolus injection of 125 μg octreotide caused a smaller decrease in the wedged hepatic venous pressure compared with the somatostatin in the total group of patients. No change was observed during the first 2 min, while a decrease by 8 ± 7% at 5 min (N.S.), 20 ± 7% at 10 min ($P < 0.05$) and 16 ± 10% at 15 min (N.S.) was observed. No change was observed in the sub-group of chronic hepatitis patients (Figure 1, Table 2). Interestingly, in the sub-group of patients with cirrhosis, although wedged hepatic venous pressure was decreased, the observed change did not reach statistical significance at any time-point during the study. In this sub-group, wedged hepatic venous pressure was decreased by 5 ± 8% at 2 min, 9 ± 9% at 5 min, 23 ± 9% at 10 min and 19 ± 14% at 15 min (N.S.)

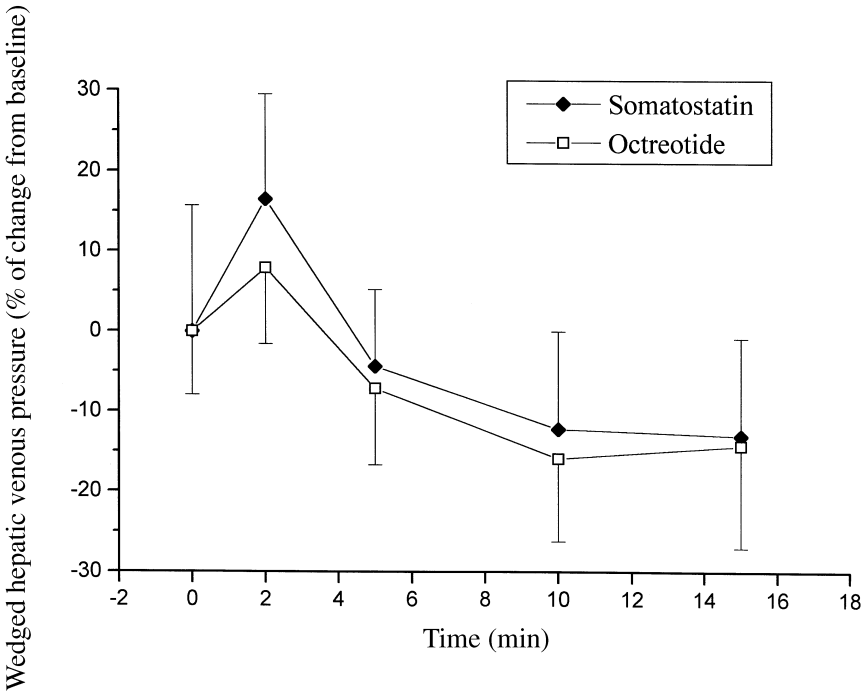

Figure 1. The effects of bolus injection of 250 μg somatostatin ($n = 8$) or 125 μg octreotide ($n = 10$) on the wedged hepatic venous pressure of chronic hepatitis patients. Data are shown as a change in percentage from the baseline (mean ± S.E.M.).

Table 2. Effect of bolus injection of 250 μg somatostatin or 125 μg octreotide on sinusoidal (wedged hepatic venous) pressure (mmHg) of chronic hepatitis patients

WHVP	Somatostatin 250 μg (n=8)	Octreotide 125 μg (n=10)
Baseline	11.5 ± 1.8	12.6 ± 1.0
2 min	13.4 ± 1.5	13.6 ± 1.2
5 min	11.0 ± 1.1	11.7 ± 1.2
10 min	10.1 ± 1.4	10.6 ± 1.3
15 min	10.0 ± 1.4	10.8 ± 1.6

WHVP, wedged hepatic venous pressure. Values are mean ± S.E.M.

(Figure 2 and Table 3). No adverse side-effects were observed at any time during the administration of either drug.

Nitric oxide levels

The basal serum NO_2^-/NO_3^- levels of blood samples drawn directly from the hepatic vein were 56.0 ± 2.6 mmol/mL. Mean values obtained for cirrhotic patients were 55.4 ± 3.0 mmol/mL and did not differ significantly from values obtained for chronic hepatitis patients 56.7 ± 4.5 mmol/mL. No change was observed in serum NO_2^-/NO_3^- levels before and after treatment with somatostatin or octreotide for any sub-group of patients (Table 4). No correlation was observed between the wedged hepatic venous pressure values and hepatic vein NO levels (before injection $r = 0.22$, $P = 0.271$; after injection $r = 0.217$, $P = 0.308$).

DISCUSSION

Somatostatin has been proposed as a treatment for variceal or severe portal gastropathy bleeding because of its ability to decrease portal pressure without significant adverse systemic effects.[2, 13, 16] The effect of somatostatin is possibly mediated through its ability to cause a selective splanchnic vasoconstriction and reduction of splanchnic blood flow.[2, 5, 17] Although initial reports were conflicting, further haemodynamic studies proved the efficacy of somatostatin in modifying portal pressure and supported the rational for the use of the drug in acute variceal bleeding.[2, 4, 5] In a double-blind, placebo-controlled haemodynamic study, Cirera *et al.* demonstrated that a single bolus injection of 250 μg somatostatin produced a rapid and intense fall of 52% and 45% in portal pressure gradient and azygos blood flow, respectively.[4] In our study, a similar treatment caused a maximum of 34 ± 7% reduction in sinusoidal pressure in the sub-group of cirrhotic patients. This is consistent with the findings of Cirera *et al.*, where the recorded reduction in

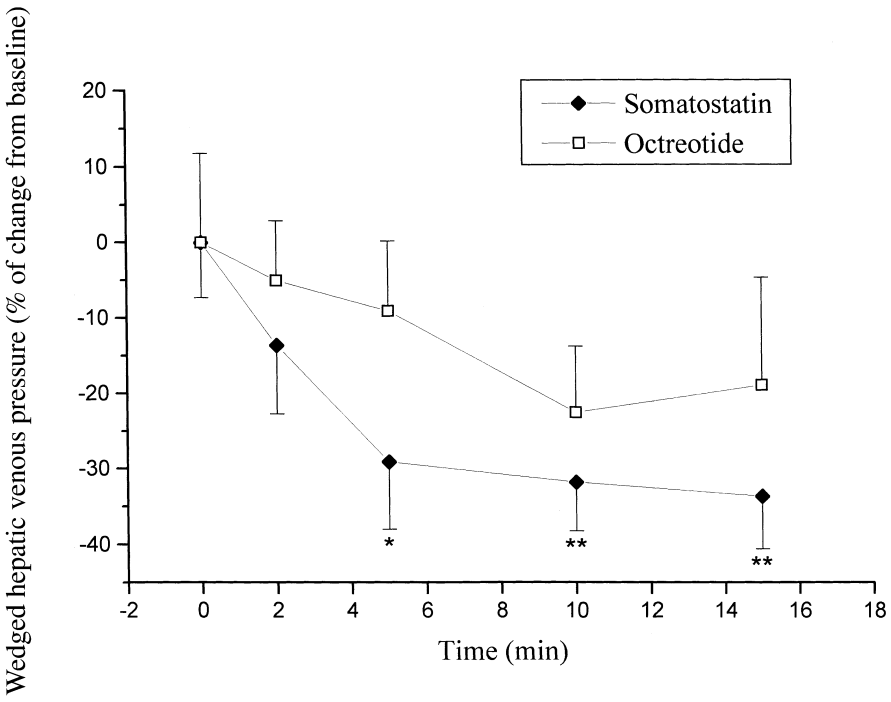

Figure 2. The effects of bolus injection of 250 μg somatostatin ($n = 6$) or 125 μg octreotide ($n = 9$) on the wedged hepatic venous pressure of cirrhotic patients. Data are shown as a change in percentage from the baseline (mean ± S.E.M.). Statistical significance of the difference from baseline values $^{*}P < 0.05$, $^{**}P < 0.01$.

hepatic venous pressure gradient was attributed to a significant decline in wedged hepatic venous pressure accompanied by a marked increase in free hepatic vein pressure.[4]

The rapid effect of bolus injection of somatostatin on hepatic circulation, confirmed by the present study, is the most pronounced effect ever observed with a pharmacological agent used for the treatment of portal hypertension and may be of great clinical relevance. According to the European ABOVE study conducted among 205 patients with cirrhosis and upper gastrointestinal bleeding, the early administration of repeated boluses of 250 μg somatostatin, followed by a continuous infusion, resulted in a reduction of cases with active variceal bleeding at the time of emergency endoscopy. As a consequence, sclerotheraphy was easier to perform, the amount of blood transfused was lower and death or rescue therapy was less frequent.[18] Part of the beneficial effect of the above treatment, particularly the decrease in frequency of active bleeding during emergency endoscopy, may be attributed to the acute reduction in portal pressure gradient and collateral flow observed with the bolus administration of somatostatin.

Table 3. Effect of bolus injection of 250 μg somatostatin or 125 μg octreotide on sinusoidal (wedged hepatic venous) pressure (mmHg) of cirrhotic patients

WHVP	Somatostatin 250 μg (n=6)	Octreotide 125 μg (n=9)
Baseline	18.3 ± 1.3	17.1 ± 2.0
2 min	15.8 ± 1.7	16.3 ± 1.4
5 min	13.0 ± 1.6*	15.6 ± 1.6
10 min	12.5 ± 1.2**	13.3 ± 1.5
15 min	12.2 ± 1.3**	13.9 ± 2.4

Values are mean ± S.E.M. Statistical significance of the difference from baseline values $^{*}P < 0.05$, $^{**}P < 0.01$.

The short half life of somatostatin has led to the development of synthetic octapeptide analogues with a longer biological half life, such as octreotide.[5] Initial reports have shown that this agent is capable of reducing portal pressure in animals as well as in cirrhotic patients.[5, 19] Subsequent studies, however, produced controversial results.[6, 7] A placebo-controlled study conducted by Nevens *et al.*, comparing the effect of octreotide with that of terlipressin on the variceal pressure, concluded that the bolus injection of 50 μg octreotide produced no change in variceal pressure.[20] Furthermore, Moller *et al.*, in a study with a small number of patients ($n = 13$), demonstrated that a bolus injection of 100 μg octreotide followed by a continuous infusion had no effect on either the wedged hepatic and free hepatic venous pressures or on the hepatic venous pressure gradient.[21]

	Somatostatin 250 μg		Octreotide 125 μg	
	Baseline	15 min	Baseline	15 min
CH patients	57.7 ± 7.9	58.9 ± 9.2	56.3 ± 5.8	62.8 ± 7.1
Cirrhotic patients	56.7 ± 4.0	49.6 ± 6.4	54.4 ± 4.6	50.4 ± 3.7

Values are mean ± S.E.M.

Table 4. Effects of bolus injection of 250 μg somatostatin or 12 μg of octreotide on serum NO_2^-/NO_3^- levels (mmol/mL) in patients with chronic hepatitis and cirrhosis

In the present study, the bolus injection of 125 μg octreotide showed, in contrast to somatostatin, a statistically significant maximum decrease of 23 ± 9% of the wedged hepatic venous pressure only at 10 min in the total group of patients. However, when cirrhotic and chronic hepatitis patients were separately analysed, no change in sinusoidal pressure could be found. Moller *et al.* also observed a transient and insignificant decrease in hepatic venous pressure gradient at 10 min post-injection, suggesting that a rapid desensitization to the effects of octreotide occurs in patients with cirrhosis.[21] We conclude that bolus injection of octreotide is not as effective as somatostatin in acutely reducing wedged hepatic venous pressure as the observed effects are transient and insignificant. The clinical relevance of this finding remains to be established. The international trial coordinated by Burroughs *et al.*, comparing the early administration of continuous infusion of octreotide in 193 patients with bleeding oesophageal varices before sclerotheraphy failed to show any benefit compared to placebo.[22] An initial bolus was not administered in their study. It seems, therefore, that octreotide is less effective than somatostatin in acutely modifying hepatic haemodynamics.

It has been reported that both somatostatin and octreotide mediate their effects by splanchnic vasoconstriction.[23] However, the exact mechanism of action remains unknown. The speed of onset of the haemodynamic effects may suggest either a direct effect on the vasculature or a modification of paracrine vasoactive factors such as nitric oxide.[17, 24] Nitric oxide (NO) seems to play an important role in splanchnic vasodilation in cirrhotic patients.[25] The finding of almost complete normalization of splanchnic haemodynamics, with a reduction in portal venous inflow and an increase in splanchnic vascular resistance in portal hypertensive rats by the acute administration of a non-specific NO synthesis inhibitor clearly demonstrates the importance of NO.[26, 27] There are several reports indicating that somatostatin can mediate NO production both *in vitro* and *in vivo*.[28, 29] *In situ* studies on isolated saphenous arteries and veins from different species demonstrated that somatostatin may directly cause arterial vasodilation and venous vasoconstriction by NO-dependent mechanisms.[12, 30] Considering the above regional differences in NO-dependent vascular responses to somatostatin, we investigated whether a bolus infusion of somatostatin modifies the local concentration of NO.

Previous investigations have demonstrated increased levels of nitric oxide in the hepatic vein of patients with cirrhosis compared to normal controls.[31] We found no difference in baseline local concentrations of NO between patients with chronic hepatitis and cirrhosis. No normal controls were included in our study. An additional reason for this discrepancy may be that the majority of the patients included in our study had a low Child–Pugh score, while NO overproduction is probably a finding related to later stages of cirrhosis.[15] Furthermore, we failed to demonstrate any significant changes in local levels of NO after the administration of somatostatin or octreotide, nor did we find any correlation between NO and wedged hepatic venous pressure values, either before or after injection of both drugs. Our findings are consistent with previously published data.

In an *in vitro* study in portal hypertensive rats, Sieber *et al.* observed that octreotide did not modify the vascular effects of *N*–-nitro-L-arginine, an antagonist of NO synthase. The authors suggested that octreotide does not exert a direct effect on NO formation.[13] Sabat *et al.* also failed to demonstrate changes in serum levels of NO_2^-/NO_3^- after the subcutaneous administration of octreotide in cirrhotic patients.[9] Furthermore, Chatila *et al.*, using venous occlusion plethysmography, observed that an intra-arterial dose of octreotide produced an immediate vasoconstriction to the infused arm. This direct effect was not accompanied by changes in local concentration of NO products. Moreover, octreotide had no inhibitory effect on NO-induced vasodilation by metacholine.[8] Finally, venoconstriction of the human

saphenous vein by somatostatin has been shown to occur by an NO-independent mechanism because it was present in the absence of a functional endothelium. These reports and the findings of the present study suggest that the acute vasoactive effect of somatostatin in the sinusoidal pressure is independent of NO.

To conclude, we have shown that a single bolus injection of somatostatin can cause a rapid, significant and relatively protracted decrease in wedged hepatic venous pressure in cirrhotic patients. Octreotide is not as effective as somatostatin in acutely reducing wedged hepatic venous pressure. This somatostatin effect is probably mediated by an NO-independent mechanism.

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