SHORT COMMUNICATION

Oral absorption of the somatostatin analogue SMS 201–995: theoretical and practical implications

HERMANN S. FUESSL, JAN DOMIN AND STEPHEN R. BLOOM
Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London

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Summary

1. Oral administration of SMS 201–995 (SMS), a subcutaneously injectable somatostatin analogue, was investigated in five healthy volunteers, who drank 2 mg of SMS with 75 g of glucose.

2. Mean maximal plasma SMS concentrations after the 2 mg oral dose were comparable with those after subcutaneous injection of 50 μg, although the peak was delayed (90 vs 15 min).

3. Biological activity of absorbed SMS was shown by significant and lasting suppression of plasma insulin concentrations, resulting in significant hyperglycaemia at 90 and 120 min compared with the control study.

4. The feasibility of oral administration of SMS may extend its use in the treatment of acromegaly and gut endocrine tumours. Other peptide hormone analogues, structurally 'protected' against enzymatic degradation, may also be active orally and thus be useful therapeutically.

Key words: oral administration, pharmacokinetics, somatostatin analogues.

Abbreviation: SMS, SMS 201–995.

Introduction

The therapeutic potential of many biologically active peptides is restricted by the need for parenteral administration. One such peptide is somatostatin, whose actions include suppression of growth hormone release [1] and inhibition of many gastrointestinal and pancreatic endocrine and exocrine functions [2, 3]. Somatostatin and its analogues have been shown to suppress abnormal peptide hormone secretion in acromegaly [4] and various gut-associated endocrine tumours [5, 6].

However, the use of native somatostatin and many of its analogues is limited by their rapid degradation and short circulating half-life, which in the case of the native peptide can be circumvented only by continuous intravenous infusion [7].

SMS 201–995 (SMS; Sandoz, Basle, Switzerland) is a recently synthesized somatostatin analogue whose structure confers outstanding resistance to enzymatic breakdown and which is active when injected subcutaneously [8]. SMS is increasingly used in the treatment of acromegaly [9, 10] and pancreatic endocrine tumours [6]. The present study aimed to discover whether this 'protected' peptide was absorbed after oral administration, which might avoid the need for multiple daily injections.

Subjects and methods

Five healthy male volunteers, aged 24–36 years, were each studied on two occasions 1 week apart. After an overnight fast, they drank 75 g of glucose in 200 ml of water containing either SMS (2 mg:4 ml of the 500 μg/ml injectable formulation) or an equal volume of SMS diluent (sodium acetate/acetic acid buffer, pH 4.0). The order of administration was random. Subsequently, each subject received a single subcutaneous injection of 50 μg of SMS. The test protocol was approved by the Hospital Ethical Committee and all subjects gave informed consent to the study.

Venous blood was taken into heparinized tubes containing 400 k.i.u. of aprotinin/ml of blood, 15
min before and at intervals up to 120 min after SMS administration. Plasma was separated by immediate centrifugation, frozen on dry ice and stored at $-20^\circ$C for subsequent measurement of SMS, insulin and glucose concentrations.

Plasma glucose concentration was measured by an autoanalyser (glucose oxidase method) and insulin by radioimmunoassay [11]. Plasma SMS concentration was measured by a specific and sensitive radioimmunoassay [8] whose detection limit is 50 pmol/l and which can detect differences of 0.25 fmol/tube with 95% confidence. The antiserum SMS-Rba (kindly provided by Dr P. Marbach, Sandoz Ltd, Basle) was specific for SMS and did not cross-react with native somatostatin-14 or somatostatin-28. The tyrosinated derivative of SMS (DTyr'SMS) was iodinated by the lactoperoxidase technique [12].

Results are expressed as means ± SEM, and differences between SMS and control data were examined by Student’s paired t-test.

Results

Oral SMS administration had no side-effects during, or in the 24 h after, the study and subcutaneous injection was followed only by mild and transient abdominal discomfort in two subjects.

Plasma SMS concentrations after oral (2 mg) and subcutaneous (50 μg) doses are shown in Fig. 1(a). After oral administration, mean plasma SMS rose to a plateau value of 1.5–1.6 nmol/l between 90 and 120 min, while a peak level of 2.3 nmol/l was reached 15–30 min after subcutaneous injection, falling gradually thereafter.

The physiological insulin rise after glucose ingestion was abolished by oral SMS, with significant insulin suppression between 30 and 120 min (Fig. 1b).

Plasma glucose concentrations (Fig. 1c) were significantly greater after oral SMS than during the control study, at 90 min (9.3 ± 0.4 vs 5.9 ± 0.4 mmol/l) and at 120 min (12.2 ± 1.1 vs 5.5 ± 0.3 mmol/l). The total area under the glycaemic curve after oral SMS was significantly greater than in the control study (8277 ± 312 vs 5798 ± 229 mmol/l, 120 min, $P < 0.001$).

Discussion

Somatostatin analogues show considerable therapeutic promise in several endocrine and gastrointestinal diseases, including acromegaly [9, 10], pancreatic and carcinoid tumours [6, 13], insulin-dependent diabetes [14] and ileostomy diarrhoea [15]. Long-term treatment of these conditions has become feasible with the development of long-acting, subcutaneously injectable somatostatin analogues such as SMS 201–995. Although many patients tolerate multiple daily injections because of the impressive symptomatic relief which they obtain, injections are nevertheless uncomfortable and inconvenient and oral administration would be a considerable advantage.

The remarkable stability of SMS in vitro against enzymatic degradation [8] led us to investigate the possible oral use of this valuable drug. SMS was given orally in glucose solution, which appears to enhance its intestinal absorption (unpublished

![Fig. 1](image-url)
work). Plasma levels after a 2 mg oral dose were comparable with those after a 50 μg subcutaneous dose; in view of the long-lasting endocrine effects and flat dose–response curves of peptide hormone inhibition, the delayed time-course after oral administration is probably of little consequence. Biological activity of orally absorbed SMS was demonstrated by effective and prolonged suppression of plasma insulin levels, resulting in late deterioration in glucose tolerance, as has been observed after subcutaneous injection in normal subjects [16]. Other gut hormones (not examined in this preliminary study) were presumably also suppressed [17].

Further studies will be needed to define the possible variability of orally administered SMS and its possible efficacy in the various diseases currently treated by SMS injections. A different formulation for oral administration may obviate the necessity for relatively large doses of glucose to be given to encourage absorption.

Orally administered SMS may find a place in the long-term treatment of several endocrine and gastrointestinal conditions. Perhaps more importantly, it may become of the first of a new 'generation' of peptide hormone analogues whose structure has been deliberately modified to resist enzymatic degradation, thus allowing oral administration.

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References