CASE REPORT

Symptomatic hypoglycemia during imatinib mesylate in a non-diabetic female patient with gastrointestinal stromal tumor

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ABSTRACT. Imatinib mesylate is a selective competitive inhibitor of the bcr-abl tyrosine kinase and c-KIT. Other kinases, such as phosphatidylinositol-3'-kinase (PI-3K) involved in insulin signaling, have also been shown to be indirectly affected by imatinib. A recent report described a lowering of blood glucose levels in Type 2 diabetic patients treated with imatinib resulting in a reduction of oral anti-diabetic medication or insulin dosage. We present a female non-diabetic patient with a resected gastrointestinal stromal tumor with an increased insulin response following an oral glucose challenge and hypoglycemic episodes following imatinib therapy. In addition to a rise in insulin sensitivity, the patient showed inappropriately high insulin secretion rates in relation to the actual blood glucose concentrations during and after the completion of imatinib treatment. The symptoms suggestive of hypoglycemia such as dizziness and shivering formerly observed in patients treated with imatinib may be related to hypoglycemic glucose concentrations. Physicians treating patients with imatinib should be aware of the possible occurrence of hypoglycemic episodes in non-diabetic patients.

INTRODUCTION

Imatinib mesylate (Novartis, Basel, Switzerland) is a selective competitive inhibitor of the bcr-abl tyrosine kinase (1-3). In its standard dosage (400 mg/day) it also inhibits the receptor for platelet-derived growth factor (PDGF) and the KIT receptor tyrosine kinase and is able to influence the phosphatidylinositol-3'-kinase (PI-3K) pathway (4-6). Imatinib causes growth arrest and induces apoptosis in bcr-abl- and c-kit-positive cells and has shown a good efficacy in patients with Philadelphia-chromosome positive chronic myelocytic leukemia (Ph+ CML) (1) as well as in patients with advanced gastrointestinal stromal tumors (GIST) (7, 8).

In patients with Type 2 diabetes treatment with imatinib lowered fasting blood glucose levels, resulting in a consecutive reduction of oral anti-diabetic medication or insulin dosage (9-11). The mechanism of the anti-diabetic effect of imatinib is unclear. It is postulated that insulin sensitizing effects of the drug might be due to an interference with negative feedback regulators of insulin signaling, such as PI-3K and its downstream effectors Akt and the extracellularly regulated kinase (ERK) (12-15). We present the case of symptomatic hypoglycemia in a non-diabetic female patient treated with imatinib for GIST. In this patient, parameters for insulin secretion and insulin sensitivity were systematically obtained during imatinib therapy and 8 weeks after completion. The well-known symptoms associated with imatinib treatment such as dizziness and shivering may be caused by subnormal glucose concentrations in these patients.

CASE REPORT

We report on a 62-yr old female patient [height 168 cm, weight 51 kg, body mass index (BMI) 18.1]...
kg/m², her body weight did not change during ob-
servation] with a completely resected GIST of the
stomach. Since the tumor was only adherent to the
stomach, a surgical removal of a small part of the
minor curvature was sufficient to ensure a complete
radical (R0) resection of the tumor. During this proce-
dure a selective proximal vagotomy was performed
in the gastric angulus region. The histopathological
examination revealed a GIST with a high mitotic rate
and the patient was allocated to enter a randomized
prospective trial on imatinib mesylate at our institu-
tion. Besides that, she had no relevant past medical
history except for a successfully eradicated Helico-
bacter pylori positive gastritis in 2000 and took no
concurrent medication. Our patient had no family
history of diabetes or obesity.
She was started on adjuvant imatinib treatment 11
weeks after abdominal laparotomy for the primary
Imatinib was initially well tolerated and caused only
a few side effects such as World Health Organization
(WHO) grade I nausea and grade I diarrhea. During
the latter course of imatinib therapy, the patient
complained of recurrent symptoms of dizziness, shiv-
ering, and nausea, symptoms that are known side
effects of treatment with imatinib. Her husband, a
Type 1 diabetic patient, interpreted the symptoms,
which occurred at least twice a week independently
of food intake or time of the day, as hypoglycemic
episodes and initiated blood glucose measurements
of his wife during such episodes with his own glu-
cose meter.
During these episodes blood glucose levels below
40 mg/dl (2.24 mmol/l) were documented. The
range of these measured blood glucose levels var-
ied between 30 mg/dl (1.68 mmol/l) and 38 mg/dl
(2.13 mmol/l).
Further diagnostic procedures were initiated at the
next clinic visit. Routine laboratory analysis includ-
ing liver enzymes was normal and the glycosylated
hemoglobin (HbA₁c) was within the normal range.
A standard 75 g oral glucose tolerance test (OGTT)
revealed a fasting plasma glucose concentration of
87 mg/dl (4.87 mmol/l) and 2-h plasma glucose of 42
mg/dl (2.35 mmol/l) (Fig. 1). The patient was taught
to perform regular blood glucose measurements on
herself. She further received dietary advice to eat
frequent small meals and to limit the intake of carbo-
hydrates with high glycemic index.
A dumping syndrome as a consequence of gastric
surgery or an insulinoma were excluded by perform-
ing a scintigraphy for gastric emptying and by a 72-
h-fasting-test, respectively. The course of volume
change and gastric emptying were within the normal
range (Fig. 2).
Additionally, paraneoplastic overproduction of IGF-
II occasionally observed in patients with GIST and
possibly responsible for hypoglycemia was excluded
(16). In our patient IGF-I (114 ng/ml, normal range
71-290 ng/ml) and IGF-II (512 ng/ml, normal range

![Graph](image_url)

**Fig. 1 - Oral glucose tolerance test (OGTT) with glucose (mmol/l),
insulin (pmol/l) and C-peptide (pmol/l) concentrations under im-
atinib therapy (●●) and 8 weeks after the completion of imatinib
therapy (○○). Insulin sensitivity and insulin secretion were estimat-
ed from the OGTT using validated indices (17, 18). Insulin sensitiv-
ity during imatinib therapy was 11.5 arbitrary units (a.u.) and 7.4
a.u. after imatinib therapy.**