Effect of the Tyrosine Kinase Inhibitors (Sunitinib, Sorafenib, Dasatinib, and Imatinib) on Blood Glucose Levels in Diabetic and Non-diabetic Patients in General Clinical Practice (Poster)

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Effect of the Tyrosine Kinase Inhibitors (Sunitinib, Sorafenib, Dasatinib, and Imatinib) on Blood Glucose Levels in Diabetic and Non-diabetic Patients in General Clinical Practice

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Introduction:

Tyrosine kinase is a key enzyme utilized in many intracellular messaging pathways. Understanding of the role of particular tyrosine kinases in various malignancies has allowed for the design of compounds, the tyrosine kinase inhibitors (TKIs). TKIs have proven to be very successful in the treatment of a wide variety of malignant diseases including chronic myeloid leukemia (CML), Philadelphia chromosome positive acute lymphoblastic leukemia (ALL), renal cell carcinoma (RCC) and gastrointenstinal stromal tumors (GIST). Given the widespread nature of tyrosine kinase as a target and the promiscuous nature of the various inhibitors, it would not be surprising that these drugs would have effects beyond the expected result of targeting merely the tyrosine kinase of interest. Scattered reports have suggested that these agents appear to affect blood glucose levels [1-5].

Methods:

We studied the blood glucose (BG) concentrations on blood samples drawn before, during and after TKI therapy retrospectively in both diabetic (19) (all type II diabetes) and non-diabetic (61) patients treated with dasatinib (8), imatinib (39), sorafenib (23) and sunitinib (30) in general clinical practice. Samples were mixed but most were daytime non-fasting.

Results:

See Table 1 for demographic information. All 4 drugs resulted in statistically significant decreased blood glucose levels in both diabetic and non-diabetic patients that resolved with cessation of treatment. Mean decreases blood glucose values for both non-diabetic and diabetic patients for dasatinib were – 53 mg/dl ($p<0.001$), imatinib – 9 mg/dl ($p=0.03$), sorafenib – 12 mg/dl ($p<0.001$) and sunitinib - 14 mg/dl ($p<0.001$). See Figure 1. Forty seven percent (8/17) of the patients with diabetes were able to discontinue their medications, including insulin in some patients. One diabetic patient developed symptomatic hypoglycemia on sunitinib. See Table 2 for adjustments made to diabetic medications.

Table 1: Demographic Information

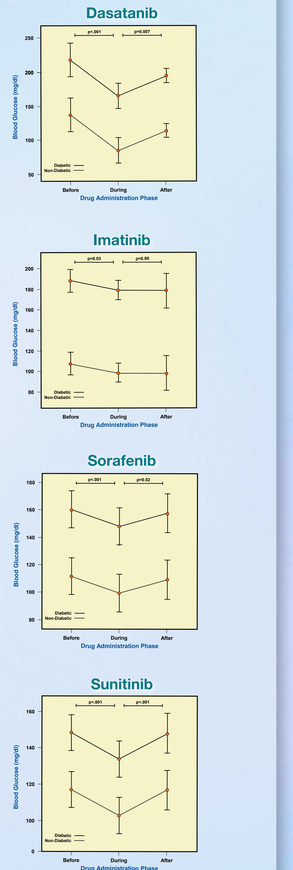
Drug	Total Patients	Mean Age	Race	Gender	Diagnosis	Diabetes
Imatinib	39	53	white, 35 black, 3 asian, 1	female, 23 male, 16	CML, 25 GIST, 13 ALL, 1	yes, 6 no, 33
Dasatinib	8	56	white, 7 black, 1	female, 3 male, 5	CML, 8	yes, 1* no, 7
Sorafenib	23	65	white, 22 black, 1	female, 5 male, 18	RCC, 23	yes, 5 no, 18
Sunitinib	30	66	white, 30	female, 8 male, 22	RCC, 28 GIST, 2	yes, 7** no, 23

*One patient in this group overlapped in the diabetic imatinib group
**One patient in this group overlapped with the diabetic sorafenib group

Table 2: Diabetic medication changes made while on TKI

Patient #	TKI	Diabetes meds before start of treatment	Diabetes meds on treatment
6	Imatinib Dasatinib	glyburide/metformin 2.5/500 Qdaily glyburide/metformin 5/1000 BID glyburide/metformin 5/1000 BID	glyburide/metformin 5/1000 BID pioglitazone 30mg Qdaily pioglitazone 30mg Qdaily glyburide/metformin 5/1000 BID
14	Imatinib	insulin 70/30 25U Qam, 15U Qpm metformin 500mg BID	glyburide/metformin 5/1000 BID
19	Imatinib	none	none
20	Imatinib	glipizide XL (dose unknown)	sitagliptin/metformin50/500BID
23	Imatinib	none	metformin 500mg BID
29	Imatinib	glipizide 10mg Qdaily	none
48	Sunitinib Sorafenib	insulin (unknown dose) insulin (unknown dose)	none none
57	Sorafenib	none	none
60	Sorafenib	metformin 500mg BID rosiglitazone 4mg Qdaily glipizide XL 10mg Qdaily	none
62	Sorafenib	metformin (unknown dose) glipizide (unknown dose)	none
63	Sorafenib	metformin 500mg BID pioglitazone 30mg Qdaily	sitagliptin (unknown dose)
67	Sunitinib	sitagliptin (unknown dose) meformin (unknown dose)	none
69	Sunitinib	insulin glargine (unknown dose) Insulin aspart (unknown dose)	none
71	Sunitinib	metformin 850mg BID glimepiride 4mg Qdaily	none
73	Sunitinib	glimepiride 4mg Qdaily	glipizide 5mg Qdaily
74	Sunitinib	none	none
80	Sunitinib	insulin glargine (unknown dose) insulin aspart (unknown dose)	none

Figure 1: Blood glucose levels before, during, and after treatment with a TKI (bars indicate standard error)



Conclusions:

The mechanism for the hypoglycemic effect of these drugs is unclear, but of the 4 agents tested, c-kit is a common target. C-kit has been shown to play a role in pancreatic β-cell survival in mouse models, so it is unclear why an inhibitor of the c-kit tyrosine kinase would improve blood glucose levels. It is important for clinicians to keep the potentially hypoglycemic effects of these agents in mind, as symptomatic hypoglycemia can occur and modification of hypoglycemic agents may be required. These results also suggest that inhibition of a tyrosine kinase, be it c-kit or some other undefined target, may improve diabetes mellitus and deserves further study as a potentially therapeutic option.

References:

1. Billemont B, Medioni J, Taillade L, et al. Blood glucose levels in patients with metastatic renal cell carcinoma treated with sunitinib. Br J Cancer 2008 pp. 1-3.
2. Veneri D, Franchini M, Bonora E. Imatinib and regression of type 2 diabetes. NEJM 2005 352(10):1049-1050.
3. Breccia M, Muscaritoli M, Aversa Z, et al. Imatinib mesylate may improve fasting blood glucose in diabetic Ph+ chronic myelogenous leukemia patients responsive to treatment. J Clin Oncology 2004 22(22):4653-5.
4. Breccia M, Muscaritoli M, Cannella L, et al. Fasting glucose improvement under dasatinib treatment in accelerated phase chronic myeloid leukemia patient unresponsive to imatinib and nilotinib. Leukemia Res 2008 32:1626-8.
5. Haap M, Gallwitz B, Thamer C, et al. Symptomatic hypoglycemia during imatinib mesylate in a non-diabetic female patient with gastrointestinal stromal tumor. J Endocrin Inv 2007 30(8):688-92.