Cocaine abuse may influence the response to imatinib in CML patients

Haematologica 2007; 92:(3)e41-e42

To the Editor:

Cocaine is a 2-beta-carbomethoxy-3beta-benzoxytropane, which effects local anesthetic action by blocking the initiation or conduction of nerve impulse [1]. Many drugs of abuse are substrates (amphetamines, codeine, nicotine) or inhibitors (cocaine) of polymorphic cytochrome p450 enzyme, which is the same metabolic pathway of imatinib mesylate É, the presently standard drug for Ph+ chronic myeloid leukemia (CML).

We describe here two patients with Ph+ CML, who during imatinib treatment practiced cocaine abuse, which concomitantly increased several side effects while response to imatinib was reduced.

Case 1. A 32 year-old male referred to our institute for severe splenomegaly (200 mm) and leucocytosis (WBC 148x10^9/l). Diagnosis of Ph+ CML was made on the basis of cytogenetic (standard t(9;22) translocation) and molecular analyses (b2a2 bcr/abl transcript). In the past, the patient had been addicted to heroine, but at CML diagnosis he was on therapy with only buprenorfine. Imatinib was started at the standard dose of 400 mg/day, after a cytoreduction with hydroxyurea, and a complete hematological remission (CHR) was reached after 7 weeks. Side effects were recorded during imatinib therapy, consisting of sweating, headache, restlessness and muscle cramps. CHR was lost after 12 weeks of treatment and cytogenetic analysis (FISH) performed at that time showed that 120 out of 170 examined nuclei (70 %) were bcr/abl positive. The patient did confess a cocaine abuse, started from week 10 of imatinib treatment (Figure1.). Side effects, such as nervousness, cramps and diarrhea became more evident in concomitance with cocaine abuse. The dose of imatinib was continued at 400 mg/day, until week 30, when it was increased to 600 mg for secondary hematological resistance.

Case 2. A 44 year-old male was diagnosed as having chronic phase CML, in February 2006, for the presence of leucocytosis (101X10^9/l) and standard t(9;22) translocation at cytogenetic analysis. After a short period of cytoreduction with hydroxyurea, the patient was started on imatinib at standard dose (400 mg/day) and CHR was reached after 3 weeks of treatment. Especially after the third month, severe side effects were recorded which included profuse sweat, headache, nervousness, diarrhea, cramps, fever and faint episode. Cytogenetic analysis performed after 12 weeks of treatment showed 5 out of 15 cells (30%) to be Ph+. CHR was lost at 14 weeks of treatment (WBC 11X10^9/l): cocaine abuse during imatinib treatment was confessed to have been practiced, starting from the previous four weeks and thereafter. During cocaine abuse, the full imatinib dose of 400 mg/day was maintained by the patient; at week 20, while on imatinib and cocaine co-administration, loss of CHR and a bcr/abl ratio increase were observed (Figure 2. shows time-line of the patient).

Imatinib is a specific tyrosine kinase inhibitor of bcr/abl transcript originating from the Ph chromosome [3]. The drug is metabolized by cytocrome p450 CYP3A4, with a consequent inhibition of CYP2D6, CYP4A isoenzymes, which may lead to clearance reduction for co-administered drugs with the same metabolic pathway [4]. Many pharmacological interactions have been described and for a number of drugs plasma levels may be increased by imatinib [5-7].

Cocaine is hepatotoxic in several species, including man, and results in the inhibition of CYP2A activities [8]. In fact it is well known in animal models that repeated administration of cocaine decreases CYP1A1/2, CYP2A4/5, CYP2Cx, CYP2E1, CYP3A enzymes activities, which are principally responsible for the N-demethylation in human and mouse liver microsomes [8].

Due to the fact that CYP3A4 enzyme is the main responsible for the imatinib metabolism, several cases of drug-drug interactions are reported. These include, for instance, ketoconazole (a CYP3A4 inhibitor) which increases exposure to imatinib [5], or an increase of mean C_{max} of simvastatin [6], a substrate of CYP3A. Our two cases may suggest a likely interference in the cocaine metabolism by imatinib co-administration leading to severe side effects [8]. Conversely, no clear explanation can be given for the concomitant reduction of imatinib efficacy, for which other factors could be hypothesized to independently interfere with drug compliance or cellular pharmacodynamics. Adverse reactions to cocaine abuse may be related to high plasma levels resulting from excessive absorption of the drug: side effects involve central nervous system or cardiovascular system, with nervousness, tremors and finally clonico-tonic convulsions, slow heart rate, vasoconstriction, mydriasis. Cocaine is also pyrogenic, thus augmenting heat production in muscular activity, which is also affected by imatinib toxicity. Although subject of speculation, the side effects recorded in our two patients might have been exacerbated by the interference of the two drugs, imatinib and cocaine. Unfortunately, no data on plasma levels of the drugs at the time of clinical observation, nor stored specimens to be investigated later were available, which could add strength to our suggestion.

Thus, we stresses on the importance of particular attention to be rendered in clinical practice for investigations to pharmacological interactions between imatinib and other drugs, including drug of abuse, especially those known as being substrates of polymorphic enzymes of cytocrome p450.

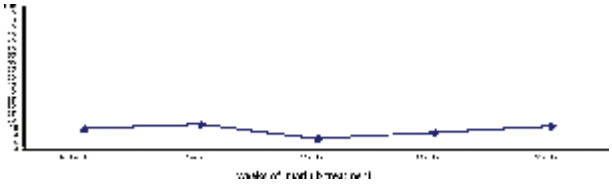

Figure 1. Hematological and cytogenetic response of first patient

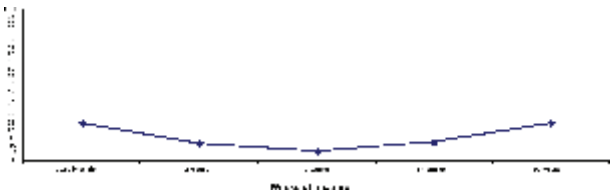

Figure 2. Clinical and biological response of case n. 2

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