Letter to the Editors

Suicide attempt with an overdose of imatinib

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Imatinib is approved for the treatment of chronic myelogenous leukaemia (CML) as well as gastrointestinal stromal tumour (GIST), both of which show dysregulated imatinib-sensitive tyrosine kinase activity. Imatinib is rapidly absorbed after oral administration (bioavailability 86%) and is mainly metabolized by the CYP3A4 and CYP3A5 isoenzymes of the liver [1]. Although the drug is usually well-tolerated, grade 1–2 adverse effects, such as musculoskeletal events, are frequently observed [2–4]. In a phase I clinical trial in patients with CML, the minimum therapeutic dose of imatinib required to obtain an optimal therapeutic response was determined to be 300 mg day⁻¹. However, the maximum tolerated dose has not yet been defined. In addition, there have been few case reports of imatinib overdose [5]. We herein report the results of a pharmacokinetic analysis in a patient with CML who took 2000 mg of imatinib as a single dose together with brotizolam and triazolam in an attempt to commit suicide.

Case report

A 47-year-old Japanese woman had been diagnosed as having chronic phase CML 6 years previously. She had been initiated on treatment with imatinib (400 mg day⁻¹), which had yielded a complete molecular response 10 months later. Despite the subsequent dose reduction to 200 mg day⁻¹ because of the development of side effects such as nausea, oedema and muscle pain, the complete molecular response had been maintained. Serum creatinine phosphokinase (CK) concentrations had remained within the normal range and the white blood cell count had remained at around 3000 μl^{-1} throughout the course. The patient was brought to our emergency room after she was found lying unconscious at home following an attempted suicide after taking 2000 mg imatinib together with 12.5 mg brotizolam and 3.5 mg triazolam. On admission, her vital signs were stable, and the findings on physical examination were unremarkable, except for the

Figure 1

Plasma concentrations of imatinib (●) and creatinine phosphokinase (○)

comatose status. Haematological examination revealed a white blood cell count of 11 600 μl^{-1} with 92.7% neutrophils, a haemoglobin value of 11.1 g dl⁻¹ and a platelet count of $19.8 \times 10^4 \mu\text{l}^{-1}$. The results of blood chemistry were unremarkable and the serum CK concentration was normal. Gastric lavage and haemodialysis were not required and the patient regained consciousness with fluid replacement within 6 h after admission. However, on the following day, she started complaining of severe muscle cramps all over her body and the plasma CK concentration increased to 3880 IU l⁻¹. Her temperature remained normal and there was no clinical evidence of malignant hyperthermia. The serum concentration of imatinib was 3580 ng ml⁻¹ at 6 h after admission and increased to 4700 ng ml⁻¹ on the following day. Eventually, the CK concentrations decreased and returned to normal by the end of 2 weeks. The plasma concentration of imatinib also decreased proportionally, although a marked delay of the t_{max} was noted (Figure 1). The concentrations of active metabolites were not measured. The patient was discharged after 1 week and

imatinib 200 mg day⁻¹ was reinstated 4 weeks later without subsequent development of adverse effects or abnormal laboratory data.

Discussion

This report describes a high plasma concentration of imatinib caused by intake of an overdose along with two minor tranquillizers, brotizolam and triazolam. The loss of consciousness was thought to be due to the benzodiazepines, brotizolam and triazolam. Although the mean $t_{\max}$ of imatinib was found to be 2–4 h in a phase I trial conducted in CML patients (dose range 50 to 750 mg once daily) [6], it increased to 30 h in our patient, suggesting that its absorption was markedly prolonged. The maximum plasma imatinib concentration of 4700 ng ml⁻¹ in this patient seemed to be less than proportional to the maximum concentration determined when the daily dose was increased to 750 mg ($C_{\max}$ after imatinib 750 mg day⁻¹: 3016 ± 1040 ng ml⁻¹) [6]. AUC(0–∞) was 81.7 µg ml⁻¹ h after a dose of 1000 mg. However in this case (dose of 2000 mg), AUC(0–120 h) was 280 µg ml⁻¹ h calculated by the trapezoidal method. The elimination half-life of the drug was reported to be about 20 h in a phase I study [6], and was the same, 20 h, in this case. Despite the concomitant use of minor tranquillizers inhibiting one of the CYP3A4/5 enzymes, the elimination half-life was not prolonged. Overdose of brotizolam and triazolam have not been reported to cause marked prolongation of $t_{\max}$. However, it has recently been reported that imatinib blocked spontaneous mechanical activity in the intestine of mice [7, 8]. Some reports suggested that imatinib inhibits the c-kit/CD117 tyrosine-kinase expressed in the interstitial cells of Cajal, which function as pacemaking cells for the small intestine in both animals and humans [8, 9]. The findings in our patient suggested that imatinib inhibited the peristalsis of the small intestine, which resulted in marked prolongation of absorption of the large dose of imatinib as compared with the clinical conventional dose. But in such a case, the AUC(0–∞) does not increase non-linearly with the dose. Adverse effects associated with elevated serum CK concentrations are found frequently in patients on treatment with imatinib. We therefore suggest that monitoring of the plasma CK concentration should be undertaken, especially in patients placed on higher doses of imatinib.

Several reports have suggested that higher doses of imatinib might be more effective, especially in patients with advanced disease. However, higher doses may also cause more frequent and more serious adverse events [10]. Thus, in our patient, the 2000 mg overdose of imatinib did not result in a fatal outcome, but was associated with marked prolongation of the drug's absorption.

Competing Interests

There are no competing interests to declare.

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standard-dose therapy in patients with chronic myelogenous leukemia. *Blood* 2003; 101: 473–5.

RECEIVED

15 December 2010

ACCEPTED

15 March 2012

ACCEPTED ARTICLE PUBLISHED ONLINE

22 March 2012

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