Clinical pharmacology of the tyrosine kinase inhibitors imatinib and sunitinib

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Is rectal administration an alternative route for imatinib?

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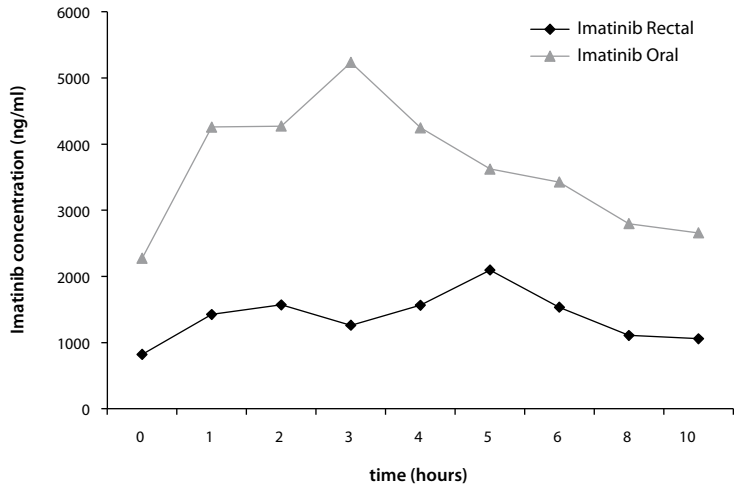
A 52 year old woman with metastatic gastro-intestinal stromal tumor (GIST) presented herself in March 2006 with tumor-related intra-abdominal obstructions and diffuse intra-abdominal bleeding. Priorly, the metastatic GIST was successfully treated with 400mg imatinib since 2002 but now appeared to be progressive again. The patient underwent palliative resection of multiple bleeding peritoneal tumor deposits. When confronted with GIST progression, as seen in this patient, the dose of imatinib should be elevated from 400 mg /day to 800 mg / day [1]. However, a major limitation for treatment in this patient was that, due to the gastro-intestinal obstructions, she was unable to take anything orally, including the imatinib tablets for 8 days prior to surgery. Unfortunately, imatinib is available as a tablet formulation only. Therefore, in this patient we tested the rectal route of administration as an alternative way to administer the drug.

The day following surgery, the patient received imatinib 400 mg b.i.d. with the imatinib oral tablets being administered rectally. After the fourth dose of imatinib given rectally we collected blood samples at t = 0, 1, 2, 3, 4, 5, 6, 8 and 10 hours. The patient volunteered in a pharmacokinetic study a year before [2]. In the study, after informed consent, we collected steady state blood levels of imatinib at the same time points as described above, but after an oral dose of 400 mg imatinib. This enabled us to compare the area under the concentration-time (AUC) curve following oral and rectal administration of imatinib in this patient. Plasma concentrations of imatinib were analyzed at The Netherlands Cancer Institute by a validated HPLC-UV assay with a variation coefficient within the generally accepted 15% range and a lower limit of quantification of 10ng/ml. $AUC_{0\text{-}10hr}$ after the oral administration of 400 mg imatinib was 35,508 and it was 14,243 ng/ml *h after rectal administration (Figure 1) calculated by the trapezoidal method. Assuming relatively small intraindividual variation in pharmacokinetics, comparison of the AUCs indicates that at least 40% of the oral imatinib levels are reached by rectal administration. About 40% will be a slight underestimation because steady-state conditions were not fully reached. The AUC after the fourth rectal dose was estimated at 80-90% of the steady-state AUC.

The $t_{1/2}$ of imatinib is ~18 hours [3]. In the 9 days before rectal administration of imatinib the body is cleared from imatinib. Therefore, the AUC measured after the fourth rectal dose of imatinib is solely produced by absorbance of imatinib from the rectum and is not influenced by the oral dose used before.

The lack of alternative dosing forms of imatinib sometimes causes problems in clinical practice. Patients with GIST may show obstruction or narrowing of the gastro-intestinal tract causing problems to take food and drugs orally. These patients are unable to take imatinib treatment. Based on our observation, in these circumstances, rectal administration of a double dose

Figure 1 Representative plasma concentrations versus time profile of imatinib after rectal or oral administration of 400 mg



of imatinib could be a good alternative. Imatinib mesylate is a highly water soluble drug with a bioavailability of nearly 100% when taken orally [4]. This characteristic readily predicts absorption from the rectal mucosa. Indeed, in the patient presented here, we demonstrated by plasma level measurement that imatinib could be administered rectally resulting in a 40% drug exposure. Therefore, doubling the dose is anticipated to reach a similar drug exposure compared to when given orally.

References

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