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Review

Clinical Pharmacokinetics of Imatinib Mesylate

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Abstract. *This review presents the clinical pharmacokinetics of imatinib mesylate. Aspects regarding absorption, tissue distribution, elimination and kinetic interactions are also discussed.*

Imatinib (formerly known as STI 571 or CGP 57148B) is a recent oral anticancer agent currently approved in the treatment of Philadelphia chromosome- positive chronic myelogenous leukemia (CML) and metastatic gastro-intestinal stromal tumors (GIST). The rational and quite rapid development of imatinib (3 years between the first clinical trial in patients with CML and the approval in 2001 in the United States), combined with the promising clinical results observed in the treatments of these two rare cancers, has led to extensive literature including several comprehensive reviews (1-8). The aim of this paper was to review the clinical pharmacokinetics of imatinib.

Pharmacological properties

Imatinib is a 2-phenylaminopyrimidine derivative that acts as an enzyme inhibitor. Imatinib blocks the tyrosine kinase activity of key proteins involved in the pathogenesis of CML and GIST, by inhibiting the binding of adenosine triphosphate (ATP) on the enzyme domain. Hence, imatinib displays activity towards Bcr-Abl, the chimeric protein resulting from a reciprocal translocation between the long arms of chromosomes 9 and 22 (Philadelphia translocation), which is found in 95% of patients with CML. Likewise, imatinib inhibits the deregulated tyrosine activity of the mutated receptor c-kit extensively expressed (85%) in GIST, a subgroup of soft-tissue sarcomas. The mechanism of action of imatinib also includes inhibition of the tyrosine kinase activity of the mutated platelet-derived growth factor receptor (PDGFR) (9) and the promotion of activation of natural killer cells (10). This could explain the activity of imatinib in the subset of GIST that do not express mutated c-kit (*i.e.* those with mutated PDGFR or those without any mutated tyrosine receptor) (10,11). Preclinical studies have demonstrated the kinase inhibition both on purified enzymes and cells lines, as well as inhibition of tumor growth *in vitro* and *in vivo* (8). The IC_{50} (concentration leading to a 50% decrease in kinase activity) for protein autophosphorylation of purified Bcr-Abl is around 0.025 μM (0.015 mg/l). In cell lines, the IC_{50} for tyrosine phosphorylation are higher, at around 0.25 μM (0.15 mg/l) and 0.1 μM (0.06 mg/l) with regard to cellular Bcr-Abl and c-Kit, respectively (8).

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Drug formulation and administration

Imatinib is administered orally and is formulated in hard capsules or tablets (United States, France) as a salt (imatinib methane sulfonate or mesylate, molecular weight: 589.7). Each tablet contains 100 or 400 mg of imatinib free base. The hard capsule is dosed at 100mg of base. The recommended dosage for adult patients with Philadelphia chromosome-positive CML at its various phases (chronic, accelerated, blast crisis) or Kit-positive unresectable and /or metastatic GIST is 400mg or 600mg given once daily with a meal, as a monotherapy. In children with CML, daily doses range from 260mg/m^2 to 340mg/m^2. The treatment is continued until disease progression or unacceptable toxicity.

Analytical methodology

To date, several validated assays have been published (12-17). Imatinib and its main metabolite CGP 74588 (N-desmethyl-imatinib) have been separated and quantified in biological fluids by liquid chromatography with mass spectrometry (12-14) or ultraviolet (UV) detection (15-17) set between 260nm and 270nm. The use of tandem mass spectrometry has led to lower limits of quantitation (LLOQ)

of 1 and 2 ng/ml for the parent drug and its metabolite, respectively, after processing spiked monkey plasma (12). The techniques using mass spectrometry or UV detection have a higher LLOQ (30 ng/ml) but they permit the quantitation of imatinib in plasma during 72h after the oral administration of a low dose (200 mg). Besides plasma, Le Coutre *et al.* (16) have proposed a method for the determination of imatinib and CGP 74588 in urine and cerebrospinal fluid using UV detection. The LLOQ were not reported.

Pharmacokinetics properties

The pharmacokinetics of imatinib have been investigated in healthy volunteers (extremely rare for an anticancer agent) and in patients with Philadelphia chromosome-positive CML or acute lymphocytic leukemia. To our knowledge, the data concerning the patients with GIST have not yet been reported.

Absorption. The absolute bioavailability of imatinib in its hard capsule form and in an oral solution (not commercially available) given as single doses has been determined in 12 healthy volunteers (18). When compared with an intravenous formulation (100 mg as a 1-h infusion, also not commercially available), the mean absolute bioavailability of the capsule (400 mg as 4 capsules) was 98.3% indicating a complete absorption and the lack of intestinal or hepatic first pass effects. The absolute bioavailability of the oral solution was 97.2%. The kinetic profiles of imatinib tablets and capsules, administered as a single dose of 400mg, have been evaluated over a sampling period of 4 days in 30 healthy volunteers (19). The 400 mg tablet form was developed to allow a single and more convenient intake of imatinib. Furthermore, the scored 100 mg tablet permits adjustments of dosage in children. The tablet form has replaced the capsule form in the United States and is about to gain approval in other parts of the world.

The kinetic profiles of imatinib given in tablets (400mg or 4x100mg) or capsules (4x100mg) as a single dose are similar with a median time (Tmax) to reach the concentration peak (Cmax) of 2.5h (range 1.5-6h). The mean Cmax were 1.6 mg/l (Standard Deviation or SD:0.6) and 1.7 mg/l (SD:0.7) after ingestion of a 400mg tablet and 4x100 mg capsules, respectively (19). Data obtained in patients do not appear to differ from those of healthy subjects. Absorption parameters have been determined in 12 adult patients with CML who were given imatinib at a dose of 400 or 600mg per day (16). The mean Cmax were 2.02 mg/l (coefficient of variation or CV: 32%) and 6.76 mg/l (CV:69%) and the mean Tmax were 4.07h (CV:37%) and 3.84h (CV:55%), after the first ingestion of 400 mg (n=6) or 600 mg (n=6), respectively (16). The most complete data are those derived from a phase I study which included 64 adult patients with CML (20). The kinetic characteristics were determined after the first administration and at steady state (day 7), with daily doses that ranged from 25 mg to 1g. The exposure to imatinib (the area under the plasma concentration-time curve or AUC calculated over 24h) was shown to increase proportionally to the dose both on day 1 and at steady state, suggesting the absence of saturation in the absorption and elimination processes. The Tmax ranged between 1.8 and 4h after a single dose and between 1 to 6.8h at steady state. At current label dose (400 mg), the Cmax increased from 1.9 mg/l (SD:0.35) after the first dose (n=4) to 2.59mg/l (SD:0.78) at steady state (n=5), respectively. The Tmax were comparable, around 3h. Similarly, the $AUC_{0\text{-}24h}$ increased from 24.8 mg.h/l (SD: 7.4) to 40.1 mg.h/l (SD:15.7) (20).

Distribution. The activity of imatinib is related to the exposure of the body to the circulating free fraction (*i.e.* the AUC calculated with the unbound concentration). With regards to the blood distribution at therapeutic concentrations, the mean fraction of imatinib in plasma was around 70% when assessed, *in vitro*, with spiked blood samples of 3 healthy volunteers (21). In plasma from CML patients (n=5), imatinib was found to be highly bound to proteins (>99%) (17). *In vitro*, imatinib binds to plasma proteins such α1 acid glycoprotein and albumin (22). In animal bearers of human leukemic cells, high concentrations of α1 acid glycoprotein have been associated with an absence of response to imatinib (22). It was suggested by the authors that high concentrations of the carrier decrease the active unbound fraction and prevent the diffusion of imatinib to the targets. Alpha1 acid glycoprotein is an acute phase reactant, the levels of which can rise after inflammatory stimuli such as cancer. Further, the same investigators reported a positive and significant correlation between α1 acid glycoprotein levels and total (bound plus unbound) imatinib peak plasma concentrations at steady state in 19 patients with CML (17). On the other hand, the relationship between α1 acid glycoprotein levels and the AUC was not significant. The addition of intravenous clindamycin, a drug known to bind with α1 acid glycoprotein and hence potentially compete with imatinib binding, was shown to cause a decrease in exposure (bound plus unbound) of 2.9-fold in 5 patients (17). The percentage of imatinib bound at 3h decreased from 99% to 96%. Nevertheless, the concentrations of unbound imatinib determined at 3h were not significantly affected. Thus, the clinical relevance of variations of imatinib binding to plasma proteins due to displacement from its proteic binding sites by another drug or to changes in the concentrations of the plasma proteins (*i.e.* α1 acid glycoprotein) is unknown. According to Benet and Hoener (23), and given the elimination characteristics of imatinib, it is unlikely that changes in plasma protein binding influence

Table I. *Pharmacokinetic parameters for imatinib in adults. Results as mean (SD).*

No. of patients	Dose (mg)	C_{max} (mg/l)	Tmax (h)	$AUC_{0\text{-}24h}$ (mg/l.h)	Cl (ml/min)	$t_{1/2}$ (hours)	Reference
30 (healthy volunteers)	400 (single dose, capsule)	1.74 (0.70)	2.5	19.9 (8.7)	285 (96.6)	15.8 (2.9)	19
6	600	6.76	3.84	85.9	147	16.9	16
6	400	2.02	4.07	37.5	187	16.6	16
8	400 (single dose)	2.35	2	24.6	NR	12.5	17
5	600 (single dose)	7.83	3	99.7	NR	12.5	17
4	400 (single dose)	1.90 (0.35)	3.1 (2.0)	24.8 (7.4)	208.3 (120)	14.8 (5.8)	20
7	600 (single dose)	3.39 (2.40)	2.9 (1.4)	39.7 (25.9)	276.6 (198.3)	10.9 (2.0)	20
5	400 (steady state)	2.59 (0.78)	3.3 (1.1)	40.1 (15.7)	186.6 (66.6)	19.3 (4.4)	20
9	600 (steady state)	3.50 (1.64)	3.1 (1.1)	51.7 (26.7)	240 (113.3)	15.6 (5.0)	20

Cmax: concentration peak; Tmax: time for concentration peak; AUC: area under the serum concentrations-time curve; Cl: clearance assuming a bioavailability of 100%; t1/2: terminal half-life; NR: not reported.

the clinical exposure of the patient. Imatinib is an oral drug with a predominant hepatic clearance (see below) and, in this case, the unbound drug exposure (the determinant of pharmacological effect) is independent of protein binding. Therefore, no clinical variation would be expected.

Investigations have been conducted to assess the distribution of imatinib in the central nervous system (CNS) by determining its levels in the cerebrospinal fluid as a surrogate. CNS recurrence can occur in patients with CML during the late phase of the disease (the blast crisis) and rarely in patients with GIST. Furthermore, imatinib has raised interest in other types of CNS cancers such CNS relapses of acute lymphoblastic leukemia (ALL) with Philadelphia translocation or gliomas. Overall, determination of imatinib in the cerebrospinal fluid of treated patients with CNS involvement of ALL or CML has demonstrated marginal diffusion with concentrations below the IC_{50} (*i.e.* 0.15 mg/l). Levels of imatinib were found to be 74-fold lower in the CSF than in plasma of 4 patients (0.044 mg/l *versus* 3.27 mg/l) (24). Similarly, 2 case reports (25, 26) indicated CSF concentrations less than 0.07 mg/l (< 3% of plasma levels) in one patient (600 mg per day) and 0.017 mg/l (*versus* 1.57 mg/l in the serum) in the other (200 mg per day). Finally, Le Coutre *et al.* (16) reported mean imatinib concentrations of 0.038 mg/l in CSF from 17 patients with ALL (400 or 600 mg daily) *versus* 3.37 mg/l in the plasma. More complete CSF kinetics have been achieved in nonhuman primates (n=3) over 24h (27). Again, the penetration of imatinib in the CSF was weak with a mean ratio of CSF/plasma AUC of 5% (SD:2). Animal experiments suggest that the modest diffusion in the CNS is imputable to the transmembrane drug transporter P-glycoprotein (P-gp or ABCB1). P-gp encoded in man by the gene MDR1 was originally identified for its role in multidrug resistance to anticancer agents. P-gp is also a pharmacokinetic determinant acting as an efflux pump that prevents the passage of some oral drugs across the epithelial cells of the digestive tract and that is involved in the elimination processes (biliary excretion, renal and intestinal secretions). In addition, P-gp is expressed in brain capillary endothelial cells, participating in the concept of the blood brain barrier (28, 29). *In vitro*, imatinib is transported by P-gp (30, 31). Knock-out mice for the murine equivalent of MDR1 (no expression of P-gp) exibit a brain to plasma ratio 6-to 7-fold greater than that of wild-type mice (expressing P-gp) after intravenous injection (31). Hence, P-gp could limit the distribution of imatinib in the brain. It has to be stressed that P-gp expressed on the apical side of enterocytes and involved in the limited absorption of some oral drugs (*i.e.* ciclosporin) has apparently no impact on imatinib bioavailability since it is around 98%.

Metabolism. The metabolic profile of imatinib has not yet been published. According to the package insert, imatinib is mainly biotransformed by the isoenzyme cytochrome P450 (CYP) 3A4. Other isoforms such CYP1A2, CYP2D6, CYP2C9 and CYP2C19 appear to be involved in the metabolism. The main metabolite CGP 74588 or N-desmethyl-imatinib exibits an *in vitro* activity comparable to that of the parent drug.

Excretion. The elimination pathways of imatinib remain mostly unpublished. When determined in 2 patients with CML, the amount of imatinib in urine represented 2.7 and 4.1% of the administered dose (16). In addition, N-desmethyl-imatinib was also found in very low amounts (1.7 and 2% of the administered dose in the urine) (16). The biliary excretion has been investigated in one patient with normal liver tests

Table II. *Pharmacokinetic parameters for imatinib in children. Results as mean (SD).*

No. of children	Dose (mg/m^2)	C_{max} (mg/l)	Tmax (h)	AUC_{0-24h} (mg/l.h)	Vd (l)	Cl (ml/min)	$t_{1/2}$ (hours)	Reference
6	260 (day 1)	3.6 (2.0)	3.5 (2.5)	51.0 (34.9)	119 (83)	148.3 (96.6)	8.9 (1.2)	33
8	340 (day 1)	2.5 (0.9)	3.7 (2.1)	32.1 (13.0)	167 (84)	213.3 (113.3)	9.2 (1.9)	33
4	440 (day 1)	5.4 (4.3)	5.0 (2.0)	76.1 (54.8)	190 (213)	155.0 (156.3)	12.8 (2.5)	33
4	570 (day 1)	8.5 (9.2)	2.9 (1.3)	106.7 (113.6)	109 (88)	93.3 (46.6)	14.8 (12.9)	33

Cmax: concentration peak; Tmax: time for concentration peak; AUC: area under the serum concentrations-time curve; Vd: volume of distribution assuming a bioavailability of 100%; Cl: clearance assuming a bioavailability of 100%; t1/2: terminal half-life.

receiving imatinib (400 mg daily). The amount of the parent drug and the CGP 74588 metabolite represented 17.7 and 2.1% of the daily dose, respectively (32).

Pharmacokinetic parameters. The pharmacokinetic parameters of imatinib given at therapeutic dosages in adult patients are presented in Table I. The exposition to imatinib administered once-daily appeared to increase on chronic administration. Hence, the AUC calculated over 24h were 24.8 mg/l.h (SD:7.4) on day 1 and 40.1 mg/l.h (SD:15.7) at steady state in patients receiving a daily dose of 400 mg (20). Overall, the kinetics of imatinib in patients with CML receiving a daily dose of 400 mg or 600mg are characterized, at steady state, by a Cmax ranging from 2.6 to 3.5 mg/l, a terminal half-life of 15h to 19h (calculated over a 2-day period) and a total body clearance of around 200ml/min. With regard to the IC_{50} for Bcr-Abl (0.15 mg/l), the plasma through concentrations were well above, around 1.2 mg/l in 14 patients receiving 400mg or 600mg (20). According to the product label, the kinetics of imatinib are comparable in GIST and CML patients.

Special populations

Children. Imatinib is approved for the treatment of children with Philadelphia chromosome-positive CML with a dosage ajusted to the body surface area (from 260 to 340mg/m^2 daily). It has also been evaluated in Philadelphia-positive ALL (33) and a case report mentioned its use in a child with GIST (34). The kinetic profile of imatinib was investigated in 22 children with Philadelphia chromosome-positive leukemia during a phase I study (n=31, median age: 14 years, range 3-20 years) (33). Pharmacokinetic parameters were determined on day 1 at once-daily dosages ranging from 260 to 570 mg/m^2 (Table II). At approved dosages (*i.e.*, 260 and 340 mg/m^2), the Cmax were 3.6 mg/l (SD:2.0) and 2.5 mg/l (SD: 0.9), respectively with a Tmax around 3.5h. Regarding the half-life, the sampling period (20h from the Tmax) might have been too short for an accurate determination. Parameters on day 8 were partially reported (33). Hence, the mean oral clearance was 128 $ml/min/m^2$ (SD:76.6) considering all dosages. In addition, the AUC_{0-24h} calculated for the 8 children receiving 340 mg/m^2 daily was 1.7 times higher than that calculated on day 1. Unfortunately, the terminal half-life was not reported. Overall, the oral clearance at steady state appears similar to that in adults.

Renal dysfunction. The kidneys represent a minor pathway for the elimination of imatinib. Partial data concerning the use of imatinib in patients with various degrees of renal dysfunction have been reported in abstract forms (35, 36). The authors indicated an increase in the AUC in patients with mild dysfunction (*i.e.*, creatinine clearance 40-59 ml/min) and a decrease in imatinib clearance with worsening dysfunction. Hence, the AUC_{0-24h} were at steady state 39.6 mg/l.h (SD:8) and 84.6 mg/l.h (SD:23.9) in patients with normal renal function and in those with mild dysfunction receiving a daily dose of 400 mg, respectively. Nevertheless, no dosage adjustments are currently mentioned in the prescribing information.

Hepatic dysfunction. Imatinib is biotransformed and mainly excreted in the feces. Preliminary data published in an abstract form (37) have suggested that the AUC normalized to the dose increased by 50% at steady state in patients with various degrees of liver disease. Again, no dosing recommendations are yet available for patients with liver dysfunction.

Factors influencing pharmacokinetics

The pharmacokinetics of imatinib in adult patients with CML are characterized by a large interpatient variability. At steady state, the coefficients of variation (CV) for AUC_{0-24h} were 39% and 51% in patients treated with daily doses of 400mg (n=5) and 600mg (n=9), respectively (20). Body weight or body surface did not significantly influence imatinib AUC, justifying the fixed dose in adults (20).

Sources of variability appear to include the CYP3A activity (*i.e.* CYP3A4, CYP3A5) and the genetic polymorphism of P-gp, as has been reported in an abstract form (38). Hence, exposures (AUC) to imatinib and to the metabolite CGP 74588 determined on day 1 and at steady state in 18 patients were shown to correlate with CYP3A activity assessed, *in vivo*, with the probe drugs erythromycin and midazolam. Furthermore, the authors suggested that 3 genetic variants of P-gp (not stated in the abstract) could influence imatinib AUC at steady state. Various single nucleotide polymorphisms (SNP) or genetic variants have been identified for the MDR1 gene. Some of the SNP have been associated with variations of P-gp expression and, in some cases, in alterations of pharmacokinetics (digoxin, tacrolimus) (39). With regard to imatinib, homozygotes patients for a variant MDR1 gene (*i.e.* with a lower expression of P-gp than the patients with the wild-type gene) had a higher AUC. These preliminary findings could lead to a more rational dosing of imatinib, although the clinical impact of pharmacokinetic variability in adults remains to be established.

In children, a large interpatient variability in kinetic parameters has also been observed (33). The CV of $AUC_{0\text{-}24h}$ determined at steady state for 6 children receiving 260 mg/m^2 daily was 68%. At dose levels ranging from 260 to 570 mg/m^2, the variability was not affected when the dosage was expressed as body weight.

The effect of food on imatinib pharmacokinetics at steady state has been examined in 10 patients with CML receiving a daily dose of 400mg (40). Comparison of kinetic parameters between fasted and fed states did not lead to significant modifications. The labelling information recommends taking imatinib with a meal.

Pharmacodynamics

Pharmacodynamics deals with the relationship between pharmacokinetics and the clinical effects (therapeutic or toxic). As outlined previously, the clinical relevance of imatinib kinetic variability is unknown in adult patients with CML or GIST. Whether exposure might correlate with toxic effects or inadequate response and, hence, justify blood monitoring has to be established.

In 22 children with Philadelphia chromosome-positive leukemia, the variability in drug exposure had no impact on the white blood cells count after one month (33).

Drug-drug pharmacokinetic interactions

Pharmacokinetic interactions commonly occur *via* drug-metabolizing enzymes or drug transporters. As seen above, imatinib is mainly metabolized by the CYP3A subfamily enzymes and has been shown, *in vitro*, to be a competitive inhibitor of the isoenzymes CYP3A, CYP2C9 and CYP2D6. In addition, it interacts *in vitro* both as a substrate and an inhibitor with the transporters P-gp (30) and Breast Cancer Resistance Protein (BCRP or ABCG2) (41, 42). It should be noted that an inhibitor for an enzyme or a transporter is not necessarily a substrate for this same protein. Hence, imatinib is given chronically and is potentially susceptible to numerous kinetic interactions. Concomitant drugs may alter the exposure to imatinib or imatinib may change the pharmacokinetics of co-administered drugs.

Drugs that change imatinib kinetics. Inhibition of metabolism or transport by a co-administered medication can lead to an increase of imatinib exposure. One paper regarding this type of interaction has been published but the clinical significance (*i.e.*, potential toxic effects) remains unknown. Inhibitors of CYP3A, such as the antifungal agents itraconazole or ketoconazole, may increase imatinib concentrations. Hence, ketoconazole given as a single dose (400 mg) significantly increased the exposure to imatinib by 40% in 14 healthy volunteers who were administered a single low dose of the anticancer agent (200 mg) (43). Conversely, the apparent clearance increased from 193 ml/min to 271 ml/min consistent with a reduction of metabolism of the anticancer agent (ketoconazole is a weak inhibitor of P-gp). The terminal half-lives of imatinib were comparable (around 20h) but the calculating period (20h from the Tmax) appears too short for a valid estimation, probably because of the low dosage that did not enable the determination of concentrations after 24h. No significant clinical effect was reported in these healthy subjects. Similarly, inhibitors of P-gp transport (itraconazole, ciclosporin) may reduce biliary excretion or enhance CNS passage.

Inducers of CYP3A and P-gp may reduce the exposure to imatinib and have the potential to compromise the therapeutic activity. Contrasting with inhibition mechanisms, inducers such as rifampin, carbamazepine, phenobarbital or the herbal product St John's Wort (hypericum perforatum) do not directly interact with enzymes or transporters. In fact, they activate proteins called orphan nuclear receptors such as pregnane X receptor (PXR or SXR) or constitutive androstane receptor (CAR). These nuclear receptors act as transcriptional factors regulating the expression of genes coding for CYP and transporters (44, 45). Drugs that activate nuclear receptors act as pleiotropic inducers and explain why inducers of CYP3A, such as rifampin or the herbal product St John's Wort, are also inducers of P-gp (both drugs are ligands for PXR).

Reduced exposure to imatinib has been reported in healthy volunteers who received rifampin or St John's Wort and in a patient taking phenytoin. The combination of oral

rifampin (600mg daily) with imatinib (400mg single dose) in 10 volunteers led to a reduction of the $AUC_{0\text{-}24h}$ by 68%, associated with an increase in the $AUC_{0\text{-}24h}$ of the metabolite CGP 74588 by 23.9% (46). Similarly, in 10 volunteers receiving St John's Wort (300 mg 3 times daily for 2 weeks), the AUC of imatinib (400 mg single dose) was shown to decrease by 32% (47). Another study, including 12 healthy subjects, reported comparable results (significant decrease of the AUC by 30%) (48). Finally, one patient receiving phenytoin had a reduced exposure to imatinib (3.7 mg/l.h *versus* 20 mg/l.h for other patients) associated with a lack of hematological response (20). The patient responded when the anticonvulsant was discontinued and the dosage of imatinib escalated from 350mg to 500mg. Unfortunately, the concentrations were not determined after the withdrawal of phenytoin. Hence, combinations with CYP3A and P-gp inducers (*i.e.*, ligands for the nuclear receptors PXR or CAR) must be avoided.

Drugs whose kinetics are altered by imatinib. Imatinib may alter the pharmacokinetics of numerous combined medications by inhibition of enzymatic pathways (particularly CYP3A, the isoform considered to be involved in the metabolism of 50% of all drugs) or cellular transport. The AUC of the lipid-regulating drug simvastatin (40mg, single dose) was shown to increase 3-fold when combined with imatinib (400mg daily) in 20 patients with CML, associated with a reduction in the apparent clearance of 70% (49). No toxic effect attributable to simvastatin (myopathy or rabdomyolysis) was observed, although it was administered as a single dose. Simvastatin is a CYP3A substrate and is not significantly transported by P-gp *in vitro* (50). Therefore, the mechanism of interaction is probably due to an inhibition of metabolism by imatinib. Therefore, caution is needed when imatinib is associated with a drug known to be a substrate for CYP3A, CYP2C9 (warfarin), CYP2D6 (some antidepressants), P-gp (digoxin) and BCRP (mitoxantrone, topotecan, methotrexate).

Conclusion

The publication of pharmacokinetic data included in the prescribing information (metabolism, elimination) is awaited. The pharmacodynamics of imatinib merit further investigation in adults, particularly the clinical relevance of pharmacokinetic variability and the identification of eventual kinetic determinants that could predict clinical response.

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