AIDS Rev 1999; 1: 167-178

Clinical Pharmacokinetics of Antiretroviral Drugs

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Abstract

The interest in the pharmacokinetics of antiretroviral drugs has gained considerable interest during the last years. It has been shown that the pharmacokinetics of a drug can be an important determinant of antiviral efficacy or toxicity, especially for the protease inhibitors, but also for the non-nucleoside reverse transcriptase inhibitors. For the nucleoside reverse transcriptase inhibitors, such relationships are less clear. This manuscript deals with the basic pharmacokinetic properties of the currently available antiretroviral drugs. Furthermore, several drug-drug interactions are discussed, and the penetration of drugs in several compartments of the body, such as the brain, are highlighted.

Key words

Therapeutic drug monitoring (TDM). Pharmacokinetics. Drug levels. Antiretroviral drugs.

Introduction

In this paper an overview of the clinical pharmacokinetics of the currently available antiretroviral drugs is provided. Three classes of drugs will be discussed: the nucleoside reverse transcriptase inhibitors, the non nucleoside reverse transcriptase inhibitors, and the protease inhibitors. The representatives of these classes are discussed separately, and key pharmacokinetic parameters are provided, as well as the penetration of the drugs into different compartments of the body (such as the cerebrospinal fluid), and some drug-drug interactions.

Nucleoside reverse transcriptase inhibitors (NRTIs)

NRTIs belong to the first class of antiretroviral drugs that were developed. At this moment, six representatives are licensed by the FDA: zidovudine, didanosine, zalcitabine, stavudine, lamivudine, and abacavir; several other NRTIs are now in (pre)clinical development.

Combinations of NRTIs have now become established as the foundation of regimens for the treatment of HIV-infection.

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Zidovudine

Zidovudine (AZT, 3'-azido-2',3'-dideoxythymidine, Fig. 1) was approved by the FDA in 1987, and it was the first antiretroviral agent to be clinically used on a widespread basis. Zidovudine is a deoxythymidine analogue, and the structural difference with thymidine is that the 3'-hydroxyl group is replaced by an azido (N_3) group. Zidovudine is monophosphorylated by thymidine kinase, a cell-cycle dependent enzyme, and zidovudine is therefore more active in dividing than in resting cells[1,2].

Zidovudine is rapidly and well absorbed after oral administration with a bioavailability of approximately 65%. Maximum plasma concentrations are reached within 30-90 min after ingestion. After an oral dose of 200 mg, maximum concentrations are

Table 1. *Steady-state pharmacokinetics of nucleoside reverse transcriptase inhibitors.*

Drug	Dose (mg)	Bioavailability (%)	Half-life (h)	AUC# (h*µg/mL)	C_{max} (µg/mL)
Zidovudine	200	65	1	2.0	1.2
Stavudine	40	82-99	1.6	1.9	0.85
Zalcitabine	0.75	86	1.5	0.03	0.012
Lamivudine	150	82	6	12	1.5
Didanosine	200	19-40	1.4	1.2	0.9
Abacavir	300	76-100	1.2	5.8	2.2

#during one dosing interval

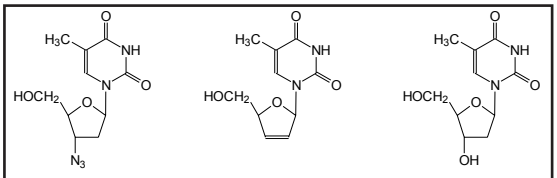

Fig. 1. *Molecular structure of zidovudine (left), stavudine (middle) and deoxythymidine (right).*

in the range of 1.2 µg/mL. The plasma elimination half-life of the drug is about one hour. Since the intracellular half-life of the pharmacologically active anabolite, zidovudine-triphosphate, is longer (about 3 h), zidovudine can be ingested in *tid* or *bid* dosing regimens. Zidovudine penetrates the cerebrospinal fluid (CSF) well (ratios of CSF and plasma concentrations can be well over unity)[3-5]. Zidovudine has been detected in semen, saliva, and penetrates the placenta[6-8].

Concomitant ingestion of zidovudine with food reduces the maximum plasma concentration C_{max} and delays the time to C_{max}. However, the area under the plasma concentration versus time curve (AUC) is not affected[9-12]. It is now recommended that zidovudine can be ingested with or without a meal. Decreased absorption of zidovudine after oral administration has been observed in patients with diarrhea[13].

Zidovudine is metabolised to an inactive glucuronide metabolite and this is the main route of elimination of the drug from the body (75%). Approximately 15-20% of an oral zidovudine dose is excreted unchanged in the urine. Another pathway of metabolism is the reduction of the azido-function to yield 3'-amino-3'-deoxythymidine[14]. This compound is 5-7-fold more cytotoxic than zidovudine, but concentrations of this metabolite are 100-fold lower as compared to zidovudine[15]. The clinical relevance of this potentially cytotoxic metabolite is therefore questionable.

Zidovudine glucuronide concentrations are high in patients with severe renal dysfunction. Haemodialysis removes the glucuronide metabolite from the body, but has a negligible effect on zidovudine concentrations. Thus, patients with endstage renal disease and haemodialysis should receive lower doses than patients with normal renal function.

Several attempts have been made to correlate zidovudine plasma pharmacokinetics and the drug's efficacy and toxicity. In general, these efforts have failed[16]. This is not surprising if we realise that all NRTIs can be considered prodrugs. They are only pharmacologically active after intracellular phosphorylation to their corresponding triphosphates. Intracellular zidovudine phosphate concentrations correlated better with efficacy (triphosphate derivative) and toxicity (monophosphate derivative) and, though technically more difficult to assess than plasma concentrations, show more promise as a predictor of efficacy or toxicity of the drug.

Stavudine

Stavudine (d4T, 2',3'-didehydro-2'-3'-dideoxythymidine, Fig. 1) is, like zidovudine, a deoxythymidine derivative. Stavudine is monophosphorylated by thymidine kinase, a cell-cycle dependent enzyme, and the drug is more active in dividing than in resting cells[1,2]. The affinity for thymidine kinase is higher for zidovudine as compared to stavudine (K_m values for this enzyme are 138 µM and 3 µM for zidovudine and stavudine, respectively), and these drugs should therefore not be administered concomitantly[17,18]. Concomitant administration leads to decreased phosphorylation of stavudine.

Stavudine is rapidly and well absorbed with a bioavailability between 82 and 99%[19-21]. C_{max} is reached 0.5 to 0.75 h after administration and is in the range of 0.85 µg/mL after a 40 mg dose. The absorption rate of stavudine is decreased by intake of food, but the overall bioavailability is not affected[22]. Therefore, stavudine can be ingested with or without food. Stavudine penetrates the cerebrospinal fluid of HIV-1-infected patients well[23]. The drug readily crosses the placenta in animal studies, most likely by simple diffusion[24-25].

For patients with a body weight below 60 kg, the recommended dose is twice daily 30 mg, for patients with a body weight of 60 kg or higher, the recommended dose is 40 mg *bid*. The elimination half-life of the drug in plasma after an oral 40 mg dose is 1.6 h, but the half-life of the intracellular stavudine triphosphate is 3.5 h, making *bid* dosing possible[26].

Dosage adjustments are necessary in patients with reduced renal clearance, as the elimination half-life and AUC of stavudine are increased in these patients[27]. The dose of stavudine does not require adjustment in patients with hepatic impairment as the pharmacokinetics of stavudine are not affected in patients with cirrhosis of the liver[28].

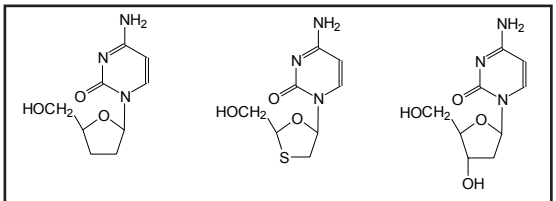

Fig. 2. *Molecular structure of zalcitabine (left), lamivudine (middle) and deoxycytidine (right).*

Zalcitabine

Zalcitabine (ddC, 2',3'-dideoxycytidine, Fig. 2) is a deoxycytidine analogue in which the 3'-hydroxyl group of the sugar compound is replaced with a hydrogen atom (Fig. 2). Zalcitabine is intracellularly phosphorylated to the pharmacologically active zalcitabine triphosphate[29]. Zalcitabine is mainly active in resting cells[1,2].

Zalcitabine is well absorbed after oral administration, with a bioavailability of approximately 86%[30,31]. Maximum concentrations in plasma are reached 1-2 h after ingestion of the drug. Concomitant administration of zalcitabine with food decreased the C_{max} and increased the time to C_{max}. The AUC was also reduced with 14%, but this change was not considered clinically significant[32]. Zalcitabine penetrates the cerebrospinal fluid moderately, with concentrations in this matrix reaching approximately 20% of those reached in plasma[33].

The elimination half-life of the drug is approximately 1.5 h. Zalcitabine is mainly excreted unchanged in the urine; 62% of an oral dose is excreted unchanged via this route. The main metabolite of zalcitabine in the urine is dideoxyuridine. Approximately 10% of an oral dose of zalcitabine is excreted in the faeces, as unchanged drug or as dideoxyuridine[34]. Patients with impaired renal function show a decreased clearance of the drug, and dosage adjustment (0.75 mg *bid*, or 0.75 mg *qd*) is advised in these patients[34]. The recommended dosage of zalcitabine in patients with normal renal function is 0.75 mg *tid*.

Zalcitabine pharmacokinetics in children have been investigated. In general, lower bioavailability and/or increased clearance of the drug is observed in this population as compared with adults[35,36].

The coadministration of zalcitabine and an aluminium hydroxide/magnesium hydroxide antacid mixture led to a 25% decrease in bioavailability of the drug. Zalcitabine should therefore not be coadministered with antacids[37]. Zalcitabine should not be administered concomitantly with lamivudine, another cytidine analogue, as both drugs compete for the same enzymes for intracellular phosphorylation.

Lamivudine

Lamivudine (3TC, 2'-deoxy-3'-thiacytidine, Fig. 2) is, like zalcitabine, a deoxycytidine derivative (Fig. 2). Lamivudine is phosphorylated to the pharmacologically active triphosphate derivative, and is mainly active in resting cell populations[38]. It was originally synthesized as a racemic mixture of (+) and (-) enantiomers and showed potent activity against HIV[39]. Subsequently, it was demonstrated that the (-) enantiomer had greater antiretroviral activity than the (+) enantiomer, but less activity against DNA polymerase, and less cellular toxicity *in vitro*[40,41]. Thus, the (-) enantiomer (lamivudine) was further developed as an antiretroviral drug.

Lamivudine is rapidly absorbed after oral administration with a time to C_{max} of about 1 h, and 82% bioavailability. Ingestion of lamivudine with food decreases C_{max} and increases time to Cmax, but does not affect the bioavailability of the drug. The C_{max} in plasma after an oral dose is in the range of 1.5 µg/mL. The elimination half-life of the drug is approximately 6 h, which is relative long for an nucleoside reverse transcriptase inhibitor. The majority of the drug is excreted as unchanged drug in the urine (70%), and 5-10% of an oral dose is metabolised to inactive sulfoxide metabolites.

Concomitant use of zidovudine leads to an increase of the zidovudine bioavailability of 13%. This interaction is not considered significant and no adjustment of the dosage is required.

The oral clearance of lamivudine is decreased in patients with impaired liver function. Patients with a creatinine clearance below 50 mL/min require dosage adjustment (150 mg *qd*), and the dosage should be further reduced in patients with a creatinine clearance below 30 mL/min.

Lamivudine penetrates the cerebrospinal fluid (the mean ratio of concomitant cerebrospinal fluid and plasma concentrations is approximately 0.12). The absolute concentrations in the cerebrospinal fluid exceed IC50 values for most wild-type viruses[23].

Didanosine

Didanosine (ddI, 2',3'-dideoxyinosine, Fig. 3) is intracellularly converted to didanosine monophosphate and is subsequently aminated to dideoxyadenosine monophosphate. This compound is converted to dideoxyadenosine triphosphate, the putative pharmacologically active anabolite of didanosine (Fig. 3).

Didanosine is an acid-labile compound, which makes it susceptible to degradation in the acidic environment of the stomach. Didanosine is therefore formulated with buffering salts (powder or tablets) to increase the pH of the contents of the stomach. Didanosine is best absorbed on an empty stomach; ingestion of the drug with food de-

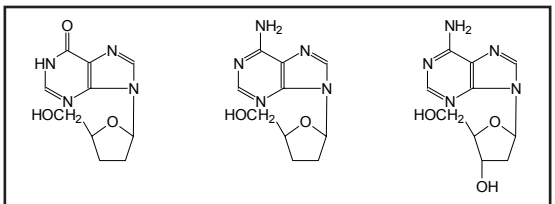

Fig. 3. *Molecular structure of didanosine (left), dideoxyadenosine (middle) and deoxyadenosine (right).*

creases the bioavailability with approximately 50%[42-45]. The buffer of the didanosine formulation gives rise to several drug-drug interactions. Drugs that require an acidic environment of the stomach to be absorbed (indinavir, delavirdine, ketoconazole) should not be taken concomitantly with didanosine. Drugs that adsorb to the metal ions of the buffer (tetracyclines, ciprofloxacin) should also be ingested separately.

The elimination half-life of the drug in plasma is relatively short (1.4 h), but the half-life of the intracellular dideoxyadenosine triphosphate anabolite is 12-24 h, making once daily dosing of the drug feasible[46]. Didanosine penetrates the cerebrospinal fluid moderately[47].

Approximately 30-60% of an oral dose of didanosine is excreted unchanged in the urine. Patients with renal impairment (creatinine clearance below 60 mL/min) require adjustment of the dosage. The advised dose of didanosine (chewable tablets) is 200 mg *bid* (400 mg *qd*) for patients with a body weight of 60 kg or more, and 125 mg *bid* (250 mg *qd*) for patients with a body weight below 60 kg.

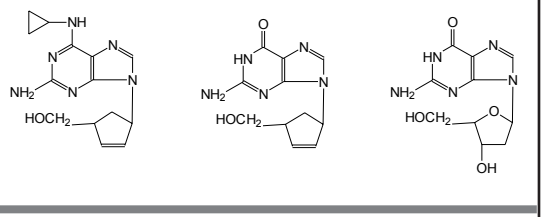

Fig. 4. *Molecular structure of abacavir (left), carbovir (middle) and deoxyguanosine (right).*

Abacavir

Abacavir (1592U89, Fig. 4) is anabolised via a unique intracellular mechanism to yield carbovir triphosphate, a deoxyguanosine analogue. The first step is the phosphorylation to abacavir monophosphate[48]. A cytosolic enzyme subsequently converts abacavir monophosphate to carbovir monophosphate, that is further phosphorylated to the pharmacologically active carbovir triphosphate.

Abacavir has good bioavailability in animal studies after oral administration (76-100%)[49-50]. The drug is rapidly absorbed (the C_{max} is reached after 0.7 – 1.7 h) and administration with food delays the time to C_{max}, decreases the C_{max} with 35%, and decreases the AUC with only 5%[51]. The drug shows favourable penetration of the cerebrospinal fluid[52].

Abacavir is metabolised to abacavir glucuronide, and is a substrate of alcohol dehydrogenase.

Non nucleoside reverse transcriptase inhibitors (NNRTIs)

Non nucleoside reverse transcriptase inhibitors share the same target enzyme as the NRTIs. The NNRTIs, however, are non-competitive inhibitors of the viral reverse transcriptase. They comprise a heterogeneous group of compounds. The pharmacokinetics of nevirapine, delavirdine, and efavirenz will be discussed in this section.

Nevirapine

Nevirapine (11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido-(3,2-b:2',3'-e)(1,4)diazepin-6-one, Fig. 5) is a member of the dipyridodiazepinone class. Nevirapine does not compete with template or nucleoside triphosphates, but binds directly to the reverse transcriptase enzyme. The activity of nevirapine is specific for HIV-1; it is inactive against HIV-2 and does not bind to human DNA polymerases.

Nevirapine is readily absorbed after oral administration with a bioavailability exceeding 90%[53]. Concurrent administration of food or antacids does not affect the bioavailability of the drug. Administration of the drug with food decreases C_{max} and increases the time to reach C_{max}. Nevirapine can be ingested with or without food.

Nevirapine readily penetrates different compartments of the body, such as the cerebrospinal fluid, the placenta, and the drug can be detected in breast milk[54-55]. The drug is approximately 60% bound to plasma proteins.

Nevirapine shows the phenomenon of autoinduction. This results in a 1.5- to 2-fold increase of the apparent oral clearance of nevirapine after prolonged administration. The half-life of nevirapine in plasma decreases accordingly from 45 h after single dose administration, to 25-30 h after multiple doses. Due to the autoinduction phenomenon, the licensed dose of nevirapine is 200 mg *qd* during the first two weeks of therapy, and 200 mg *bid* after 2 weeks of therapy. Regarding the long half-life of the drug in plasma, nevirapine can most likely also be administered in a 400 mg *qd* regimen, and several studies are now investigating this option.

Nevirapine induces cytochrome P450 enzymes, and this gives rise to a number of drug-drug interactions.

Table 2. *Steady state pharmacokinetics of non-nucleoside reverse transcriptase inhibitors.*

Drug	Dose (mg)	Bioavailability (%)	Half-life (h)	AUC# (h*µg/mL)	C_{max} (µg/mL)
Nevirapine	200	93	25-30	86	5.0
Delavirdine	400	85$	5,8	99	19
Efavirenz	600	NR	40-55	58	4.1

#during one dosing interval
$relative bioavailability of tablets as compared with an oral solution.

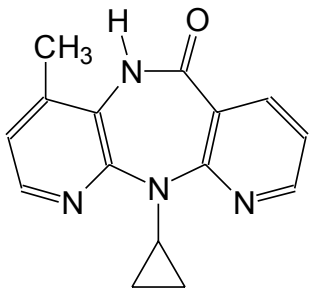

Fig. 5. *Molecular structure of nevirapine.*

Interaction studies with nevirapine and the protease inhibitors saquinavir, indinavir, ritonavir and nelfinavir revealed that nevirapine decreases the exposure of saquinavir and indinavir with approximately 30%. Nevirapine has no effect on the exposure to ritonavir, and the reported effect on the pharmacokinetics of nelfinavir are contradictional (either no change or a 30% decrease in exposure to nelfinavir).

It is now recommended not to combine nevirapine and saquinavir (Invirase® formulation, hard gelatin capsules). Whether or not the dosage of indinavir and nelfinavir require adjustment when combined with nevirapine (to 1,000 mg *tid* for the protease inhibitors) is subject of discussion and warrants further investigation.

Nevirapine reduces concentrations of ketoconazole, methadone and ethinyl estradiol. The concentrations of nevirapine are reduced by coadministration of rifampin and rifabutin, and these drugs should not be used together.

Delavirdine

Delavirdine (1-(3-(isopropylamino)-2-pyridyl)-4-((5-methane sulfonaminodoindol-2-yl) carbonyl) piperazine, Fig. 6) is a bisheteroarylpiperazine (BHAP) non nucleoside reverse transcriptase inhibitor with high activity against HIV-1, and no affinity for HIV-2 reverse transcriptase or DNA polymerases.

Delavirdine is in general well and rapidly absorbed (C_{max} is reached 1 h after administration), but requires an acidic pH of the stomach as the molecule is not soluble at high pH values. Delavirdine should therefore not be administered with didanosine (the formulation of didanosine contains buffers to increase gastric pH), and coadministration of H2-receptor antagonists and proton pump inhibitors is expected to decrease bioavailability of delavirdine[56]. Delavirdine can be ingested with or without food in the recommended dosage of 400 mg *tid*. The bioavailability of delavirdine tablets relative to an oral solution of the drug is 85%.

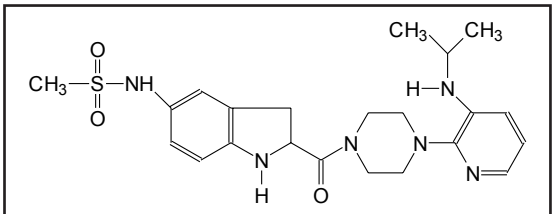

Fig. 6. *Molecular structure of delavirdine.*

Delavirdine is extensively bound to plasma proteins (98%) and appears to penetrate the cerebrospinal fluid poorly (0.4% of concomitantly achieved concentrations in plasma). Delavirdine concentrations in saliva and semen are approximately 6% and 2%, respectively, as compared with plasma concentrations.

Delavirdine is converted to several inactive metabolites, mainly via N-desalkylation and pyridine hydroxylation by the cytochrome P450 enzymes 3A4 and 2D6. The half-life of the drug in plasma is reported to be 5.8 h, with a wide range from 2 to 11 h.

Delavirdine is an inhibitor of the cytochrome P450 system. When combined with saquinavir, or indinavir, the exposure to these protease inhibitors is increased by 5-fold, and 2-fold, respectively[57]. Delavirdine does not affect exposure to ritonavir. Several drugs are contraindicated, because of the inhibition of their metabolism by delavirdine, and the subsequent increase of their exposure: Terfenadine, astemizole, cisapride, triazolam, alprazolam, and midazolam.

Several drugs increase the exposure of delavirdine when concomitantly administered, such as ketoconazole, clarithromycin, fluoxetine, and ritonavir. The exposure to delavirdine is decreased by coadministration of inducers of the cytochrome P450 3A enzyme, such as rifampin, rifabutin, carbamazepine, phenobarbital, and phenytoin.

Efavirenz

Efavirenz (DMP-266, (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one, Fig. 7) is an HIV-1-specific non nucleoside reverse transcriptase inhibitor with no activity against HIV-2 reverse transcriptase or human DNA polymerases.

C_{max} values for efavirenz in plasma are reached 3-5 h after administration of the drug (in the recommended dosage of 600 mg *qd*). Efavirenz can be taken with or without food; a high-fat meal can in-

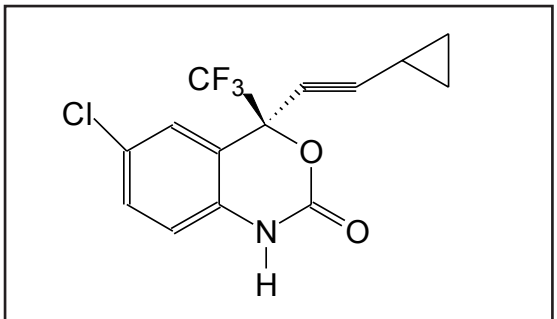

Fig. 7. *Molecular structure of efavirenz.*

crease the bioavailability of efavirenz and should be avoided.

Efavirenz is highly bound to plasma proteins (> 99%), predominantly to albumin. Cerebrospinal fluid concentrations of efavirenz are approximately 0.7% of those concomitantly observed in plasma (and free-drug concentrations are approximately 3-fold higher in the cerebrospinal fluid as compared with plasma). Efavirenz is primarily metabolised via the cytochrome P450 enzyme system to a number of hydroxylated metabolites. These metabolites are subsequently glucuronidated and are inactive against HIV-1 infection. *In vitro* studies have revealed that the isozymes 3A4 and 2B6 are mainly responsible for the metabolism of efavirenz[58].

Efavirenz, like nevirapine, is subject to autoinduction of its metabolism. After single doses, the half-life in plasma is 52-76 h, and after administration of the drug for 10 days, the half-life decreases to 40-55 h. This long half-life makes *qd* dosing of the drug feasible.

Efavirenz induces the cytochrome P450 3A4 enzyme, and *in vitro* studies showed that efavirenz inhibits the isozymes 2C9, 2C19, and 3A4. Astemizole, midazolam, triazolam, cisapride, and ergot derivatives should not be coadministered with efavirenz due to the increase of plasma concentrations of these drugs by the inhibition of their metabolism by efavirenz. Efavirenz decreases plasma concentrations of saquinavir (Fortovase®) and these drugs should not be administered concomitantly. Surprisingly, saquinavir (Fortovase®) decreased efavirenz concentrations with 12%. When combined with indinavir, the dosage of this protease inhibitor should be increased to 1,000 mg *tid*. The exposure to nelfinavir is increased when combined with efavirenz (approximately 20%), and no dose adjustment is required when these drugs are combined[58]. Combination of ritonavir and efavirenz results in a 20% increase of exposure of both drugs, and the clinical consequence of this interaction is not known. Rifampin decreases efavirenz exposure with 26%; the clinical significance of this interaction is currently not known.

Protease inhibitors

Protease inhibitors exert their action by the inhibition of a viral protease, an enzyme that processes and cleaves large precursor proteins to yield structural proteins and replicative enzymes[59]. Inhibition of the viral protease leads to production of immature, non-infectious virus particles.

In 1996, approximately 30 protease inhibitors were in (pre)clinical development. In this section, 4 currently licensed protease inhibitors (saquinavir, indinavir, ritonavir, and nelfinavir) will be discussed.

Saquinavir

Saquinavir (RO 31-8959. N-Tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2quinolylcarbonyl)-L-asparaginyl]amino]butyl]-(4aS, 8aS)-isoquinoline-3(S)-carboxamide metharesulfonate). (Fig. 8) was the first member of its class to be approved in 1995 in the USA by the FDA under its accelerated approval regulations for use in combination with approved nucleoside reverse transcriptase inhibitors in patients with advanced HIV infection. Saquinavir has been approved in the European Community in October 1996. It is a peptide derivative, which is a transition-state mimetic of the Phe-Pro peptide bond. Two pharmaceutical formulations of the drug are Invirase® («hard gelatin capsules») and Fortovase® («soft gelatin capsules») with an improved oral bioavailability.

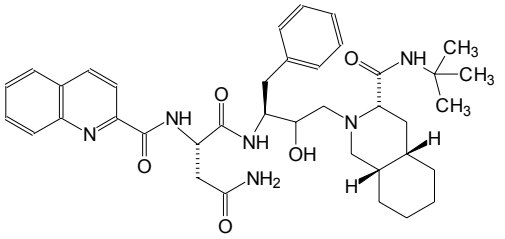

Fig. 8. *Molecular structure of saquinavir.*

Hard gelatin formulation, Invirase®. As a result of limited absorption and extensive first-pass metabolism, the bioavailability of a single 600 mg oral saquinavir dose (Invirase®) taken with food is 4%. In the fasting state the bioavailability is 18 times lower[60,61]. In healthy volunteers the maximum plasma concentration (C_{max}) after a single 600 mg oral dose taken with food is 66.1 ng/mL[60-62]. Saquinavir should always be taken with food. After multiple doses the C_{max} was 90.4 ng/mL[60]. Time to C_{max} (T_{max}) is 3-4 h after administration of saquinavir

Table 3. *Steady-state pharmacokinetics of protease inhibitors.*

Drug	Dose (mg)	Bioavailability (%)	Half-life (h)	AUC# (h*µg/mL)	C_{max} (µg/mL)
Saquinavir (Invirase®)	600	4	2.0	0.8	0.20
Saquinavir (Fortovase™)	1,200	NR	2.0	7.2	2.2
Indinavir	800	30	1.5	17	7.0
Ritonavir	600	NR	3 - 5	61	11.2
Nelfinavir	750	20-80	3.5 - 5	18	4.0

#during one dosing interval

capsules with food[60,61]. Administration of saquinavir suspension in a fasted state yielded a T_{max} value of 0.77 h[63]. Steady-state plasma concentrations of saquinavir in HIV-1 infected patients appear to be higher than in healthy volunteers with a C_{max} of 242.3 ng/mL after multiple oral doses of 600 mg[60]. Saquinavir is highly bound to plasma proteins (> 98%)[64]. The value for total plasma clearance was 98.8 L/h, and the terminal plasma half-life was 13.2 h; in steady-state, the observed elimination half-life from plasma is approximately 2 h[61]. Elimination of saquinavir is predominantly non-renal; after a 600 mg oral dose, 88% was detected in the faeces, whilst 1% was excreted in the urine[60]. Saquinavir pharmacokinetics appear to be non-linear, with higher dosages leading to a more than proportional increase in the area under the concentration *versus* time curve (AUC) and C_{max}[60]. Saquinavir is rapidly metabolised by the cytochrome P450-3A4 isoenzyme to a number of inactive mono- and dihydroxylated metabolites[60,65]. The pharmacokinetics of saquinavir in HIV-1 infected patients with severe diarrhoea or wasting syndrome have been investigated[66]. Preliminary results indicate that plasma concentrations of saquinavir are at least equal to those achieved in healthy volunteers. Saquinavir pharmacokinetics have not been studied in patients with hepatic or renal insufficiency. Concentrations of saquinavir in the cerebrospinal fluid are negligible.

Like all protease inhibitors, a number of drug-drug interactions are reported for saquinavir. (For a review on drug-drug interactions with protease inhibitors, see reference 67). Rifampin, rifabutin, nevirapine, efavirenz, carbamazepine, phenytoin and phenobarbital decrease saquinavir concentrations to subtherapeutic levels and should not be administered concomitantly. The use of terfenadine, astemizole, and cisapride is contraindicated since saquinavir increases exposure to these drugs to possibly toxic levels.

Saquinavir concentrations are greatly improved by coadministration of ritonavir, and nelfinavir, with approximately 20- and 3-fold, respectively. This has led to widespread use of the combination of ritonavir and saquinavir (both 400 mg *bid*).

Soft gelatin formulation, Fortovase®. The newly developed soft gelatin formulation of saquinavir provides improved bioavailability of the drug. Concentrations of saquinavir in plasma are approximately 10-fold higher with the soft gelatin formulation (1,200 mg *tid*) as compared with the hard gelatin formulation (600 mg *tid*). The soft gelatin formulation of the drug should also always be taken with food. (For drug interactions and metabolism of saquinavir in this formulation, see the hard gelatin formulation).

Indinavir

Indinavir (L-735,524, MK-639, [1(1S,2R),5(S)]-2,3,5-trideoxy-N-(2,3-dihydro-2-hydroxy-1H-indeen-1-yl)-5-[2-[[1,1,-dimethylethyl)-amino]carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(fenylmethyl)-D-erytro-pentonamide, Fig. 9) is another and potent representative of the protease inhibitors. It is also recommended as part of the post exposure prophylaxis regimen. In the USA indinavir is approved by the FDA under its accelerated approval regulations for use as monotherapy or in combination with approved nucleoside analogues in patients with HIV infection. Indinavir has been approved in the European Community in October 1996.

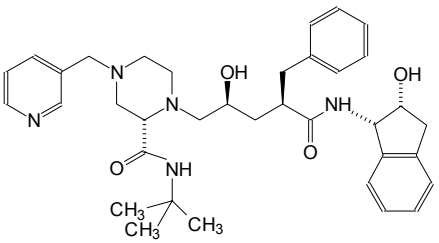

Fig. 9. *Molecular structure of indinavir.*

Initially starting from a peptide renin lead compound, a series of hydroxyethylene dipeptide inhibitors of HIV protease were developed[68,69]. Though highly potent, these compounds lack aqueous solubility and desirable pharmacokinetic properties. The incorporation of an amine resulted in hydroxyaminopentane amides, in which potent antiviral activity and acceptable bioavailability are combined[70,71].

Indinavir is rapidly absorbed with a bioavailability of approximately 30% (C_{max} values are generally reached within 1 h after administration). The drug should be ingested on an empty stomach, or with a light meal. Indinavir requires an acidic environment of the stomach and should therefore not be administered with didanosine. The plasma elimination half-life of indinavir is 1.5 h. The sulphate salt of indinavir results in smaller inter-subject variability compared to the base, and indinavir is now being administered as a sulphate. In single- and multiple-dose studies the AUC increased disproportional with dose. Little accumulation in plasma occurred following multiple doses (< 30% increase in AUC). The plasma protein binding of 60% is relatively low compared to saquinavir and ritonavir[72]. Indinavir might benefit from lower plasma protein binding; this may result in more substantial penetration into cerebrospinal fluid[64].

Possibly, women have a higher exposure to the drug as compared with men. Seven metabolites of indinavir have been detected in the urine of healthy volunteers[73]. The cytochrome P450 3A4 appears to be the major enzyme responsible for formation of metabolites. The metabolites comprised < 0.5% of the dose in the first 4 h after administration. The cumulative amount of unchanged indinavir in the urine is approximately 12% of the administered dose. Patients who use indinavir should take extra fluid to prevent the precipitation of indinavir in the kidneys.

Indinavir is an inhibitor of the cytochrome P450 enzyme system and this gives rise to a number of drug-drug interactions (see reference 67 for an overview).

Rifampin decreases indinavir concentrations to subtherapeutic levels, and should not be administered with indinavir. Indinavir (1,000 mg *tid*) can be used in combination with rifabutin (with decreasing the rifabutin dose with a factor 2). Indinavir should not be concomitantly used with terfenadine, astemizole, and cisapride due to the increase of exposure to these drugs to possibly toxic concentrations.

Ritonavir

Ritonavir (ABT-538, (2S,3S,5S)-5-[N[N-[[N-methyl-N-[(2-isopropyl-4-thiazolyl)methyl] amino]-carbonyl]valinyl]amino]-2-[N[(5-thiazolyl)methoxy-carnonyl]amino]-1,6-difenyl-3-hydroxyhexane, Fig. 10) was approved by the FDA in the USA for use alone or in combination with approved nucleoside analogues in patients with advanced HIV infection. Approval for patients with advanced HIV infection was based on data demonstrating delay in disease progression and reduction of mortality. Ritonavir was also approved by the FDA under its accelerated approval regulations for patients with early HIV infection based on a beneficial effect on surrogate parameters. In the European Union ritonavir was the first HIV protease inhibitor to be approved in August 1996 for use in combination with antiretroviral nucleoside analogue(s) in HIV-infected adult patients with advanced or progressive immunodeficiency.

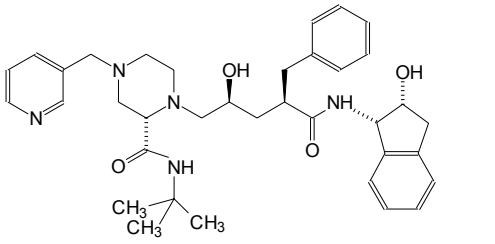

Fig. 10. *Molecular structure of ritonavir.*

The pharmacokinetics of ritonavir were studied in two groups of HIV-1 infected patients[74]. Ritonavir was administered under fasting conditions in single oral doses of 100, 200, 400, 600, 800, and 1,000 mg. C_{max} and AUC of ritonavir increased non-linearly with the mean normalised (100 mg) C_{max} and AUC increasing from 0.416 µg/mL and 3.480 µg·h/mL at 100 mg to 1.27 µg/mL and 12.31 µg·h/mL at 1,000 mg, respectively. The mean T_{max} ranged from 3.8 h for 100 mg to 3.1 h for 1,000 mg. The nonlinear increase of C_{max} and AUC was attributed to saturable first-pass metabolism. The major elimination pathway of ritonavir is by cytochrome P450 3A4 and, to a lesser extent, cytochrome P450 2D6 related metabolism[75]. Four metabolites have been identified in humans and only one, the isopropylthiazole oxidation metabolite, has been found in the systemic circulation and seems to be as active as the parent compound[75]. After oral administration, 20% to 40% of unchanged ritonavir is recovered in human faeces[75]. Renal clearance of ritonavir is less than 2 mL/min. The half-life of ritonavir is approximately 3 - 5 h.

The pharmacokinetics of the currently recommended dose (600 mg *bid*) in 10 HIV-1 infected patients have been characterized[76]. A C_{max} of 11.2 µg/mL after 3.3 h, an AUC of 60.8 µg·h/mL and a trough plasma concentration of 3.03 µg/mL were reported. The half-life of ritonavir was 3.2 h with an apparent clearance of the drug of 8.9 L/h. With this recommended dose regimen ritonavir plasma concentrations were above the targeted effective concentration (based on *in vitro* data, the functional 90% effective concentration, after adjustment for binding to protein, is 2·1 µg/mL)[76].

Ritonavir is approximately 99% bound to plasma proteins. Limited data in patients showed that ritonavir is present in very low concentrations in the cerebrospinal fluid, reflecting the free concentration in plasma[75]. No effect on relative bioavailability was detected when ritonavir oral liquid formulation was administered with either water, Advera®, Ensure®, or chocolate milk in healthy volunteers[77]. The oral bioavailability in humans has not been reported. Subgroup analyses revealed a significant reduction of the AUC of 18% in smokers versus non-smokers. Another subgroup analysis of patients with high versus low body weight revealed that AUC values did not correlate with body weight[75].

Ritonavir shows autoinduction of its metabolism, and the dosage of the drug is gradually increased after start of therapy, generally from 300 mg *bid* during the first 3 days, to 400 mg and 500 mg *bid* during the subsequent two periods of three days. Finally, the dosage for ritonavir is increased to 600 mg *bid*. Due to its potent inhibition of the metabolism of other protease inhibitors, ritonavir is increasingly being coadministered with saquinavir, indinavir and nelfinavir.

Ritonavir is a potent inhibitor of cytochrome P450 isozyms 3A4 and 2D6. Furthermore, ritonavir induces several hydroxylation and glucuronidation steps, making this drug prone to many drug-drug interactions. (For an extensive review on drug-drug interactions with ritonavir,[67]).

Nelfinavir

Nelfinavir (AG1343, (3S,4aS,8aS)-N-tert-butyl-2-[(2R,3R)-3-(3,2-cresotamido)-2-hydroxy-4-

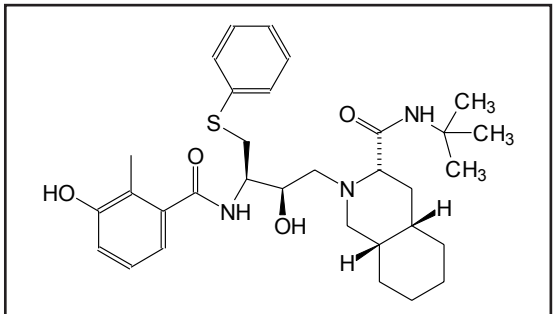

Fig.11. *Molecular structure of nelfinavir.*

(fenylthio)-butyl] decahydro-3-isochinolinecarboxamide, Fig. 11) is the most recently licensed protease inhibitor for the treatment of HIV-1 infection.

Maximum plasma concentrations of nelfinavir are reached approximately 3.5 h after administration of the drug[78-80]. The absorption of nelfinavir is reduced when taken on an empty stomach. Preferably, the drug should therefore be ingested with food. Nelfinavir is extensively bound to plasma proteins (98%) and shows poor penetration of the cerebrospinal fluid. Nelfinavir is extensively metabolised by the cytochrome P450 enzyme system and two active metabolites have been identified: One with anti-HIV activity comparable to the parent compound, and one with an activity in the range of 10-20% of the parent compound[81].

Nelfinavir is metabolised by 4 isozymes of the cytochrome P450 system: 3A4, 2C19, 2C9, and 2D6. The mean elimination half-life of nelfinavir is between 3.5 and 5 h, and the drug can most likely also be administered in a *bid* dosing regimen (1,250 mg *bid*) as well as in the licensed dosage of 750 mg *tid*.

Nelfinavir acts as an inhibitor of cytochrome P450 enzymes and shows a number of drug-drug interactions (see reference 80 for an overview). Of note, nelfinavir shows also some liver enzyme inducing properties, causing a decrease of ethinyl estradiol concentrations when this drug is concomitantly administered. Concentrations of nelfinavir are decreased when administered with rifampin, and these drugs should not be administered together. When concomitantly given with rifabutin, the rifabutin dose should be halved, and the dosage of nelfinavir should be increased to 1,000 mg tid. Nelfinavir should not be administered with amiodarone, astemizole, cisapride, quinidine, ergot derivatives, midazolam, triazolam, and terfenadine, as nelfinavir may increase concentrations of these drugs to possibly toxic levels.

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