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Concise overview of the clinical pharmacokinetics of dideoxynucleoside antiretroviral agents

David M. Burger, Pieter L. Meenhorst and Jos H. Beijnen

Introduction

In this paper a concise review will be given of the clinical pharmacokinetics of the dideoxynucleoside antiretroviral agents zidovudine (AZT, Retrovir®), didanosine (ddl, Videx®) and zalcitabine (ddC, Hivid®) (Fig. 1). These agents have now been licensed in most European countries for the treatment of infection with the human immunodeficiency virus (HIV), the causative agent of the acquired immunodeficiency syndrome (AIDS). Zidovudine delays progression of HIV infection and prolongs survival in patients with AIDS [1]. Switching from zidovudine to didanosine [2-3] or to zalcitabine [4] therapy has been shown to be clinically beneficial after prolonged use of zidovudine, whereas combination therapy with zidovudine and didanosine [5] or with zidovudine and zalcitabine [6] results in more prolonged increases in CD4⁺ T-lymphocyte counts than with these agents in monotherapy. Therefore, these three drugs will remain the mainstay of antiretroviral drug treatment for the near future and a thorough knowledge of the clinical pharmacokinetics is needed to optimize their therapeutic use. In this short review special attention will be paid to possibly altered pharmacokinetics in special circumstances, such as hepatic and renal dysfunction, pregnancy, stage of disease, etc. The relevance of therapeutic drug monitoring of antiretroviral agents to support the pharmacotherapy of patients with HIV infection is discussed at the end of this review. Related reviews on this subject can be found in the literature [7-12]. A summary of the pharmacokinetic parameters of the three drugs is presented in Table 1. A review of possible drug-drug interactions involving antiretroviral agents will be the subject of a forthcoming paper.

Zidovudine

Absorption

Zidovudine is rapidly and completely absorbed after oral administration, but first-pass metabolism reduces the oral bioavailability to about 65%. Several investigators have demonstrated that concomitant ingestion of zidovudine capsules with food influences the pharmacokinetic parameters of zidovudine [13-16]. A high-fat meal [13], breakfast [14-16], or a protein-rich meal [15] reduces the maximum plasma concentration (C_{max}) of zidovudine and delays the time to achieve C_{max} (t_{max}). However, the total absorption of zidovudine [measured as the area under the concentration-time curve (AUC)] was only slightly, or not, diminished in these studies, which had a sufficient sampling interval to calculate the AUC [14-16]. Although patients prefer the ingestion of zidovudine capsules with food to avoid gastrointestinal side-effects, this cannot be recommended as long as the relevance of decreased C_{max} levels has not been established.

A decreased absorption of zidovudine has been

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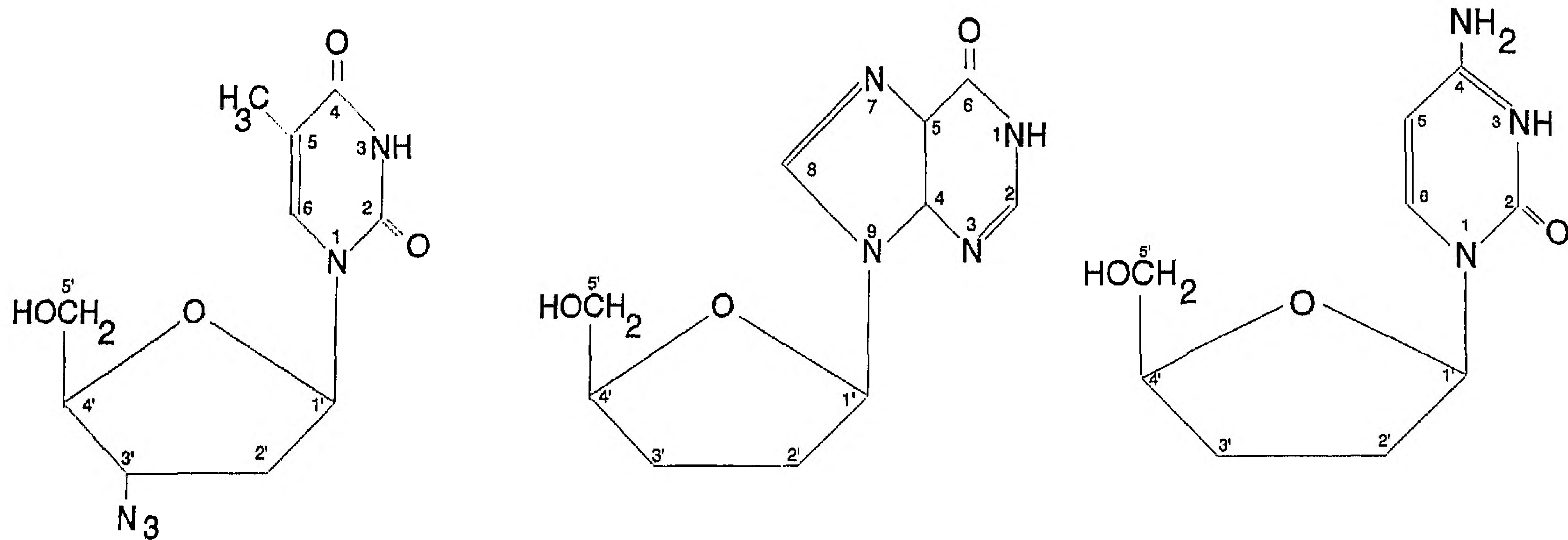
Keywords

Didanosine
Pharmacokinetics
Therapeutic drug monitoring
Zalcitabine
Zidovudine

Abstract

In this paper aspects of the clinical pharmacokinetics of the antiretroviral agents zidovudine, didanosine and zalcitabine are reviewed. Special attention is paid to possibly altered pharmacokinetics in special circumstances, such as hepatic and renal dysfunction, pregnancy, stage of disease, etc. The dideoxynucleoside antiretroviral agents have some clinical pharmacokinetic properties in common (rapid absorption and elimination), but substantial differences exist in their degree of absorption, metabolism and penetration into the cerebrospinal fluid. All agents display wide interpatient variability in pharmacokinetic parameters. The relevance of therapeutic drug monitoring of antiretroviral agents is also discussed.

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▲ **Figure 1**
Zidovudine (left), didanosine (centre) and zalcitabine (right)

found in patients with mild to severe diarrhoea [17; Kapembwa *et al*, unpublished observations]. Because zidovudine is relatively water soluble, differences in gastrointestinal transit time are thought to be the underlying mechanism of this decreased absorption pattern [17].

Distribution

Plasma protein binding of zidovudine is low, 7-38%. Zidovudine is widely distributed throughout body water and tissues, with a volume of distribution at steady state (V_{ss}) of approximately 1.8 l/kg. It has been hypothesized that V_{ss} is lower in patients with AIDS than in asymptomatic HIV-infected individuals. The reason for this difference is unclear, but may be related to disease-induced changes in body composition [18]. The resulting higher plasma concentrations of zidovudine in patients with more advanced disease may then lead to greater toxicity.

The distribution of zidovudine into specific compartments has been the subject of several investigations. The distribution of zidovudine into semen has been associated with a decreased detection of HIV in the semen of men with CD4 counts lower

than 200 per μ l [19]. Zidovudine distribution into saliva [20] is of particular interest because the ease of collection and avoidance of blood handling could make saliva a favourable matrix for therapeutic drug monitoring.

Zidovudine crosses the placenta and has been measured in neonatal blood [21-23]. It is not yet known whether pregnancy affects the pharmacokinetics of zidovudine. In one study, an increase in V_{ss} and in zidovudine clearance during pregnancy was explained by the usual increase in body weight, plasma volume and renal and hepatic blood flow seen during pregnancy [21]. The pharmacokinetics of zidovudine were also monitored 3-4 weeks post-partum and at that time the pharmacokinetic parameters were no longer different from those reported in HIV-infected men. In another study, pharmacokinetic parameters during pregnancy were similar to those reported in HIV-infected men [22]. It should be noted that this comparison does not account for any influence of sex on the clearance of zidovudine. It is still not known whether zidovudine penetrates into breast milk.

Finally, an important compartment in zidovudine pharmacokinetics is the cerebrospinal fluid (CSF). Zidovudine has been measured in CSF in relatively high concentrations [24]. This supports a role for zidovudine in the treatment and prevention of HIV-related neurological disorders.

Table 1 Pharmacokinetic parameters [7-12]

Parameter*	Zidovudine	Didanosine	Zalcitabine
F (%)	65	40 -50	80
C_{max} (mg/l)	0.5-1	0.8- 1.2	0.010-0.015
t_{max} (h)	0.5-1	1	1
$t_{1/2}$ (h)	1	1-2	1-2
CL ($l \cdot h^{-1} \cdot kg^{-1}$)	1.5-2.0	1	0.2 -0.3
V_{ss} (l/kg)	1.5-2.5	0.8- 1.2	0.5
PB (%)	20	<5	<5
f_{ur} (%)	15 -20	10-40	75

*F: oral bioavailability; C_{max} : maximum plasma concentration [plasma levels at t_{max} after standard oral doses of zidovudine (200 mg), didanosine (200 mg) or zalcitabine (0.75 mg)]; t_{max} : time to maximum concentration; $t_{1/2}$: terminal elimination half-life; CL: total body clearance; V_{ss} : steady-state volume of distribution; PB: protein binding; f_{ur} : urinary recovery of parent drug.

Metabolism and excretion

Zidovudine is extensively metabolized in the liver to the inactive glucuronide of zidovudine, which is excreted renally (Fig. 2). Its elimination half-life is similar to that of the parent compound (≈ 1 h), which may indicate formation-limited elimination of zidovudine glucuronide. Zidovudine glucuronide concentrations in plasma are usually higher than those of zidovudine, probably due to a smaller V_{ss} for zidovudine glucuronide. Approximately 15-20% of an oral zidovudine dose is excreted unchanged in the urine and approximately 75% as zidovudine glucuronide. Extrahepatic metabolism of zidovudine to zidovudine glucuronide has been demonstrated in human renal and gut microsomes [25].

It has been assumed for a long time that zidovudine glucuronide is the only metabolite of zido-

vudine; however, it has recently been demonstrated that two other metabolites of zidovudine can be found in plasma, namely, 3'-amino-3'-deoxythymidine and its glucuronide, which are formed by the reduction of the azido moiety in zidovudine and zidovudine glucuronide [26].

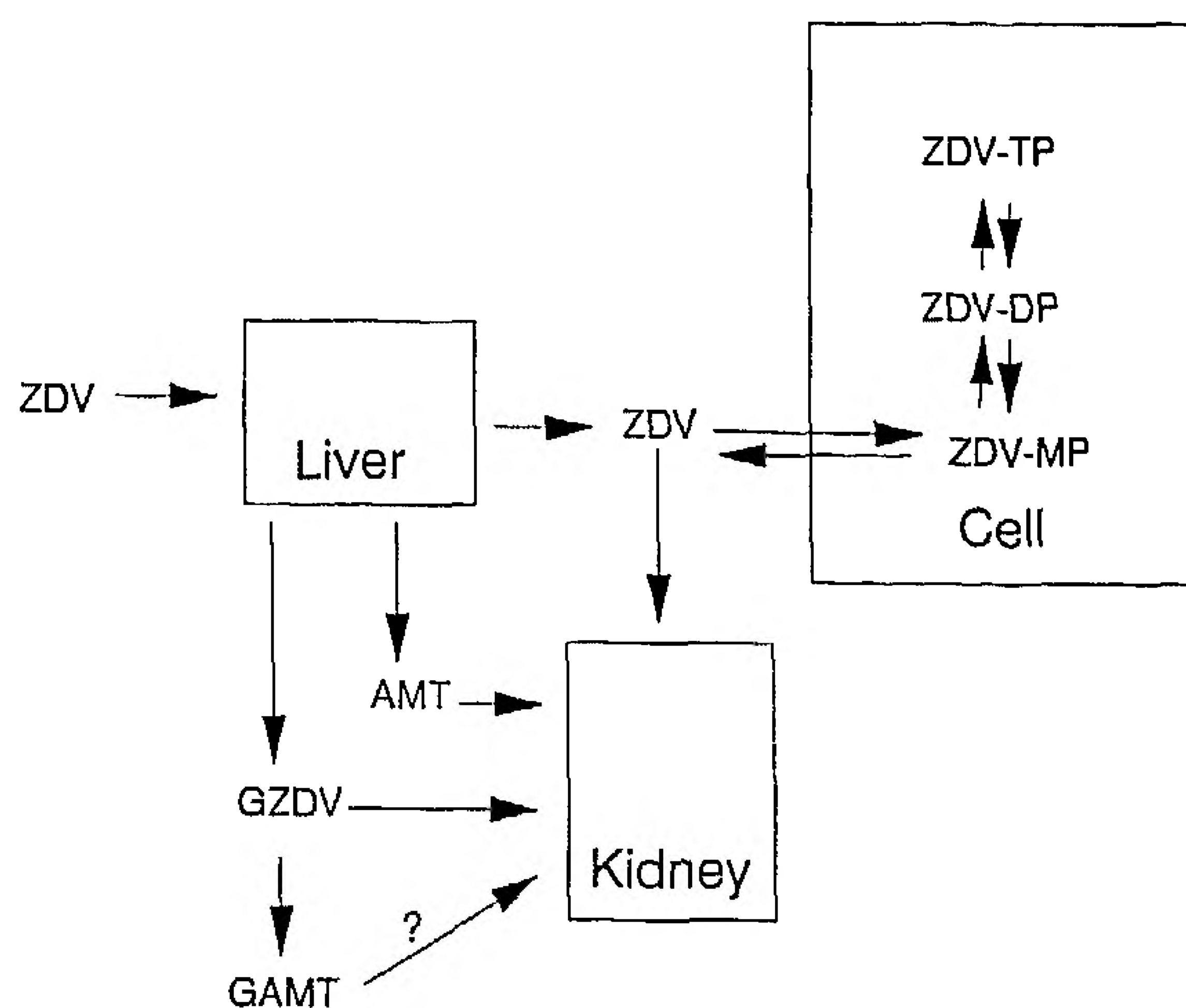
On the basis of the pharmacokinetic profile of zidovudine, it can be expected that zidovudine elimination is decreased in hepatic dysfunction, but not, or only marginally, in renal dysfunction. This statement requires some refinement. A reduced clearance of zidovudine has indeed been found in patients with various types of liver disease [27-28]; however, there are also data that the elimination half-life ($t_{1/2}$) of zidovudine is prolonged and that the clearance is reduced in patients with severe renal impairment [29-31]. The reduction in clearance appears larger than the expected 15-20% contribution of the kidneys to the total body clearance. Zidovudine glucuronide levels are very high in patients with severe renal dysfunction. Haemodialysis removes zidovudine glucuronide from plasma, but it has only a marginal effect on zidovudine levels. Because of the reduced clearance of zidovudine and the negligible effect of haemodialysis on zidovudine levels, patients with end-stage renal disease and haemodialysis should receive lower doses than patients with normal renal function.

Besides impaired hepatic or renal function, several other factors potentially influence the clearance of zidovudine. An altered pattern of drug metabolism has been observed in patients with AIDS compared with asymptomatic patients or HIV-negative controls [32]. The zidovudine $t_{1/2}$ is increased to approximately 15 h in neonates, and levels of zidovudine and zidovudine glucuronide are nearly equal in neonatal plasma [21-22]. However, the glucuronidation system rapidly matures and zidovudine pharmacokinetics becomes similar in adults and in infants aged about 1 month [33]. Data on zidovudine clearance in the elderly are scarce, but type-2 metabolic processes, such as glucuronidation, are usually not age-dependent [34].

Didanosine

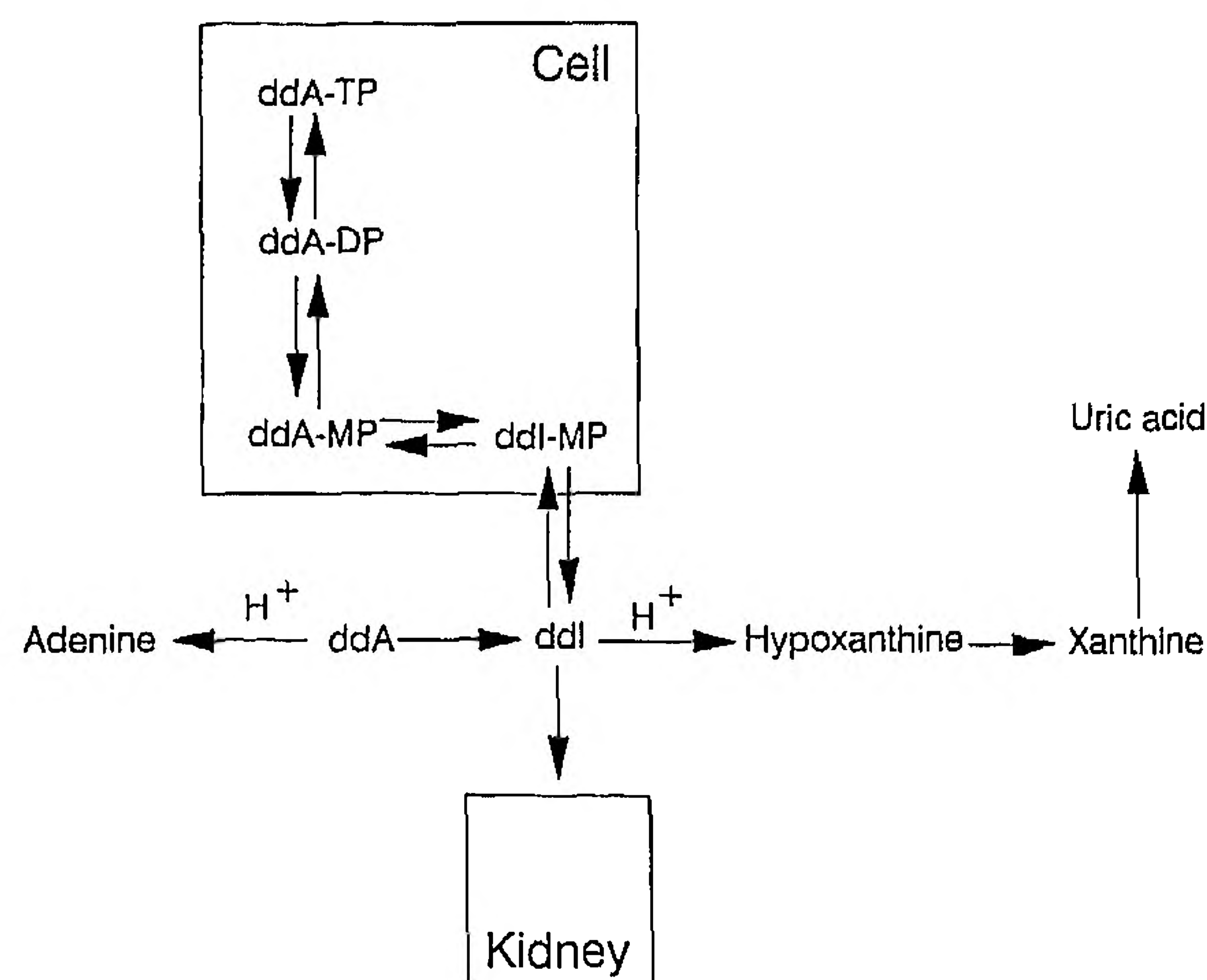
Absorption

The *N*-glycosidic bond of didanosine is very acid labile and in the presence of acid didanosine degrades into hypoxanthine and dideoxyribose (Fig. 3). The degradation of didanosine in acid (pH 3) is very rapid and only 10% of the parent drug remains after 10 min at 37°C [35-36]. Therefore, to achieve sufficient bioavailability, didanosine has to be administered to fasting patients in combination with antacid. The bioavailability of the currently available didanosine formulations is 40% and 50% for sachets and chewable/dispersible tablets, respectively. Despite frequent gastrointestinal complaints after ingestion of the didanosine tablets, it must be strongly recommended that didanosine should not be taken with food because this reduces the bioavailability of didanosine by 50% [37]. In phase-I studies, bioavailability was dose-dependent, suggesting saturation of intestinal transport mechanisms or increased degradation in the stomach. In all pharmacokinetic



▲ **Figure 2**

Metabolic and elimination pathways of zidovudine (ZDV). GZDV: zidovudine glucuronide; AMT: 3'-amino-3'-deoxythymidine; GAMT: 3'-amino-3'-deoxythymidine glucuronide; MP: monophosphate; DP: diphosphate; TP: triphosphate



▲ **Figure 3**

Metabolic and elimination pathways of didanosine (ddI). ddA: 2',3'-dideoxyadenosine; MP: monophosphate; DP: diphosphate; TP: triphosphate

studies, wide interpatient variability was observed in didanosine bioavailability.

Distribution

Protein binding of didanosine is less than 5%. The V_{ss} is about 1.0 l/kg, indicating that it is distributed to tissues less than zidovudine, which is possibly due to differences in lipid solubility. As is the case with zidovudine, knowledge of didanosine distribution into specific compartments is relevant, although there are fewer data on this topic for didanosine. Pregnancy did not appear to influence the V_{ss} of didanosine in two HIV-infected women [38]. Didanosine crosses the placenta, but placental/foetal concentrations are only 20-50% of maternal concentrations because of placental metabolism [38-39]. Studies of the penetration of didanosine into the CSF have been hampered by the relatively high detection limits of available analytical methods. Experience with CSF analyses at our laboratory indicates that didanosine levels are 30-50 ng/ml 4 h after a dose of 250 mg. CSF concentrations of zidovudine are usually two times higher.

Metabolism and excretion

The total body clearance of didanosine is approximately $1.0 \text{ l}\cdot\text{h}^{-1}\cdot\text{kg}^{-1}$ with 30-50% renal clearance. The remaining, non-renal clearance is attributed to metabolism and/or biliary excretion. Extensive metabolism occurs, via three different metabolic pathways, leading to dideoxyadenosine triphosphate, the active intracellular form, uric acid and purine in the purine metabolic pool. *In vitro* conversion to hypoxanthine has been found in erythrocytes, indicating that blood samples should be centrifuged immediately after collection [40].

As expected, didanosine clearance is reduced in patients with renal dysfunction [41]. Haemodialysis removes didanosine from plasma, although a 4 h dialysis removes only 20% of the didanosine dose. Although more data are required, it appears that daily administration of 125 mg in tablets is a reasonable option in patients with end-stage renal failure. While the manufacturer recommends that a reduction in dosage should be considered in patients with hepatic dysfunction, there are no data available to support this. The pharmacokinetic parameters of didanosine appeared to be similar in children and adults, with the exception of a lower bioavailability in children, although this might be related to inadequate antacid doses [42].

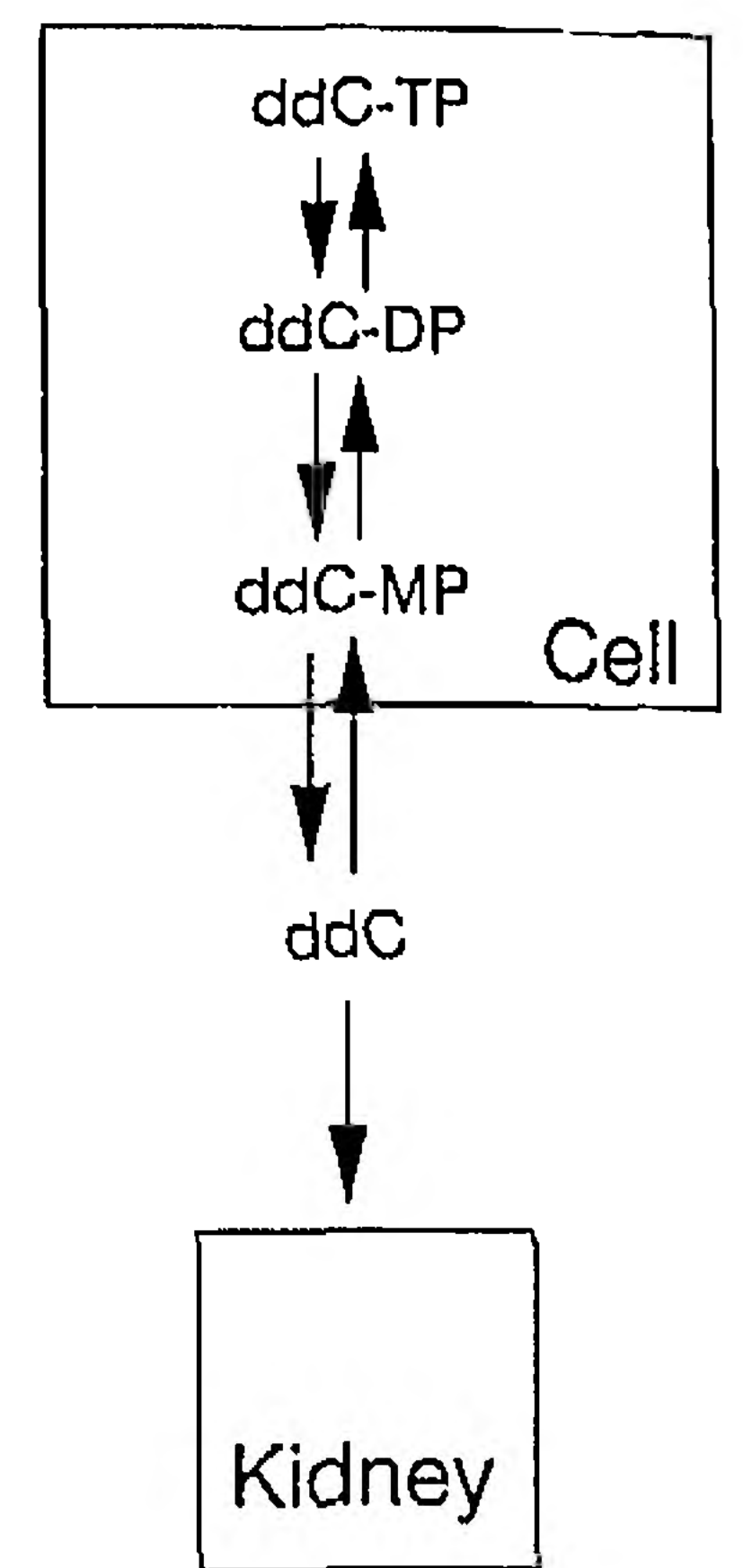
Zalcitabine

Absorption

Usually, zalcitabine is rapidly and almost completely absorbed with a bioavailability of 70-90%. Food reduces the rate and extent of absorption.

Distribution

Protein binding of zalcitabine is less than 4%. V_{ss} is about 0.5 l/kg, which is considerably lower than for zidovudine or didanosine. Zalcitabine concentrations in the CSF are usually below the detection limit of high-pressure liquid chromatography methods, but using combined chromatographic-mass spectro-



▲ **Figure 4**

Metabolic and elimination pathways of zalcitabine (ddC). MP: monophosphate; DP: diphosphate; TP: triphosphate

metric techniques zalcitabine concentrations in the CSF of 6-11 ng/ml could be detected 2-3.5 h after the start of a 1 h infusion.

Metabolism and excretion

So far, no hepatic metabolites of zalcitabine have been identified in humans (Fig. 4). A deamination product, dideoxyuridine, has been found in the plasma, urine and CSF of monkeys [43]. Because of the predominant renal elimination pathway of zalcitabine, it can be expected that zalcitabine clearance depends on creatinine clearance. A population pharmacokinetic study demonstrated that zalcitabine clearance was related to creatinine clearance and to body weight [44]. The pharmacokinetics of zalcitabine are similar in children and in adults.

Therapeutic drug monitoring of antiretroviral agents

For several reasons, the dideoxynucleosides are good candidates for therapeutic drug monitoring. First, interpatient variability in pharmacokinetic parameters is large and this makes the dose a less reliable parameter of drug exposure than the plasma concentration. Furthermore, the toxicity of dideoxynucleoside agents is significant and this leads to a narrow therapeutic window. However, a therapeutic range has not been defined for any of the drugs so far. This is mainly due to the difficulty of measuring the pharmacodynamics of antiretroviral agents. The primary endpoint of antiretroviral therapy is a reduction in mortality, but the short-term effects are only measurable by monitoring surrogate markers, such as CD4 count, p24-antigenaemia and HIV viraemia. In addition, the clinical response can also be measured as weight gain, decreased energy and reduction of the incidence of opportunistic infections, but these are rather unspecific endpoints which also depend on, for example, chemoprophylaxis. Furthermore, drug-related toxicity is common in HIV-infected patients, which makes it difficult to attribute a specific toxic effect to one drug. It is also known that side-effects

may depend on the stage of disease, as has been shown for anaemia induced by zidovudine.

Thus, therapeutic drug monitoring is justified on the grounds of the pharmacokinetic properties of the antiretroviral agents, but is hindered by unspecific or surrogate measurements of antiviral efficacy and toxicity. Nevertheless, there are indications that relationships between pharmacokinetic and pharmacodynamic parameters exist. Although Balis *et al.* could not demonstrate a relationship between plasma or CSF levels of zidovudine and a change in full-scale IQ scores in HIV-infected children, a significant relationship between the steady-state concentration of zidovudine after continuous infusion and the development of neutropenia was observed [45]. Preliminary data show that relationships exist between zidovudine concentrations and increases in CD4 counts [Chiang H *et al.*, unpublished observations] and between zidovudine concentrations and anaemia in children [46].

For didanosine, these pharmacokinetic-pharmacodynamic relationships have been studied in more detail than for zidovudine. These studies have used data from several phase-I trials that evaluated a wide range of didanosine doses for efficacy and toxicity. Drusano *et al.* demonstrated a significant correlation between cumulative didanosine exposure and suppression of circulating p24 antigen [47]. An increase in CD4 count was better related to the starting CD4 count than to the AUC of didanosine. Baltangady *et al.* used the average steady-state plasma concentration (C_{ss}), calculated by dividing the average daily dose by the apparent oral didanosine clearance and related this to the effects of didanosine on CD4 count, p24 antigenaemia and weight gain in 61 patients in a 12-week phase-I trial [48]. Significant relationships between didanosine exposure and clinical outcome were observed. Preliminary data also suggest that the risk of pancreatitis was related to the C_{ss} of didanosine in these phase-I trials [49]. Finally, Balis *et al.* showed that the p24 response and a change in full-scale IQ scores were positively related to the AUC of didanosine in HIV-infected children [42].

On the basis of these observations, it appears rational to study the concept of therapeutic drug monitoring for antiretroviral agents in more detail in prospective studies. This should, ultimately, result in the definition of a therapeutic range. This concept is currently under investigation for 3'-deoxy-3'-fluorothymidine in a so-called concentration-controlled trial [Flexner C, unpublished observations]. Instead of escalating doses, patients are monitored for escalating target concentrations. With this approach, a therapeutic range might be defined before the drug is licensed. For already registered agents, extensive post-marketing studies are urgently required to obtain more knowledge of pharmacokinetic-pharmacodynamic relationships.

It could be hypothesized that a relationship between the plasma concentration of any antiretroviral agent and its antiviral efficacy can never be found because it is the intracellular triphosphate form that is the active species. For zidovudine, the total intracellular concentration of phosphorylated zidovudine in a single blood sample was not related to the plasma concentration of zidovudine [50].

However, it should be stressed that the triphosphate form was not determined separately. In addition, a subsequent study from the same investigators demonstrated a significant relationship between the AUC of intracellular total phosphorylated zidovudine and the AUC of zidovudine in plasma [51]. Analytical methods for the measurement of intracellular zidovudine triphosphate have been developed during the last years, but these are extremely labour intensive and require large volumes of blood from patients [52-53]. For these reasons, the measurement of intracellular triphosphates of antiretroviral drugs in samples from individual patients is not an acceptable option for future large population studies on the relationships between pharmacokinetic and pharmacodynamic parameters. Furthermore, the above-described results for zidovudine and didanosine demonstrate that plasma concentrations are related to antiviral efficacy and toxicity, although more studies are needed to cast more light on this issue.

Conclusions

The dideoxynucleoside antiretroviral agents have some clinical pharmacokinetic properties in common (rapid absorption and elimination), but substantial differences exist in metabolism, acid lability and penetration into the CSF. All agents display wide interpatient variability. Knowledge of the pharmacokinetic characteristics is of utmost importance to further understand the clinical effects of this class of agents. Concentration-controlled clinical trials should be included in the drug development process of all new agents. Prospective, post-marketing studies with approved drugs are needed to determine a possible therapeutic range.

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