higher than in patients with normal renal function (intradialysis, 59.9 ng/ml and > 24 hours; interdialysis, 81.9 ng/ml and 18 hours vs. 17.5ng/ml and 1 hour) (Dando and Plosker, 2003).

As the pharmacokinetic properties of adefovir in patents with moderate to severe hepatic impairment are similar to those of healthy volunteers, no dose adjustment is required in those with hepatic impairment.

5e. Drug interactions

At concentrations significantly higher than doses used *in vivo* (> 4000-fold), adefovir does not inhibit any of the following human liver CYP450 isoenzymes: CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 (Gilead Sciences, 2007). High doses of adefovir have been reported to inhibit CYP3A4 (Nekvindova *et al*., 2006).

Because adefovir is excreted through the kidneys, co-administration of adefovir with other drugs that are eliminated by or alter renal tubular excretion may increase serum concentrations of either drug (see Table 255.8).

6. ADVERSE REACTIONS AND TOXICITY

Adefovir in a dose of 10 mg is generally well tolerated, but its prolonged use may result in different side effects.

6a. Renal toxicity

Nephrotoxicity is the main side effect of adefovir, and it usually manifests as renal dysfunction, defined either as an increase in serum creatinine by > 0.5 mg/dl above baseline (Marcellin *et al*., 2003) or a decrease in glomerular filtration rate to < 50 ml/min (Ha *et al.,* 2009); or as proximal tubular dysfunction manifesting as hypophosphatemia.

Early studies assessing the renal safety of adefovir 10 mg daily are based on the integrated safety assessment of participants of clinical trials. There are no significant numbers of patients experiencing renal impairment after a median treatment duration of 15 months (Izzedine *et al*., 2004). Even if renal dysfunction occurs, it is completely reversible on discontinuation of adefovir (Yuen and Lai, 2004), or by dose reduction (Marcellin *et al*., 2003).

It is no surprise that more recent real-life data found renal dysfunction was more frequent during prolonged therapy. A study involving 292 patients with a median treatment duration of 64 months found that 9.6% developed renal impairment with glomerular filtration rate decreasing to < 50 ml/minute. Old age, preexisting cirrhosis and presence of hypertension were determinants of renal dysfunction (Tanaka *et al.,* 2014). Another cohort study compared 145 adefovir-treated patients with 145 patients unexposed to adefovir, matched by age, gender, and baseline glomerular filtration rate. The incidence of renal dysfunction was 5 cases per 100 patient-years. When compared to the unexposed group, the relative risk of renal dysfunction in adefovir-treated patients was 3.7 (95% confidence interval [CI]: 1.1–19.3). Adefovir exposure was an independent significant predictor of renal dysfunction, although age > 50 years and presence of diabetes or hypertension were also borderline significant factors (Ha *et al.,* 2009). Old age was found to be the most important risk factor in another study involving a large number of cirrhotic patients (Kim *et al.,* 2012). These studies illustrates adefovir-driven nephrotoxicity to be less of a concern in young healthy individuals (i.e. those who would participate in drug registration trials), but would be an important concern in older patients, cirrhotic patients, and patients with different co-morbidities.

Current international guidelines currently recommend monitoring of serum creatinine every 3 months in patients with medical conditions predisposing them to renal impairment and in all patients on adefovir for more than 1 year. More frequent monitoring is needed in the presence of pre-existing renal insufficiency (Lok and McMahon, 2009).

6b. Hypophosphatemia

Proximal renal tubular dysfunction is present in 15% of patients treated with long-term adefovir, clinically manifesting

Table 255.8. Drug interactions with adefovir.

Interacting drug	Nature of interaction
Lamivudine	No interaction
Zidovudine, efavirenz, nevirapine, didanosine	No interaction with adefovir doses 6–12 times that of normal 10-mg dose; didanosine AUC increased by 29% but not clinically significant
Tenofovir	No interaction
Saquinavir, delavirdine	When 120-mg dose of adefovir was combined with saquinavir and delavirdine or delavirdine alone, the concentrations of saquinavir and delavirdine were reduced by 50%; adefovir (60 mg) AUC increased by 20% in presence of saquinavir but not clinically significant
Trimethoprim–sulfamethoxazole	No interaction
Paracetamol	No interaction
Ibuprofen (800 mg three times day)	Increased adefovir C_{max} (33%) and AUC (23%) but not clinically significant; this increase appears to be due to higher oral bioavailability rather than a reduction in renal clearance
Tacrolimus	No interaction

Abbreviations: AUC: area-under-the-concentration-time curve; C_{max}: maximum concentration.
Source: Data compiled from Fletcher *et al*. (2000), Baxter (2006), Perronne (2006), and Terrault *et al*. (2009).