

gene develop extensive calcifications of the vascular system and other soft tissues [2]. However, several clinical observations revealed a positive association between OPG and vascular calcification, the advancement of coronary artery disease expressed semi-quantitatively and even mortality [3–6]. Some authors suggested that serum OPG may be the marker of low-turnover bone disease, which in turn is a well-recognized risk factor for developing vascular calcification [7–8]. Further studies are needed to clarify the role of OPG in vascular calcification and atherosclerosis, but in our opinion this factor may link these processes with bone metabolism. In summary, our study confirms the lack of an association between aortic stiffness and fetuin-A in end-stage renal disease patients, found previously by Hermans *et al.* [1]. The correlations between PWV and serum OC and OPG identified in univariate analysis may indicate the relationship between aortic stiffness and bone turnover. This observation appears to be the first ever in this issue performed exclusively in patients treated with PD.

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Reply

We thank Stompór *et al.* for sharing their valuable observations. Indeed, the presence of relations between vascular wall properties and markers of bone turnover, and disappearance of these relations in multivariate analysis are in agreement with our observations. However, it should be mentioned that, although vascular stiffness is related to vascular calcification, it is not synonymous. Neither Dr Stompór nor we assessed vascular calcifications directly. Several other factors beyond calcification also influence aortic stiffness, such as blood pressure, age, etc. In ESRD patients, a negative association between serum fetuin-A levels and coronary artery calcification (CAC) [1] and heart valve calcification [2] was recently observed. Interestingly, in diabetic patients with chronic kidney disease (CKD), the association between fetuin-A and CAC was positive [3].

Thus, vascular calcification in dialysis patients and patients with CKD is a complex, only partially understood and sometimes seemingly paradoxical phenomenon. It would be of interest to assess the relation between the parameters studied by Stompór *et al.* and vascular wall properties in a young dialysis or CKD population. This group has far less traditional cardiovascular risk factors that potentially obscure the association between arterial stiffness and arterial calcification.

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Letters

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Pharmacokinetics and dosage adjustment of oseltamivir and zanamivir in patients with renal failure

Sir,

In the last few months, more and more countries in Asia, Europe and Africa have reported cases of avian influenza in migrating birds as well as in cats and humans. The virus has expanded its geographical area, being propagated to new countries, and increasing, as a result, the size of the population at risk. As of 21 April 2006, the World Health

Organization (WHO) has reported 204 confirmed human cases of influenza A (H5N1) across nine countries, with 113 deaths (a 55% mortality rate for identified cases) [1].

Chronic renal insufficiency is frequently encountered in the general population. In the US adult population, the prevalence of chronic kidney disease is 11%. In this study, 3.0% had a glomerular filtration rate [estimated with Modification of Diet in Renal Disease (MDRD) prediction equation] <80 ml/min/1.73 m², 4.3% had <60 ml/min/1.73 m², 0.2% had <30 ml/min/1.73 m² and 0.2% had <15 ml/min/1.73 m² [2].

The neuraminidase inhibitors oseltamivir and zanamivir are active against H5N1. In the context of epidemia or pandemia of avian influenza, these two drugs will be prescribed to patients presenting a reduction in renal function. Clinicians should thus be aware of the pharmacokinetics and potential dosage adjustments of those drugs in such patients. According to available data in the literature, we provide guidelines for dosage adjustment of oseltamivir and zanamivir in patients with altered renal function.

Oseltamivir

H5N1 virus is susceptible to oseltamivir *in vitro*. Moreover, oral oseltamivir is active in animal models of influenza A (H5N1) [3]. However, there is no clear evidence showing that oseltamivir may be effective in human H5N1 disease. Despite the absence of clinical trial, oseltamivir is recommended by the WHO for use in both treatment and prophylaxis of H5N1 infection [3]. The evidence of the effectiveness of oseltamivir for prophylaxis of H5N1 infection is based on the results of trials on the prevention of ordinary influenza. The recommended dose in adults with normal renal function is 75 mg twice a day for 5 days for curative treatment and 75 mg once a day for preventive treatment.

Oseltamivir is extensively converted by hepatic esterases to its active metabolite, oseltamivir carboxylate. Neither oseltamivir nor oseltamivir carboxylate are substrates for, or inhibitors of, cytochrome P450 isoforms. Renal elimination of oseltamivir carboxylate accounts for more than 99% of the administered dose. Renal clearance (313.3 ml/min) occurs through both glomerular filtration and tubular secretion [4]. It is therefore suggested that it is necessary to adjust oseltamivir dosage in patients with renal impairment. Indeed, the pharmacokinetics of oseltamivir are modified in patients with renal failure. The clearance of the parent compound and its metabolite decrease proportionally with the reduction of creatinine clearance (CrCl). The area under the serum concentration–time curve (AUC) of the active metabolite was on average increased 10-fold in patients with severe renal impairment (CrCl <30 ml/min) as compared with individuals without renal impairment [4].

Although increased drug exposure is not associated with poor tolerance, dosage adjustment is recommended for patients with CrCl <30 ml/min. For patients with CrCl between 15 and 30 ml/min (stage 4), a dosage reduction of 50% (75 mg once daily in curative treatment and 75 mg every other day in prophylactic treatment) is recommended [5]. There are no data on the pharmacokinetics and/or the tolerance of oseltamivir in patients with CrCl <15 ml/min and in patients on dialysis. It is therefore impossible to provide recommendations for dosage adjustment in those patients (Table 1). In severe infection, higher doses (150 mg twice a day for adults) and treatment for 7–10 days are recommended [3]. If the administration of such doses is necessary, it is recommended to apply the same dosage reductions (Table 1). Oseltamivir is generally well-tolerated, but gastrointestinal side effects and dizziness may appear with increasing doses, particularly in patients with renal failure.

Zanamivir

Zanamivir is another neuraminidase inhibitor which may be recommended for the treatment of H5N1 influenza. Topical zanamivir is active in animal models of influenza A (H5N1) but has not been studied in humans with influenza A (H5N1) [3]. Nevertheless, treatment with nebulized zanamivir has been recommended in patients with H5N1 infection and with resistance to oseltamivir [6]. The recommended dosage of zanamivir by oral inhalation is 10 mg twice a day for 5 days.

Zanamivir is formulated as a dry powder for oral inhalation. Less than 20% of the dose is absorbed systemically, and 90% of the absorbed drug is excreted unchanged in urine [7]. In a pharmacokinetic study, the AUC was on average increased 2-fold in patients with CrCl between 25 and 70 ml/min and 3.5-fold in those with CrCl <25 ml/min as compared with healthy individuals after single doses administered intravenously: 4 mg for patients with CrCl between 25 and 70 ml/min and healthy participants, 2 mg for patients with CrCl <25 ml/min [8]. There are no data on the pharmacokinetics of zanamivir after oral inhalation in patients with renal failure. However, given the good tolerance after daily intravenous dosages as high as 1200 mg [8], and the limited systemic absorption after oral inhalation, the increased drug exposure for patients with renal failure is not considered clinically significant. Therefore, for orally inhaled zanamivir, no dosage adjustment is required in patients with renal impairment [5,8] (Table 1). Because the drug is almost not absorbed, it is unlikely to be removed by haemodialysis to a significant extent. It may thus be administered before or after the session on haemodialysis days without significant influence on its

Table 1. Dosing schedule of neuraminidase inhibitors for the treatment and prevention of influenza, in patients with renal insufficiency

Creatinine clearance (ml/mn)	Oseltamivir		Zanamivir
	Treatment	Prevention	
90–60	75 mg twice daily	75 mg once daily	10 mg twice daily
60–30	75 mg twice daily	75 mg once daily	10 mg twice daily
30–15	75 mg once daily	75 mg every other day	10 mg twice daily
<15 and dialysis	NA	NA	10 mg twice daily

NA, not available.

pharmacokinetics. Adverse effects with zanamivir comprise nasal and throat discomfort, headache and cough.

Conclusion

Chronic renal disease is frequent in the general population. In the case of epidemic or pandemic of avian influenza A (H5N1), the two neuraminidase inhibitors, oseltamivir and zanamivir will therefore be used in patients with renal impairment. Although zanamivir does not necessitate any adjustment of its dosage in patients with renal failure, because it is not absorbed after oral inhalation, oseltamivir dosage must be reduced by half in patients with CrCl between 15 and 30 ml/min and may be used at the usual dose when CrCl is higher.

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Nephrotoxicity of vancomycin in patients with normal serum creatinine

Sir,

The reported rate of nephrotoxicity of vancomycin (VCM) has been 7–16%. It can reach 35% with concurrent aminoglycosides and is associated with serum concentration >40 µg/ml [1]. However, in patients with normal serum

creatinine (SCr), monitoring of VCM–serum concentrations is disputable [2]. We retrospectively studied 19 patients (age 51 ± 19 years, 12 women) who had a 50% increase of their normal baseline SCr (ARF) during VCM therapy. Trough serum concentration of VCM was monitored once the ARF diagnosis was made and it was >40 µg/ml in all patients (VCMmax). Initial VCM dosing regime was unchanged up to ARF, when VCM administration was stopped. Spearman's correlations between VCMmax and age, duration of therapy (ΔT), peak SCr, albumin and bilirubin were calculated. Results (mean ± SD): VCMmax, 83 ± 12 µg/ml (range 50–289); ΔT, 12 ± 9 days; baseline SCr, 1.0 ± 0.3 mg/dl; peak SCr, 3.6 ± 2.1 mg/dl; albumin, 2.1 ± 0.6 g/dl; bilirubin, 3.8 ± 7.2 mg/dl. Oliguria was present in nine patients (47%) and seven (37%) needed dialysis. Twelve patients worsened and were admitted to ICU. Concurrent with VCM, eight patients (42%) received another nephrotoxic drug (amphotericin in five). All the patients had other cause for ARF besides VCM [severe sepsis in 16 (84%)]. Survivors were six (47%), and in two of them SCr did not return to baseline. There was no correlation between VCMmax and any of the evaluated parameters. In conclusion, in order to avoid nephrotoxic levels, even in patients with normal SCr, VCM–serum concentration monitoring should be started and its dose appropriately adjusted as soon as any potential factor for ARF superimposes.

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Associations of chronic kidney disease with the metabolic syndrome in non-diabetic elderly

Sir,

Chronic kidney disease (CKD) and the metabolic syndrome are worldwide public health problems. Few studies have reported that persons with mildly reduced kidney function are at greater risk for cardiovascular disease [1], but it remains unclear whether CKD contributes to prevalent metabolic syndrome in non-diabetic population. In addition, there are no studies that have focused on the elderly to evaluate the relationship between level of kidney function and prevalent metabolic syndrome.