Lanthanum Carbonate is Well Tolerated When Administered with Warfarin and Has No Effect on its Pharmacokinetics

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Introduction

- Lanthanum carbonate (Fosrenol™, Shire Pharmaceuticals) is a novel, non-aluminium, non-calcium phosphate binder used to control levels of serum phosphorus in patients with end-stage renal disease (ESRD). It has been shown in clinical trials to be effective and well tolerated[1,2]
- Consequently, lanthanum carbonate could be a good alternative to conventional aluminium- and calcium-based phosphate binders, which are associated with many adverse events – namely, bone and central nervous system toxicity with aluminium[3,4] and metastatic calcification with calcium-based salts[5]
- Patients with ESRD frequently receive concomitant medications and are therefore at risk of adverse events caused by drug interactions. It is important to establish whether new agents could also have an effect on concomitantly administered treatments, which could compromise their efficacy or safety
- Lanthanum carbonate demonstrates minimal systemic absorption, and the majority of the fraction that is absorbed is excreted by non-renal routes.[6] Lanthanum carbonate therefore has low potential for systemic interactions. It is possible that interactions could occur with lanthanum carbonate in the gastrointestinal tract. However, *in vitro*, lanthanum carbonate did not form complexes with drugs that are commonly prescribed for patients with ESRD
- This study was designed to investigate further the effects of lanthanum carbonate on the absorption and pharmacokinetics of a concomitantly administered drug. Warfarin is a drug used in a small but significant proportion of patients with ESRD and was selected for this study as it has a narrow therapeutic index

Methods

Study design

- An open-label, randomized, two-way crossover study was performed
- Participants were randomly assigned to two treatment groups. Participants in Group 1 received warfarin 10 mg alone, while Group 2 received warfarin 10 mg 30 minutes after a fourth dose of lanthanum carbonate (elemental lanthanum 1000 mg; 3 doses were given the day before warfarin administration). All doses of lanthanum carbonate were taken with meals
- After 16 drug-free days, participants from each group were crossed over to receive the other treatment schedule

Objectives

- To assess whether the pharmacokinetic parameters of warfarin are affected by concomitant administration of lanthanum carbonate. The parameters measured were area under the concentration curve to the last quantifiable concentration (AUC_{last}), area under the concentration curve to infinity ($AUC_{0-\infty}$), maximum observed plasma concentration (C_{max}), time to peak concentration (T_{max}) and plasma half-life ($t_{1/2}$)
- To evaluate the safety and tolerability of concomitantly administered lanthanum carbonate and warfarin

Study population

- The participants were healthy male Caucasians aged 18–35 years, with a body weight of 60–80 kg and within 15% of the ideal body weight for their height and estimated frame
- All 14 volunteers completed the study

Statistical analysis

- T_{max} was analysed non-parametrically, using the method outlined by Hauschke *et al.*[7] All other pharmacokinetic parameters were log-transformed and analysed using analyses of variance
- The differences between treatments (warfarin alone or concomitantly with lanthanum carbonate) and the 90% confidence intervals (CIs) were determined
- If the 90% CI was within the limits of 0.80–1.25 (the conventionally accepted range of bioequivalence for a log-transformed variable), it was concluded that the pharmacokinetic parameters were equivalent between treatment groups, and that lanthanum had no effect on the pharmacokinetics of warfarin

Results

Pharmacokinetics

- The mean concentration *vs.* time curves for warfarin alone and with lanthanum carbonate are shown in Figure 1
- The mean pharmacokinetic parameters of warfarin R- and S-enantiomers, alone or in combination with lanthanum are summarized in Tables 1 and 2
- The 90% CIs for the differences between treatments for all of the parameters, $AUC_{0-\infty}$, AUC_{last}, C_{max}, T_{max} and $t_{1/2}$ were all within the bioequivalence criteria of 0.80–1.25 (Tables 1 and 2)
  - Lanthanum, therefore, does not affect the pharmacokinetic parameters of warfarin
  - The rate and extent of absorption of warfarin are also not affected by lanthanum

Safety assessments

- Concomitant administration of lanthanum carbonate and warfarin was well tolerated. No serious adverse events were reported during the study
- In total, five adverse events were reported by two participants in the study. Headache and light-headedness were reported in one person after administration of warfarin alone; hypoglycaemia, joint stiffness and vasovagal syncope were reported in two participants after concomitant warfarin and lanthanum carbonate administration. The adverse events were of mild-to-moderate intensity and considered to be unrelated to the drugs used in the study
- There were no clinically significant abnormalities for any laboratory parameters, including haematology, biochemistry, virology and urine analysis during the study
- Vital signs, electrocardiograms and physical examinations also showed no clinically significant change

Figure 1. Mean concentration *vs.* time curves for a) R-Warfarin enantiomers b) S-Warfarin enantiomers

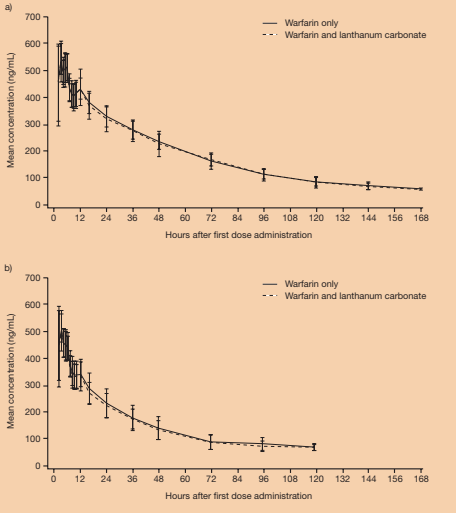

Table 1. Summary of plasma pharmacokinetic parameters for R-Warfarin enantiomers

	Mean (± SD)		Point estimate	90% CIs
	Warfarin alone	Warfarin + lanthanum carbonate		
$AUC_{0-\infty}$ (h.ng/mL)	31057 (4890)	30477 (5681)	0.972	0.92–1.03
AUC_{last} (h.ng/mL)	27223 (4404)	26400 (5173)	0.960	0.92–1.00
C_{max} (ng/mL)	558 (43)	557 (66)	0.994	0.95–1.04
T_{max} (h)	3.0 (0.6)	3.3 (1.0)	1.000	1.00–1.00
$t_{1/2}$ (h)	45.3 (7.5)	44.8 (8.7)	0.979	0.90–1.06

Table 2. Summary of plasma pharmacokinetic parameters for S-Warfarin enantiomers

	Mean (± SD)		Point estimate	90% CIs
	Warfarin alone	Warfarin + lanthanum carbonate		
$AUC_{0-\infty}$ (h.ng/mL)	18832 (5413)	17777 (4642)	0.950	0.90–1.00
AUC_{last} (h.ng/mL)	15901 (4904)	14962 (4150)	0.947	0.90–1.00
C_{max} (ng/mL)	538 (61)	542 (70)	1.006	0.97–1.04
T_{max} (h)	2.7 (0.6)	2.9 (0.8)	1.000	1.00–1.00
$t_{1/2}$ (h)	32.3 (5.8)	30.8 (6.6)	0.948	0.89–1.01

Conclusions

- **Lanthanum carbonate is an effective, well-tolerated phosphate binder, which has been shown to have no effect on the pharmacokinetics of warfarin when administered concomitantly**
- **The good safety and tolerability profile of lanthanum carbonate as established in large-scale Phase III clinical trials in patients with ESRD,[1,2] was not altered by concomitant administration with warfarin in healthy individuals**
- **These data suggest that lanthanum carbonate can be safely administered in combination with warfarin in clinical practice, without the need for additional precautions or dose adjustments**

References

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