

# Effect of oseltamivir treatment on anticoagulation: a cross-over study in warfarinized patients

Brian E. Davies,<sup>1</sup> Pau Aceves Baldó,<sup>2</sup> Sian Lennon-Chrimes<sup>2</sup> & Mike Brewster<sup>2</sup>

<sup>1</sup>Hoffmann-La Roche Inc., Nutley, NJ, USA and <sup>2</sup>Roche Products Ltd, Welwyn Garden City, UK

## WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

Although oseltamivir had not previously been reported to cause haematological toxicity, the European Medicines Agency (EMA) asked Roche to investigate potential interactions between oseltamivir and warfarin after isolated reports of an enhancement of the anticoagulant effect of warfarin during oseltamivir treatment.

## WHAT THIS STUDY ADDS

In individuals taking warfarin at stable dosages for chronic vascular or cardiac conditions, there is no evidence for a pharmacodynamic or pharmacokinetic interaction between oseltamivir and warfarin that could alter the anticoagulant effect of the latter.

## Correspondence

Dr Brian E. Davies, Clinical Pharmacology, Hoffmann-La Roche Inc., 340 Kingsland Street, Nutley, NJ 07936, USA.

Tel.: + 1 973 235 2053

Fax: + 1 973 235 5900

E-mail: brian.davies@roche.com

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## AIM

To investigate whether oseltamivir enhances the anticoagulant effect of warfarin and to evaluate any pharmacokinetic (PK) interaction between the agents.

## METHODS

Twenty volunteers (mean age 62 years) receiving daily warfarin and with INR values of 2.0–3.5 during the previous 2 weeks were randomized to concomitant oseltamivir 75 mg twice daily for 4.5 days or warfarin alone in a two-way cross-over design with a 4–8 day wash-out. Anticoagulant effects were assessed by calculating overall [AUEC(0,96 h)] and observed maximum effect ( $E_{max}$ ) increase from baseline in INR, decrease from baseline in factor VIIa, and change in vitamin K<sub>1</sub> concentrations. Plasma pharmacokinetics of (R)- and (S)-warfarin and oseltamivir were also assessed.

## RESULTS

For both treatments, changes in INR and factor VIIa during treatment were small; for net AUEC(0,96 h), least square mean values were –9.53 (oseltamivir + warfarin) and –1.69 h (warfarin alone) for INR (difference –7.84 h, 90% CI –18.86, 3.17 h), and 1.56 and 0.54 kIU l<sup>-1</sup> h, respectively, for factor VIIa (difference, 1.01 kIU l<sup>-1</sup> h; 90% CI –1.18, 3.21). Differences between the treatments in  $E_{max}$  increase from baseline for INR, decrease from baseline for factor VIIa and change from baseline in vitamin K<sub>1</sub> concentration were not statistically significant. Oseltamivir did not alter warfarin pharmacokinetics. Oseltamivir was well tolerated in this study with no clinically significant adverse safety findings.

## CONCLUSION

Concomitant administration of oseltamivir for 4.5 days to volunteers on daily warfarin had little or no effect on warfarin pharmacokinetics and no effect on pharmacodynamics.