INTRODUCTION

The guinea-pig (GP) is recognized as a good surrogate species possessing predictive value in early safety assessment of new chemical entities, in particular to evaluate the potential for delayed ventricular repolarization.

RESULTS

Vehicle (PEG200, NaCl 0.9%, 30/70, v/v)

Vehicle

PR interval (ms)

Sunitinib is a recently-approved multi-targeted tyrosine-kinase inhibitor with this agent (e.g. increases in QTc, PR and QRS intervals), likely mediated by multichannel blockade (Cohen et al., Toxicol. Appl. Pharmacol. 257(1), 74-83 (2011)). In the present study, Sunitinib was administered i.v. in the anaesthetised GP and orally in the conscious telemetered GP. Blood samplings were performed in satellite animals to evaluate Sunitinib exposure in both models.

MATERIALS & METHODS

Anaesthetised Guinea-Pigs:
- Male Dunkin-Hartley guinea-pigs weighing 320-380g; n=7.
- Surgery under isoflurane anaesthesia (2.5 to 5%).
- Telemetric monitoring of haemodynamic parameters and only slight increases in PR and QTc, mainly observed at 180 mg/kg. The comparison of plasma concentrations in both models showed that despite 5-fold higher doses tested orally, the exposure is far lower, illustrating poor oral bioavailability of Sunitinib in this condition. Therefore, although ICH guidelines recommend the use of conscious animals, anaesthetised preparations may allow higher compound exposure and better characterisation of safety profile of new drugs.

Telemetered Guinea-Pigs:
- Male Dunkin-Hartley guinea-pigs weighing 350-420g; n=7.
- Surgery under isoflurane anaesthesia (2.5 to 5%).
- Telemetric monitoring of haemodynamic parameters and only slight increases in PR and QTc, mainly observed at 180 mg/kg. The comparison of plasma concentrations in both models showed that despite 5-fold higher doses tested orally, the exposure is far lower, illustrating poor oral bioavailability of Sunitinib in this condition. Therefore, although ICH guidelines recommend the use of conscious animals, anaesthetised preparations may allow higher compound exposure and better characterisation of safety profile of new drugs.

Telemetered GP

CONCLUSION

In anaesthetised GP, Sunitinib administered i.v. induced marked dose-dependent decreases in arterial pressure and heart rate and increases in PR, QRS and QTc intervals, consistent with its multichannel blockade properties and clinical observations. In conscious telemetered animals, Sunitinib administered p.o. did not induce major effects on haemodynamic parameters and only slight increases in PR and QTc, mainly observed at 180 mg/kg. The comparison of plasma concentrations in both models showed that despite 5-fold higher doses tested orally, the exposure is far lower, illustrating poor oral bioavailability of Sunitinib in this condition. Therefore, although ICH guidelines recommend the use of conscious animals, anaesthetised preparations may allow higher compound exposure and better characterisation of safety profile of new drugs.