BMC Pharmacology

Poster presentation

Warfarin pharmacodynamics and pharmacokinetics are not affected by the soluble guanylate cyclase stimulator riociguat (BAY 63-2521)

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from 4th International Conference of cGMP Generators, Effectors and Therapeutic Implications
Regensburg, Germany. 19–21 June 2009

Published: 11 August 2009

BMC Pharmacology 2009, **9**(Suppl 1):P15 doi:10.1186/1471-2210-9-S1-P15

This abstract is available from: http://www.biomedcentral.com/1471-2210/9/S1/P15

Background

Pulmonary hypertension (PH) is a progressive and debilitating condition with a high rate of mortality. Riociguat (BAY 63-2521) is a new drug in development for PH that is well tolerated [1,2] and has superior efficacy to nitric oxide in patients with PH [2]. Treatment recommendations for PH are based on combination therapies that include warfarin. The aim of this study was to investigate potential pharmacodynamic or pharmacokinetic interactions of riociguat and warfarin.

Materials and methods

This single-centre, randomized, double-blind, placebo-controlled, crossover, interaction study included healthy male volunteers aged 18–45 years. Riociguat (2.5 mg) or placebo was administered orally three times daily (t.i.d.) for 10 days. Warfarin sodium (25 mg) was administered as a single oral dose 21 days before the study and on the 7th day of treatment with riociguat or placebo.

Results

Twenty-one of the 30 subjects valid for safety analysis reported a total of 89 treatment-emergent adverse events, all of which were of mild (n = 64) or moderate (n = 25) severity. No serious adverse events occurred. The most frequently reported treatment-emergent adverse events considered to be related to riociguat and/or warfarin were dyspepsia, headache, flatulence, nausea and vomiting. Data from 22 volunteers were valid for pharmacodynamic and pharmacokinetic analyses. A single dose of warfarin did not affect the pharmacokinetics of riociguat to a clinically relevant extent (Table 1). Riociguat at steady state did

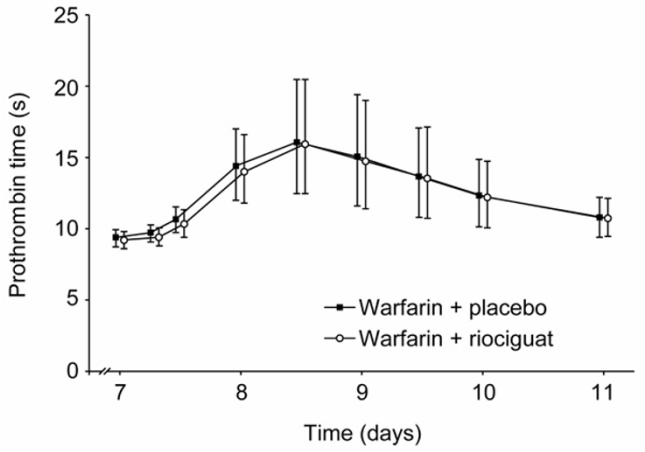

Figure 1
Prothrombin time following a single oral dose of warfarin sodium and multiple oral doses of riociguat or placebo.

Table 1: Pharmacokinetic and clotting profile parameter ratios of least squares means for warfarin and riociguat

Ratios	Analyte	Parameter	Ratio (90% CI)
(Warfarin + riociguat)/(warfarin + placebo)	R-warfarin	AUC (μg.h/L)	1.01 (0.96–1.05)
		C_{max} (μg/L)	1.02 (0.96–1.08)
	S-warfarin	AUC (μg.h/L)	1.01 (0.97–1.04)
		C_{max} (μg/L)	1.01 (0.95–1.09)
	Prothrombin time	$AUC_{(0–96)}$ (s.h)	0.99 (0.97–1.01)
	Factor VII % clotting activity	$AUC_{(0–96)}$ (%.h)	1.03 (1.00–1.06)
(Warfarin + riociguat)/riociguat	Riociguat	$AUC_{\tau,ss}$ (μg.h/L)	0.96 (0.87–1.06)
		$C_{max,SS}$ (μg/L)	0.84 (0.70–1.01)

AUC, area under the plasma concentration-time curve from zero to infinity after single dose administration; $AUC_{\tau,ss}$, AUC at steady state; $AUC_{(0–96)}$, AUC from zero to 96 h after administration of warfarin; CI, confidence interval; C_{max}, maximum drug concentration in plasma after single dose administration; $C_{max,SS}$, C_{max} at steady state.

not affect Factor VII clotting activity or prothrombin time (Table 1, Figure 1), and did not affect the pharmacokinetics of warfarin (Table 1). Thus, riociguat and warfarin can be combined in patients with PH, with no requirement for dose adaptation.

A single dose of warfarin was administered on day 7. Doses of riociguat or placebo were administered three times daily on days 1–10. Geometric means are shown, with upward bars denoting geometric means*geometric standard deviations and downward bars denoting geometric means/geometric standard deviations.

Conclusion

The combined use of riociguat with warfarin had a favourable safety profile. Riociguat at a dose of 2.5 mg t.i.d. demonstrated no pharmacodynamic interactions and no clinically relevant pharmacokinetic interactions with warfarin. Thus, the combined use of riociguat with warfarin is not expected to represent a risk and no dose adaptation is required.

References

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