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Influence of Rifampin-mediated OATP1B1/1B3 Inhibition on the Pharmacokinetics of Clazosentan

Peter Dogterom[1], Pierre-Eric Juif[2], Christine Voors-Pette[1], Mike Ufer[2], Jasper Dingemanse[2]

[1]QPS Netherlands B.V, Groningen, The Netherlands, [2]Department of Clinical Pharmacology, Idorsia Pharmaceuticals Ltd, Allschwill, Switzerland

CONTACT INFORMATION: Peter Dogterom, QPS Netherlands, Petrus Campersingel 123, 9713 AG Groningen, Netherlands. E-mail: peter.dogterom@qps.com

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PURPOSE

Endothelin-1 (ET-1) is one of the most potent vasoconstrictors known. ET-1 concentrations are increased in a number of different diseases such as aneurysmal subarachnoid hemorrhage (aSAH). As a selective endothelin A receptor antagonist (ERA), clazosentan inhibits ET-1-mediated vasoconstriction and has demonstrated efficacy by reducing the frequency and severity of cerebral vasospasm following severe aSAH that is considered as one of the major causes of morbidity and mortality in these patients. Intravenous (i.v.) clazosentan is in development for the prevention and treatment of vasospasm associated with aSAH.

In vitro studies have shown that clazosentan is a substrate of the organic-anion-transporting polypeptide (OATP) 1B1/1B3. As per FDA and EMA recommendations, interactions between clazosentan and an OATP1B1/1B3 inhibitor need to be investigated in humans. A single dose of rifampin is considered as a reference inhibitor of OATP1B1/1B3 as per FDA guidance. This study investigated the impact of rifampin-mediated OATP1B1/1B3 inhibition on the PK of clazosentan

OBJECTIVE

The primary objective of this study was:

- To evaluate the influence of a single i.v. infusion of rifampin on the pharmacokinetics of clazosentan

METHODS

Study Design: Single center, randomized, double-blind, placebo-controlled, two period cross-over study.

Subjects: 14 healthy male and female subjects, aged between 18 and 65 years of age with a BMI of 18.0 – 30 kg/m^2, were enrolled.

Treatment A: 30 min iv infusion of placebo (100 mL) followed by a 3 hr infusion of clazosentan (15 mg/h)
Treatment B: 30 min iv infusion of rifampin (600 mg/100 mL) followed by a 3 h infusion of clazosentan (15 mg/h)

PK blood sampling: Blood samples were collected at pre-dose and every 30 min from the start to the end of clazosentan infusion and 2, 5, 10, 15, 30, 45 min and 1, 1.5, 2, 3, 4, 5, 6, 7, and 21 h after the stop of clazosentan infusion.

METHODS (CONT)

Non-compartmental PK analyses were performed. The following main PK parameters were calculated for clazosentan: maximum plasma concentration (C_{max}), area under the plasma concentration-time curve (AUC) from zero to time t of the last measured concentration above the Limit of Quantification (LOQ) (AUC_{0-t}), AUC from 0 to 3 h after the start of clazosentan infusion (AUC_{0-3}), AUC from 0 to infinity ($AUC_{0-\infty}$), terminal half-life ($t_{1/2}$), clearance (CL) and volume of distribution (V_{ss})

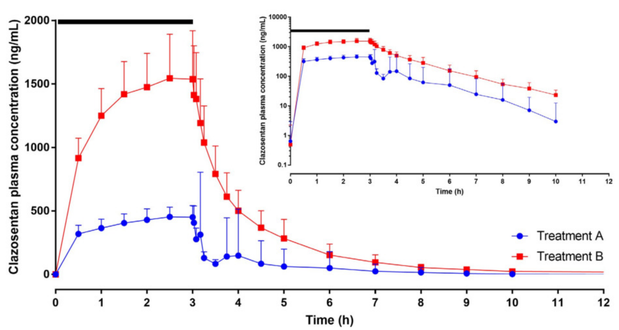
RESULTS - SUBJECTS

Fourteen subjects were included: 13 subjects completed the study as per protocol and 1 subject withdrew from the study after the first period. The overall mean age was 52.9 years (range: 19-64 years) and the mean BMI was 25.24 kg/m^2 (range 20.6 – 29.6 kg/m^2)

RESULTS – PHARMACOKINETICS

In the figure below, arithmetic mean (plus standard deviation) plasma concentrations of clazosentan in the absence and presence of rifampin are presented. In the table, a summary of the PK parameters from the two treatments is presented plus the statistical evaluation of the effect of rifampin on the PK parameters of clazosentan.

Exposure to clazosentan was approximately 3-4 times higher when administered after rifampin, as reflected by the ratio (90 % confidence interval [CI]) of the geometric mean of C_{max} (3.13 [2.53-3.88]), AUC_{0-3} (3.37 [3.07-3.70]), AUC_{0-t} (3.89 [3.24-4.66]), and $AUC_{0-\infty}$ (3.88 [3.24-4.65]). Rifampin administration led to a marked decrease in CL and V_{ss} of clazosentan of 3.9- and 2.4-fold, respectively. The ratio (90 % CI) of the geometric mean of $t_{½}$ of clazosentan (1.09 [0.96-1.24]) was not affected by rifampin.



Arithmetic mean (± standard deviation) plasma concentration-time profile (with linear scale, semilogarithmic scale shown as inset) of clazosentan after infusion of 15 mg/h clazosentan for 3 hours following a short intravenous infusion of placebo (treatment A) or rifampin (treatment B); n = 13.

		Clazosentan (A)		Clazosentan + Rifampin (B)	Clazosentan + Rifampin (Test) / Clazosentan (Reference)
	N	GM (95% CI)	N	GM (95% CI)	GMR (90% CI)
C_{max} (ng/mL)	13	518.69 [400.09, 672.45]	13	1613.33 [1444.66, 1801.69]	3.13 [2.53, 3.88]
AUC_{0-3} (ng*h/mL)	13	1077.11 [963.32, 1204.34]	13	3627.64 [3263.36, 4032.57]	3.37 [3.07, 3.70]
AUC_{0-t} (ng*h/mL)	13	1381.27 [1094.06, 1743.88]	13	5325.80 [4709.98, 6022.12]	3.89 [3.24, 4.66]
$AUC_{0-\infty}$ (ng*h/mL)		1394.88 [1105.82, 1759.49]	13	5375.89 [4755.04, 6077.79]	3.88 [3.24, 4.65]
$t_{1/2}$ (h)	13	1.36 [1.16, 1.61]	13	1.51 [1.40, 1.64]	1.09 [0.96, 1.24]
CL (mL/h)	13	32260.89 [25575.58, 40693.70]	13	8370.71 [7404.00, 9463.63]	0.26 [0.21, 0.31]
V_{ss} (mL)	13	23483.74 [20057.30, 27495.54]	13	9897.95 [8682.18, 11283.95]	0.42 [0.36, 0.49]

Summary of pharmacokinetic variables of clazosentan when infused at a dose of 15 mg/h for 3 hours after a short (30 minutes) intravenous infusion of placebo (treatment A) or rifampin (treatment B) and geometric mean ratios for the comparison of treatments (n = 13)

RESULTS – SAFETY AND TOLERABILITY

Overall, 13 of 14 exposed subjects reported 44 treatment-emergent AEs. The incidence of AEs was higher following treatment B (12 subjects, 29 AEs) compared to treatment A (7 subjects, 15 AEs). Following i.v. infusion of clazosentan, the most common AE was headache (10 out of 14 subjects, 14 AEs) with a higher incidence in treatment B (8 subjects, 9 AEs) compared to treatment A (5 subjects, 5 AEs). The incidence and frequency of AEs commonly reported after clazosentan infusion, i.e., nausea and vomiting, were also higher following treatment B compared to treatment A. All AEs resolved without sequelae.

No clinically relevant changes in clinical laboratory, vital signs, and body weight were determined.

CONCLUSIONS

- Following administration of a single i.v. dose of rifampin, exposure to clazosentan was increased by 3 – 4 fold and V_{ss} and CL were decreased by 2.4- and 3.9 fold, respectively. The $t_{1/2}$ of clazosentan was not affected by rifampin
- Clazosentan is a substrate of the OATP1B1/1B3 transporters
- Clazosentan (15 mg for 3h) administered after rifampin or its matching placebo was safe and tolerated

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