

POSTER PRESENTATION

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Effects of age and gender on the pharmacokinetics of the soluble guanylate cyclase stimulator riociguat

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Background

Pulmonary hypertension is a disabling disease associated with high mortality [1,2]. Riociguat (under review for the treatment of pulmonary hypertension) stimulates soluble guanylate cyclase, which plays an important role

in the regulation of cardiovascular tone and remodelling [3-9]. We investigated the potential effects of age and gender on the pharmacokinetics of riociguat and its primary metabolite M1 (BAY 60-4552). Safety and tolerability of riociguat were also assessed.

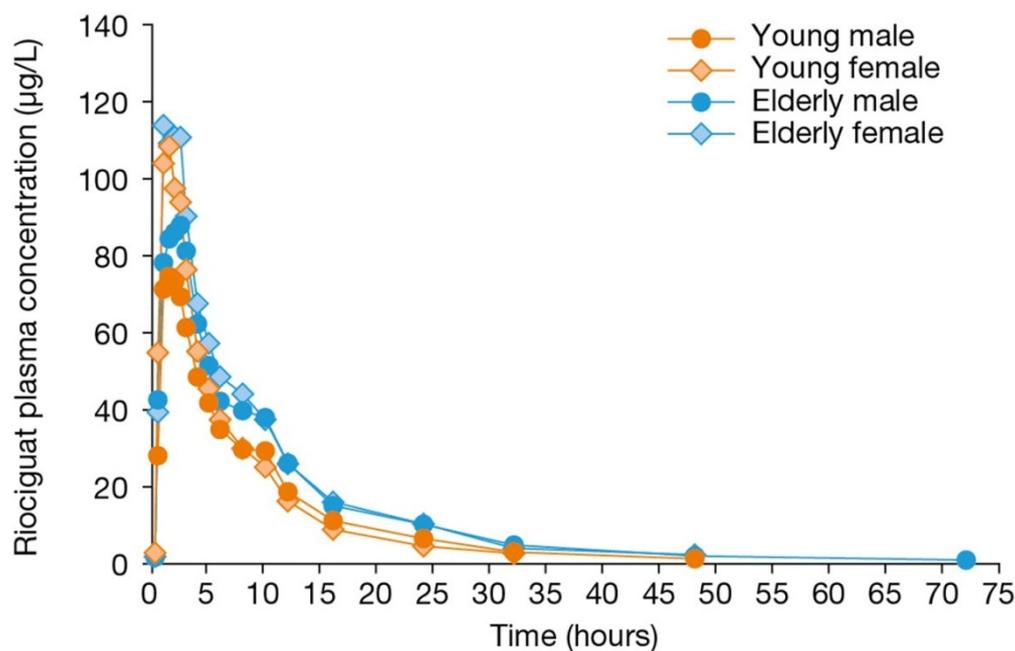


Figure 1 Mean riociguat plasma concentrations in groups of differing age and gender following administration of a single oral dose of riociguat 2.5 mg.

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Table 1 Selected pharmacokinetic parameters of riociguat and metabolite M1 (BAY 60-4552) by age and gender following a single oral dose of riociguat 2.5 mg

Parameter	Young female (n = 9)	Elderly female (n = 9)	Young male (n = 9)	Elderly male (n = 9)
Riociguat				
AUC, µg·h/L	803 (55)	1145 (36)	750 (58)	1036 (48)
C _{max} , µg/L	113 (22)	125 (35)	80.4 (25)	96.7 (32)
AUC _{norm} , g·h/L	24.8 (57)	32.6 (45)	26.5 (55)	32.8 (50)
C _{max, norm} , g/L	3.48 (20)	3.56 (36)	2.84 (23)	3.06 (22)
t _{1/2} , h	8.97 (51)	11.8 (31)	8.10 (39)	12.2 (62)
CL _R , L/h ^a	0.320 (28)	0.223 (33)	0.389 (37)	0.287 (28)
M1				
AUC, µg·h/L	640 (26)	651 (38)	476 (20)	687 (44)
C _{max} , µg/L	28.1 (53)	22.4 (52)	14.9 (44)	18.8 (71)
AUC _{norm} , g·h/L	20.5 (26)	19.2 (30)	17.4 (28)	22.5 (35)
C _{max, norm} , g/L	0.899 (51)	0.661 (42)	0.544 (51)	0.615 (65)
t _{1/2} , h	16.0 (34)	16.7 (21)	14.9 (28)	21.3 (33)
CL _R , L/h ^a	0.824 (32)	0.487 (36)	0.718 (39)	0.573 (44)

^aArithmetic mean (percentage coefficient of variation). All other parameters are expressed as geometric means (percentage coefficient of variation). AUC, area under the plasma concentration–time curve from time 0 to infinity; AUC_{norm}, AUC divided by dose per kilogram of body weight; C_{max}, maximum concentration in plasma; C_{max, norm}, C_{max} divided by dose per kilogram of body weight; t_{1/2}, terminal elimination half-life; CL_R, renal clearance.

Methods

This placebo-controlled, double-blind, single-centre study followed good clinical practice guidelines. Healthy volunteers were randomized into four groups according to age (young, 18–45 years; elderly, 64.5–80 years) and gender: young male (YM), elderly male (EM), young female (YF), elderly female (EF). All participants received a single oral tablet of riociguat 2.5 mg or placebo. Dense sampling was performed for pharmacokinetics.

Results

Forty-seven participants provided data for pharmacokinetic and safety analyses. Nine participants in each group received riociguat; three participants in each of the YM,

EM and EF groups and two participants in the YF group received placebo.

Age: the mean maximum concentration of riociguat in plasma (C_{max}) did not vary markedly between age groups (Figure 1). However, mean renal clearance was decreased in the elderly, and exposure (area under the plasma concentration–time curve [AUC]) to riociguat was approximately 40% higher in the elderly than in the young (p > 0.05) (Tables 1 & 2). When normalized for body weight, the riociguat exposure (AUC_{norm}) ratio was reduced; AUC_{norm} was approximately 30% higher in the elderly than in the young (Tables 1 & 2).

Gender: although riociguat mean C_{max} normalized for body weight (C_{max, norm}) was significantly greater in

Table 2 Comparison of selected riociguat and M1 pharmacokinetic parameters between different participant groups (ratios and 90% confidence limits)

Parameter	Elderly vs young (n = 18 per group)	Female vs male (n = 18 per group)
Riociguat		
AUC	1.40 (1.06–1.86)	1.09 (0.82–1.44)
C _{max}	1.16 (0.98–1.36)	1.35 (1.14–1.59)*
AUC _{norm}	1.28 (0.95–1.71)	0.97 (0.72–1.30)
C _{max, norm}	1.05 (0.91–1.22)	1.20 (1.03–1.38)*
t _{1/2}	1.41 (1.08–1.84)*	1.04 (0.79–1.35)
M1		
AUC	1.21 (1.00–1.46)	1.13 (0.94–1.36)
C _{max}	1.00 (0.73–1.38)	1.50 (1.09–2.05)*
AUC _{norm}	1.10 (0.93–1.30)	1.00 (0.85–1.19)
C _{max, norm}	0.91 (0.68–1.23)	1.33 (0.99–1.79)
t _{1/2}	1.22 (1.04–1.44)*	0.92 (0.78–1.08)

*p < 0.05 for ratio = 1.

AUC, area under the plasma concentration–time curve from time 0 to infinity; AUC_{norm}, AUC divided by dose per kilogram of body weight; C_{max}, maximum concentration in plasma; C_{max, norm}, C_{max} divided by dose per kilogram of body weight; t_{1/2}, terminal elimination half-life.

women than in men, no difference in exposure was observed between genders (Tables 1 & 2).

Across age groups, pharmacokinetics of M1 followed similar trends to those of riociguat, although differences were less pronounced (Tables 1 & 2). Compared with the combined placebo subgroups, the combined riociguat subgroups demonstrated an expected reduction in mean blood pressure and corresponding elevation of mean heart rate, waning approximately 16 hours post-dose. Three participants in the riociguat subgroups reported drug-related adverse events, one of which (hypotension) was classified as severe. All adverse events had resolved by completion of the study.

Conclusion

Age and gender had modest effects on riociguat and M1 pharmacokinetics, and the safety profile of riociguat was similar across all groups. Thus, no dose adjustment for age or gender is merited.

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