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Cardiovascular effects of the soluble guanylyl cyclase activator BAY 58–2667 in anesthetized dogs

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Introduction

BAY 58–2667 is a novel activator of the soluble guanylyl cyclase (sGC) with vasodilatory properties particularly in diseased blood vessels [1]. BAY 58–2667 is currently under clinical development for the treatment of acute decompensated heart failure.

Within the scope of a Safety Pharmacology study, effects on cardiovascular function and ECG were examined in anesthetized Beagle dogs after intravenous administration. Infusion rates of this placebo-controlled study were chosen to cover approximately the 10 fold of therapeutic plasma levels.

Materials and methods

Nine female and male Beagle dogs (age 1.5–3 years, body weight 10 – 15 kg) were anesthetized (neuroleptic anesthesia with droperidol/fentanyl) and artificially ventilated (N_2O/O_2) [2]. Hemodynamic parameters systolic and diastolic arterial blood pressure (BPS, BPD), left ventricular systolic and end diastolic pressure (LVP, LVEDP), left ventricular dP/dt (LVdP/dt), cardiac output (CO), central venous pressure (CVP), and heart rate (HR) were measured continuously. Total peripheral resistance (TPR) was calculated as mean arterial pressure (BPM) divided by cardiac output. ECG was recorded with standard lead II and RR, PQ, QRS, and QT interval were evaluated. QT was corrected for heart rate by Fridericia's formula (QTcF).

Groups of n = 3 dogs received 3 cumulative infusion steps of placebo (1 mM Tris buffer at pH 8.6–8.8 in saline, 0.44–0.67–3.33 ml/kg/h) or BAY 58–2667 at low (1–5–25 μg/kg/h) or at high (5–15–45 μg/kg/h) infusion rates. Infusion rates were consecutively increased every hour followed by a 2 hour washout period after stop of the final infusion step.

Systemic exposure was determined in plasma after protein precipitation and separation by high-pressure liquid chromatography and tandem mass spectrometric detection (LC/MS/MS).

Results

Cardiovascular function

BAY 58–2667 caused a plasma concentration dependent reduction of LVEDP (-98%) and CVP (-54%) followed by a vasodilation (marked reduction of TPR by -48%) which was accompanied by counter regulation with increase of HR (+113%) and LV dP/dt (+21%) as a consequence of sympathetic activation. Mean plasma levels of 17.8 μg/L at low infusion rates and 25.2 μg/L at high infusion rates were obtained (Table 1).

Hemodynamic effects of low and high infusion rates of BAY 58–2667 (placebo normalized data, relative to baseline values, means of n = 3) at end of each infusion step and end of 2 hour washout period with corresponding plasma levels.

Table 1:

-BAY 58–2667 low infusion rates

BAY 58–2667 µg/kg/h	Time min	HR Δ %	BPS Δ %	BPD Δ %	BPM Δ %	LVP Δ %	LVEDP Δ %	LVdP/dt Δ %	CVP Δ %	CO Δ %	TPR Δ %	$C_{58-2667}$ µg/L
1	60	2	-2	-2	-2	0	-8	-3	-2	-6	3	0.9
5	120	4	-14	-4	-10	-7	-40	-1	-24	-3	-5	3.4
25	180	34	-26	-2	-14	-9	-67	21	-43	27	-23	17.8
washout	300	19	-22	2	-11	-11	-22	1	-9	10	-18	0.2

-BAY 58–2667 high infusion rates

BAY 58–2667 µg/kg/h	Time min	HR Δ %	BPS Δ %	BPD Δ %	BPM Δ %	LVP Δ %	LVEDP Δ %	LVdP/dt Δ %	CVP Δ %	CO Δ %	TPR Δ %	$C_{58-2667}$ µg/L
5	60	32	-14	-4	-9	-8	-24	16	-24	13	-18	2.9
15	120	56	-34	-16	-26	-18	-65	9	-37	36	-39	8.8
45	180	113	-47	-21	-31	-18	-98	17	-54	73	-48	25.2
washout	300	34	-31	-7	-20	-20	-39	-19	-27	15	-29	0.3

ECG

Besides effects which are attributable to increased heart rate (shortening of PQ and QT interval) the ECG was not significantly affected. In particular no effects on QTcF interval were seen up to highest mean plasma levels of 25 µg/L (=0.5 $nM_{unbound}$) whereas cardiovascular effects were seen already at 3 µg/L (=0.06 $nM_{unbound}$). Electrophysiological *in vitro* investigations (in-house data) demonstrated that BAY 58–2667 elicited no effects on dog Purkinje fiber action potentials up to 1000 nM and only slight inhibition of hERG K^+ current (IC_{50} >1000 nM).

Summary

The sGC activator BAY 58–2667 was intravenously administered to anesthetized dogs at a dose-range of 1 – 45 µg/kg/hour yielding mean plasma levels of up 25 µg/L.

Observed effects are: (1) Threshold of cardiovascular effects in dogs at plasma levels of 3 µg/L comparable to that in healthy volunteers (2.5 µg/L); (2) Reduction of ventricular pre- and afterload (decrease of CVP, LVEDP, BPM); (3) Marked vasodilation (up to 48% TPR reduction); (4) No evidence for risk of QT prolongation.

References

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