BMC Pharmacology

Poster presentation

BAY 58–2667, a soluble guanylate cyclase activator, has a favourable safety profile and reduces peripheral vascular resistance in healthy male volunteers

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from 3rd International Conference on cGMP Generators, Effectors and Therapeutic Implications
Dresden, Germany. 15–17 June 2007

Published: 25 July 2007

BMC Pharmacology 2007, **7**(Suppl 1):P21 doi:10.1186/1471-2210-7-S1-P21

This abstract is available from: http://www.biomedcentral.com/1471-2210/7/S1/P21

Background

BAY 58–2667 is a soluble guanylate cyclase activator that acts independently of nitric oxide. Preclinical data indicate that BAY 58–2667 induces cyclic guanosine monophosphate (cGMP) generation and vasodilation preferentially in diseased vessels. This phase I clinical trial in healthy male volunteers was the first intravenous evaluation of BAY 58–2667 in humans.

Materials and methods

This single-site study assessed the safety, tolerability and pharmacokinetics of intravenously administered BAY 58–2667 in healthy male volunteers. For initial dose-finding, BAY582667 was administered for 2 h at doses of 15 μg/h, 45 μg/h and 100 μg/h (n = 2 per dose group). Safety parameters (adverse events [AEs], electrocardiograms [ECGs] and standard laboratory values), pharmacodynamics (heart rate [HR], mean arterial pressure [MAP], diastolic blood pressure [DBP] and plasma vasoactive hormone levels) and pharmacokinetics were assessed using a single-blinded, randomized, placebo-controlled study design: four doses of BAY 58–2667 (range: 50–200 μg/h) were administered for 2 h or 4 h to six individuals per dose group, with an additional 250 μg/h dose group (n = 5) in the 4-h infusion administration group (placebo groups, n = 7 for the 2-h dose group and n = 10 for the 4-h dose group).

Results

Sixteen AEs occurring in 12 (20%) of 59 subjects receiving BAY 58–2667 were attributed to the study compound. All were of mild intensity, including two cases of mild symptomatic hypotension. There was an increase in the frequency of cardiovascular-related AEs with increasing dose of the study compound. BAY 58–2667 had no clinically relevant effects on ECGs or laboratory values. Pharmacodynamic evaluation showed that BAY582667 increased HR in a dose-dependent manner when infused over 2 h ($P = 0.0002$) and 4 h ($P < 0.0001$). In healthy young subjects, the cardiovascular system compensates for changes in blood pressure with changes in HR to keep the blood pressure constant as long as possible. Therefore, HR is considered the most sensitive non-invasive parameter for indirect estimation of the effect of a vasodilating agent on the cardiovascular system. Pharmacodynamic evaluation also showed that BAY 58–2667 dose-dependently decreased MAP (2 h: $P = 0.0069$; 4 h: $P = 0.0008$) and DBP (2 h: $P = 0.0058$; 4 h: $P = 0.0004$). In terms of vasoactive hormones, BAY 58–2667 dose-dependently increased plasma renin activity (2 h: $P = 0.0064$; 4 h: $P = 0.0212$), angiotensin II levels (2 h: $P = 0.0042$; 4 h: $P = 0.0013$) and noradrenalin levels (2 h: $P < 0.0001$; 4 h: $P = 0.0002$), while having no significant effect on plasma aldosterone levels. Plasma levels of cGMP increased dose-dependently in the 4-h infusion groups ($P < 0.0001$), but not the 2-h

infusion groups (P = 0.7884). BAY 58–2667 pharmacokinetics showed low inter-individual variability. Plasma concentrations correlated closely with doses administered, and declined rapidly following the end of infusion.

Conclusion

BAY 58–2667 has a favourable safety profile and was well tolerated in healthy subjects. It reduced peripheral vascular resistance by dose-dependently increasing HR and plasma vasoactive hormones, and decreasing MAP and DBP. Further studies are warranted to assess the therapeutic potential of BAY 58–2667 in patients with acute decompensated heart failure and other cardiovascular diseases.