Medizinische Klinik 4
Nephrologie und Hypertensiologie
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Effects of the NO synthase inhibitor ronopterin (VAS203) on renal function in healthy volunteers

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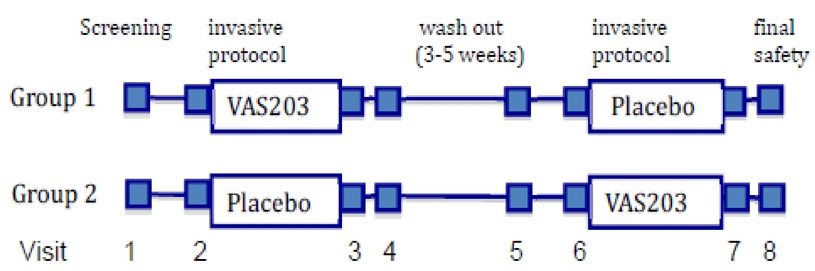
Background:

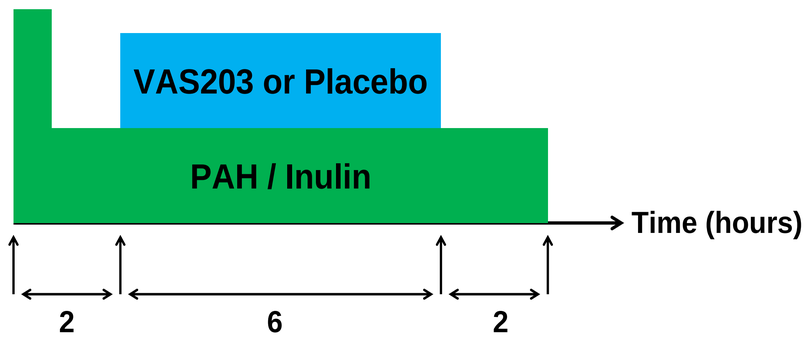
- The tetrahydrobiopterin-analogue VAS203, an inhibitor of predominantly the inducible nitric oxide synthase (iNOS), was developed to reduce secondary damage in patients with severe traumatic brain injury.
- In both the first-in-man study and an explorative phase IIa study, a dose-dependent acute kidney injury was observed in few subjects.
- The aim of the present study was to characterize in detail the pharmacological effects of VAS203 on renal hemodynamics in healthy male humans.

Methods and Study population:

- In this single-centre, double-blind, randomized, placebo-controlled cross-over phase I study 16 healthy male subjects were included.



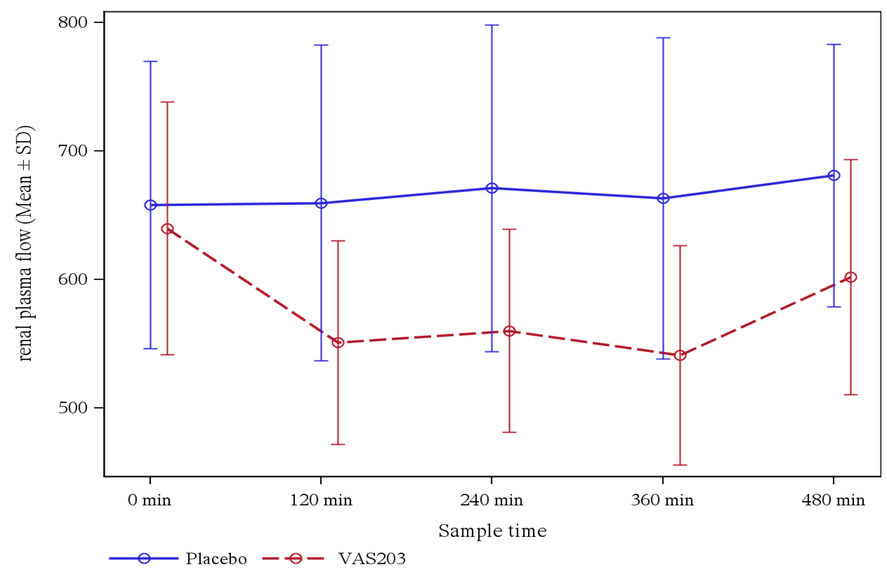
- Renal hemodynamics were assessed with constant-infusion input-clearance technique with PAH and inulin for renal plasma flow (RPF) and glomerular filtration rate (GFR). Additionally a constant infusion of VAS203 (total 10mg/kg body weight) or placebo was administered for 6 hours.



- In parallel, markers of early kidney injury (e.g. NGAL) and renal function (e.g. cystatin C) were assessed at baseline and repeatedly up to 48 hours after the start of the VAS203/placebo-infusion.
- The study was registered at www.clinicaltrials.gov (ID: NCT02992236).

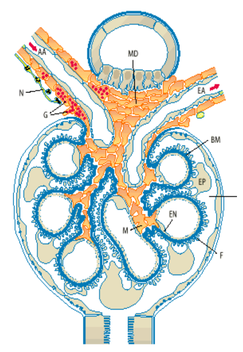
Results:

- Intravenous infusion of VAS203 resulted in a reduction of RPF, but remained unchanged with placebo, resulting in a significant decrease of RPF with VAS203 compared to placebo (p<0.0001).



- GFR also decreased during infusion of VAS203 in comparison to placebo (p<0.001).
- RPF and GFR recovered partly two hours after end of VAS203 infusion and was normal at begin of the second infusion period.
- The magnitude of the changes in RPF and GFR was in the range which can be observed under physiological conditions.
- Analysis of intraglomerular hemodynamics revealed that compared to placebo vascular resistance at the preglomerular site (R_A) increased (p<0.0001), and to lesser extent also at the postglomerular resistance (R_E) (p<0.001) resulting in a decrease of intraglomerular pressure (P_{glom}) (p<0.01).

Resistance of afferent arteriole (R_A)



Resistance of efferent arteriole (R_E)

Intraglomerular pressure (P_{glom})

- There was no change of blood pressure due to VAS203 infusion, indicative of no clinical meaningful systemic effect of VAS203.
- There was no effect on markers of early kidney injury, and on renal function in the longer follow-up (p>0.20). Also, no clinical signal of acute kidney injury was observed in any subject.

Conclusion:

Our phase I study in humans indicate that a dose of 10 mg/kg body weight VAS203 reduces renal perfusion and glomerular function within a physiological range mainly due to vasoconstriction at the preglomerular side.

This pharmacological profile corresponds to a drug with iNOS inhibition and the safety profile of VAS203 was excellent.

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