SNF472 INHIBITS VITAMIN D INDUCED CARDIOVASCULAR CALCIFICATION IN RATS

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INTRODUCTION

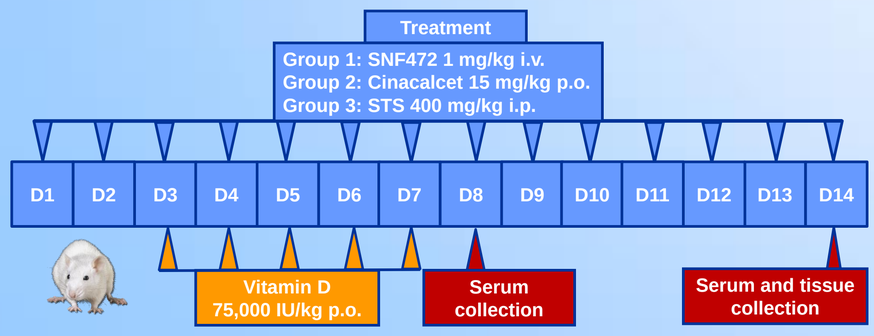
Cardiovascular calcification has been shown to be an independent predictor of cardiovascular events in CKD patients. SNF472 under development by SANIFIT, is an intravenous formulation of myo-inositol hexaphosphate, a small and highly water-soluble molecule that inhibits calcification by binding to the growing sites of the hydroxyapatite (HAP) crystal. Beneficial properties have been attributed to this compound in calcium related diseases such as the prevention of renal lithiasis[1], osteoporosis[2], cardiovascular calcification[3], sialolithiasis[4] and dental tartar[5].

AIM

To investigate the effects of SNF472 on vitamin D induced vascular calcification, and compare its activity with cinacalcet and sodium thiosulfate (STS).

MATERIALS AND METHODS

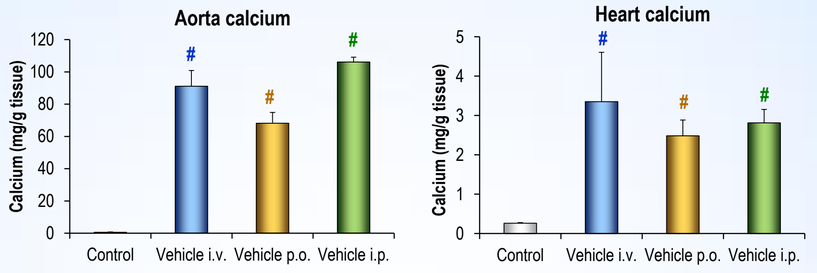
The study was done in 40 male Sprague Dawley rats divided into 3 groups of 10-16 animals. Group 1 received daily intravenous (i.v.) vehicle or 1 mg/kg SNF472. Group 2 received vehicle or 15 mg/kg of peroral (p.o.) cinacalcet. Group 3 received vehicle or 400 mg/kg of intraperitoneal (i.p.) STS. Calcification was induced by 5 daily p.o. administrations of vitamin D_3 (75,000 IU/kg) starting on day 3 of treatment. Five sham treated animals served as control. Serum samples for the determination of calcium and phosphorus concentrations were collected on days 8 and 14. Rats were sacrificed on day 14 and aortas and hearts removed for calcium analysis.



RESULTS

The administration of vitamin D_3 induced a marked increase in aortic and heart calcium levels.

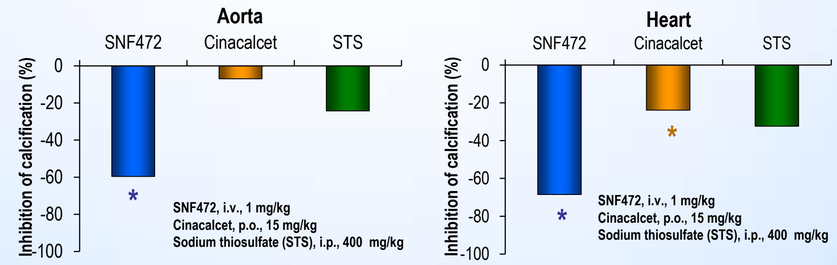
Figure 1. Aorta and heart calcification induction by 5 consecutive daily p.o. administrations of 75,000 IU/kg vitamin D_3



Statistical analysis: One-way ANOVA. (#) Differences vs Control, $p < 0.05$

The intravenous administration of SNF472 at 1 mg/kg resulted in a 60% and 68% reduction in aortic and heart tissue calcification respectively. Animals treated with cinacalcet and STS showed reductions of maximally 30%. Statistically significant reduction occurred with SNF472 in heart and aorta and with cinacalcet in heart.

Figure 2. Aorta and heart calcification inhibition by 14 daily 1 mg/kg i.v. administration of SNF472 and comparators (p.o. cinacalcet and i.p. STS)

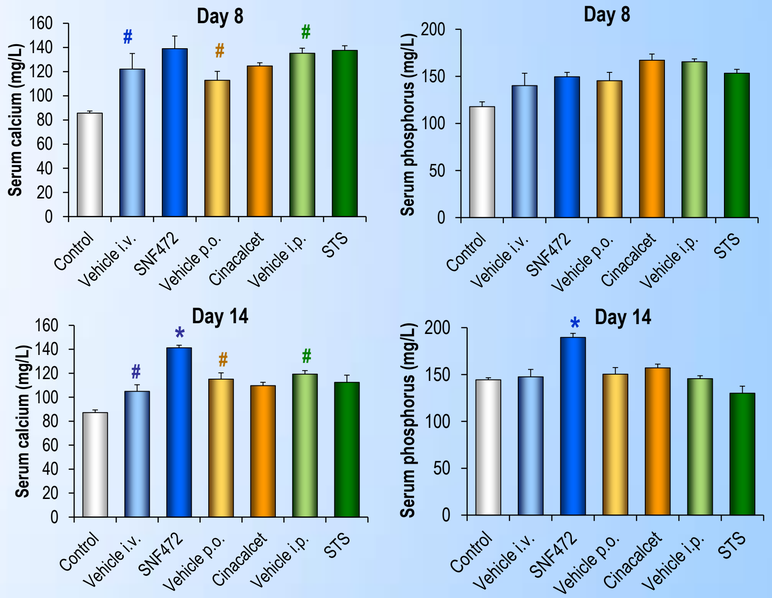


Statistical analysis: One-way ANOVA. (*) Differences vs vehicle, $p < 0.05$

Serum calcium from non treated animals increased at day 8–compared to the control group and remained increased by day 14. It was not affected by cinacalcet or STS treatment, but was significantly increased in the group of animals treated with intravenous SNF472 after 14 days of treatment.

Serum phosphorus levels were not affected by the administration of vitamin D_3 but the treatment with SNF472 slightly increased calcium and phosphorus levels in serum by day 14, which could be a mass-balance consequence due to the reduction of cardiovascular calcification in this severe model of hypercalcemia and hyperphosphatemia.

Figure 3. Calcium and phosphorus serum levels in rats treated with i.v. 1 mg/kg SNF472 or comparators (p.o. cinacalcet 15 mg/kg and i.p. STS 400 mg/kg) for 8 and 14 days



Statistical analysis: One-way ANOVA. (#) Differences vs Control, (*) differences vs vehicle, $p < 0.05$

CONCLUSIONS

SNF472 inhibits aorta and heart calcification induced by vitamin D in a rat model.

Calcification inhibition by SNF472 is significantly higher than that exerted by cinacalcet and STS.

These results suggest that SNF472 might be an alternative therapeutic principle for cardiovascular calcification treatment.

BIBLIOGRAPHY

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