21. Others

Reference

Kitagawa H, Munekage M, Matsumoto T, et al. Pharmacokinetic profiles of active ingredients and its *metabolites* derived from rikkunshito, a ghrelin enhancer, in healthy Japanese volunteers: A cross-over, randomized study. *PloS One* 2015; 10: 1-19.

1. Objectives

To analyze the pharmacokinetics of the active ingredients of rikkunshito (六君子湯) in healthy volunteers.

2. Design

Randomized controlled trial cross-over (cross over) (RCT-cross over).

3. Setting

One university department of medicine, Japan.

4. Participants

21 healthy participants. Ages 20-45, BMI 18-25. Participants had no liver, heart or vascular disease, and had not taken a supplement or pharmaceutical containing rikkunshito active ingredients. Pregnant or lactating women, and chronic alcohol or nicotine consumers were excluded.

5. Intervention

Arm 1: TSUMURA Rikkunshito (六君子湯) Extract Granules taken orally once in each of Period 1 (7.5g/day), Period 2 (2.5g/day), and Period 3 (5g/day) (n=7).
Arm 2: TSUMURA Rikkunshito (六君子湯) Extract Granules taken orally once in each of Period 1 (2.5g/day), Period 2 (5g/day), and Period 3 (7.5g/day) (n=7).
Arm 3: TSUMURA Rikkunshito (六君子湯) Extract Granules taken orally once in each of Period 1 (5g/day), Period 2 (7.5g/day), and Period 3 (2.5g/day) (n=7).

Participants took standard meals not containing active ingredients of rikkunshito from 3 days before the start of the trial. They fasted for 12 hours before taking the trial drug. Blood was sampled before taking the rikkunshito (0), then 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, and 48 hours, and the plasma was stored. A physician was in attendance.

6. Main outcome measures

Plasma concentrations of the 9 active ingredients contained in rikkunshito (Atractylodin, Atractylodin carboxylic acid, Pachymic acid, Heptamethoxyflavone, Naringenin, Nobiletin, Liquiritigenin, Isoliquiritinigenin, and 18β-Glycyrrhetinic acid), Cmax, AUC. 32 active ingredients determined by screening in preliminary tests. Atractylodin carboxylic acid was not screened, but was added to the trial as it is an Atractylodin metabolite.

7. Main results

One participant dropped out of arm 1 (after the second administration), and 2 dropped out of arm 2 (after the first and the second administrations). 1 participant dropped out of arm 1 and 1 from arm 2, leaving 19 subjects for analysis. The order of Cmax (7.5mg orally) was 18β-Glycyrrhetinic acid, Atractylodin carboxylic acid, Naringenin, Liquiritigenin, Heptamethoxyflavone, Pachymic acid, Isoliquiritinigenin, then Nobiletin. Tmax (7.5g) was 1 hour or less for Atractylodin carboxylic acid, Isoliquiritinigenin, Nobiletin, Atractylodin, and Heptamethoxyflavone and 3 hours or more for the other 4 active ingredients. Half-life (7.5g) was 10 hours or more for 18β-Glycyrrhetinic acid and Pachymic acid, and less than 10 hours for the other 7 active ingredients. There was dose dependency in the range 2.5-7.5g, for Cmax of Atractylodin and Atractylodin carboxylic acid and for AUC of 18β-Glycyrrhetinic acid and Atractylodin carboxylic acid.

8. Conclusion

The nine active ingredients of rikkunshito were pharmacokinetically analyzed after administration, finding the Cmax, Tmax, half-life and presence/absence of dose dependency of each ingredient.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Two participants dropped out, but the reasons were not mentioned.

11. Abstractor's comments

This is an unprecedented paper setting out the pharmacokinetics of the active ingredients of rikkunshito after administration to healthy subjects in a rigorously designed study. Giving consideration to these pharmacokinetics and clinical effects under clinical trial may allow for rikkunshito's mechanisms of action to be elucidated. However, as the authors mention, it would be difficult to explain the effects of rikkunshito with one ingredient. In fact, the pharmacokinetics of each ingredient differ, and the effect of rikkunshito could be exerted through the synergic action of multiple ingredients.

12. Abstractor and date

Kogure T, 29 December 2016.