

## Evidence Reports of Kampo Treatment

Task Force for Evidence Reports, the Japan Society for Oriental Medicine

Note) The quality of this RCT has not been validated by the EBM committee of the Japan Society for Oriental Medicine.

### 21. Others

#### Reference

Kitagawa H, Munekage M, Ichikawa K. et al. Pharmacokinetics of Active Components of Yokukansan, a Traditional Japanese Herbal Medicine after a Single Oral Administration to Healthy Japanese Volunteers: A Cross-Over, Randomized Study. *PLoS One* 2015 7; 1-14.

#### 1. Objectives

Pharmacokinetics of the blood concentration of active ingredients of yokukansan (抑肝散) in healthy subjects.

#### 2. Design

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

#### 3. Setting

Two university surgery departments.

#### 4. Participants

Healthy participants from 20- to 45-years, who had not taken any supplement containing yokukansan ingredients in the 3-7 days before start of the trial, and had no kidney disease, heart or vascular disease (n=21).

#### 5. Intervention

Arm 1: TSUMURA Yokukansan (抑肝散) Extract Granules 2.5g→5g→7.5g/day once administered orally (n=8).

Arm 2: TSUMURA Yokukansan (抑肝散) Extract Granules 5g→7.5g→2.5g/day once administered orally (n=7).

Arm 3: TSUMURA Yokukansan (抑肝散) Extract Granules 7.5g→2.5g→5g/day once administered orally (n=6).

A 4-week washout period was allowed before changing the dosage.

#### 6. Main outcome measures

Blood kinetics of Geissoschizine methyl ether (GM), Hirsuteine (HTE), and 18β-glycyrrhetic acid (GA)

#### 7. Main results

One participant dropped out of each of arms 1 and 3 after the first administration.

Results after taking orally 2.5g, 5g, and 7.5g respectively of TSUMURA Yokukansan (抑肝散) Extract Granules

GM: Cmax 2.5g=0.650ng/ml 5g=1.39ng/ml 7.5g=1.98ng/ml

AUC 2.5g=1.18ng/ml 5g=2.98ng/ml 7.5g=4.81ng/ml

HTE: Cmax 2.5g=0.138ng/ml 5g=0.305ng/ml 7.5g=0.450ng/ml

AUC 2.5g=0.277ng/ml 5g=0.833ng/ml 7.5g=1.50ng/ml

GA: Cmax 2.5g=57.7ng/ml 5g=84.3ng/ml 7.5g=108ng/ml

AUC 2.5g=690ng/ml 5g=1210ng/ml 7.5g=1670ng/ml

#### 8. Conclusion

GM and HTE blood concentrations increased rapidly after taking yokukansan extract (0.5-1 hour), and rapidly reached their half-lives (2-3 hours). However, GA is an aglycone of GL. Absorption of GL directly was poor, and was not detected in blood. Yet, while GA, without glycosides, has greater absorption than GM or HTE, Tmax is slower than GM or HTE, 8 hours, and its half-life is long (11 hours).

#### 9. From Kampo medicine perspective

None.

#### 10. Safety assessment in the article

No adverse event was observed during the trial.

#### 11. Abstractor's comments

This paper describes the pharmacokinetics of the active ingredients of yokukansan. Although the glycoside absorption rate is 8 times slower than alkaloids, its blood concentration was found to be 100 times greater. Although it is currently not understood how drug action is related to the fact that different ingredients reach blood concentration peaks at different times, the active ingredients in crude drugs are generally taken up into the blood in 1-8 hours, so when prescribing, the timing of administration must take those factors into account.

#### 12. Abstractor and date

Nakata H, 2 February 2017.