

## EFFECT OF ZOLPIDEM TARTRATE ON URINE VOLUME IN RATS

### Hypothesis / aims of study

Owing to its clinical efficacy, safety, tolerability and favorable pharmacokinetic profile, zolpidem tartrate is now one of the most commonly prescribed hypnotic drugs. It was recently reported that zolpidem tartrate may improve nocturia in both clinical and non-clinical studies. However, the mechanism of this effect remains unknown. Nocturia is known to have various causes, one of which is hypothesized to be the influence of urine volume. Here, we examined the effect of zolpidem tartrate on urine volume in rats.

### Study design, materials and methods

**Antidiuretic effect of a single oral administration of zolpidem tartrate in male Wistar rats.** Five rats were used at each dose tested. The rats were loaded with distilled water at a volume of 30 mL/kg po at 10 min after oral administration of zolpidem tartrate (0.1 – 10 mg/kg) and then placed in metabolic cages with no access to food or water for 2 h during the daytime. Urine was collected by test tube from 0 - 1 h and 1 - 2 h after water loading and the percentage of urine volume relative to water loading was calculated as the urinary excretion rate. Linear regression was performed to obtain the dose of test compound required to decrease urine volume up to 1 h after administration to 50% (ED<sub>50</sub>) of that in the control group.

**Inhibitory effect of zolpidem tartrate on radioligand binding to rat vasopressin V<sub>2</sub> receptor.** Plasma membranes of rat kidney medulla were used. In a competition binding assay, membrane preparations were incubated with [<sup>3</sup>H]-AVP and AVP ([Arg<sup>8</sup>]-Vasopressin) or [<sup>3</sup>H]-AVP and zolpidem tartrate (10<sup>-5</sup> M) for 1 h, and radioactivity in samples was counted with a TopCount Microplate Scintillation Counter (Packard Instrument Company). Results were expressed as the mean values of duplicate samples. The inhibition rate was calculated as follows:

$$[1 - (B - N)/(B_0 - N)] \times 100 (\%)$$

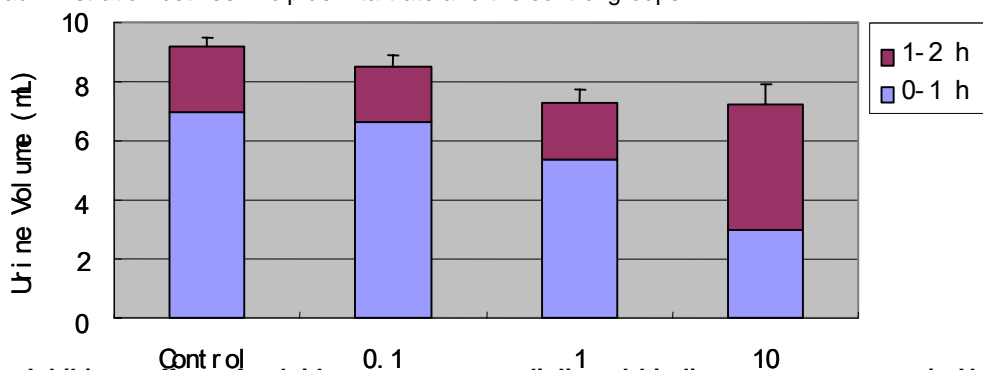
B: Radioactivity or fluorescence intensity in the tube for calculation of inhibition rate.

B<sub>0</sub>: Radioactivity or fluorescence intensity in the tube for calculation of total reaction.

N: Radioactivity or fluorescence intensity in the tube for calculation of non-specific reaction.

### Results

**Antidiuretic effect of a single oral administration of zolpidem tartrate in male Wistar rats.** Zolpidem tartrate decreased urine volume for a period of 0 to 1 h after administration in a dose-dependent fashion, with an ED<sub>50</sub> value of 6.5 mg/kg. In contrast, there were no significant differences in urine volume for the period of 0 to 2 h after administration between zolpidem tartrate and the control groups.



**Inhibitory effect of zolpidem tartrate on radioligand binding to rat vasopressin V<sub>2</sub> receptor.** AVP inhibited binding of [<sup>3</sup>H]-AVP to rat V<sub>2</sub> receptor with an inhibition rate of 99.7%. In contrast, zolpidem tartrate at 10<sup>-5</sup> M inhibited this binding by only 6.9%.

### Interpretation of results

Zolpidem tartrate decreased urine volume for 0 to 1 h after oral administration in rats. Various mechanisms for the antidiuretic effect of zolpidem tartrate have been proposed, including its causing an increase in plasma AVP levels by the induction of sleep, via the mediation of a direct V<sub>2</sub> agonist effect, and an as yet unknown action. We therefore examined whether zolpidem tartrate possess a direct V<sub>2</sub> agonistic effect. Results showed that a high concentration of zolpidem tartrate (10<sup>-5</sup> M) did not inhibit binding to V<sub>2</sub> receptors, suggesting that the antidiuretic effect of this drug is attributable to pharmacological actions other than a direct V<sub>2</sub> agonistic effect. Further investigation is needed to determine the mechanism of zolpidem tartrate on the improvement of nocturia.

### Concluding message

Zolpidem tartrate suppressed urine volume via an effect other than V<sub>2</sub> receptor agonism. This finding suggests that zolpidem tartrate may have potential in the treatment of nocturia in humans.

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**ANIMAL SUBJECTS:** This study followed the guidelines for care and use of laboratory animals and was approved by Astellas Pharma Inc.