Does theophylline really improve acute mountain sickness?

From the authors:

RÖGGLA *et al.* [1] performed a double-blind, placebo-controlled crossover trial in eight subjects to investigate the effects of "nonretardized" theophylline on oxygen tension in arterial blood (P_{a,O_2}) and carbon dioxide tension in arterial blood (P_{a,CO_2}), 2 h after ingestion of 300 mg theophylline. They did not demonstrate a significant increase of P_{a,O_2} or significant decrease of P_{a,CO_2} in the theophylline group and questioned the evidence of our study indicating a positive effect of theophylline on acute mountain sickness (AMS). However, there were major differences between both studies. First, RÖGGLA *et al.* [1] studied eight healthy volunteers at moderate altitude (2600 m) compared to 21 volunteers at 3500 m in our study, therefore decreasing substantially the incidence of AMS. It seems questionable how the authors want to evaluate an effect of theophylline on AMS, when they did not measure symptoms of AMS. Furthermore, ventilatory adaptation was measured only indirectly by means of change of blood gases without any other cardio-pulmonary parameters (respiratory frequency, pulse rate). Serum levels of theophylline in the verum group have not been reported, so it remains unclear whether the subjects reached therapeutic serum levels during blood gas analysis. Due to the oral slow-release theophylline we used, the time points chosen for measurements were not comparable and late effects (after 18 h in our investigation) were missed in the study of RÖGGLA *et al.* [1].

In our study [2], mean serum theophylline serum levels were 40.5 μM in the decompression chamber study and 51.4 μM in the high-altitude study, respectively. In both parts of our study, oxygenation was improved in the verum group. However, the increase in P_{a,O_2} or arterial oxygen saturation and the decrease in P_{a,CO_2} was not always significant, as in the study of RÖGGLA *et al.* [1]. In contrast to the known small ventilatory stimulating effects of theophylline, we

found a significant effect of theophylline on AMS, compared to placebo. However, we found no correlation between oxygenation and severity of AMS. This is in accordance to the observation that hypoxic ventilatory response and AMS are not correlated [3].

This discrepancy between the small increase in oxygenation, but definite improvement of symptoms of AMS might be explained by different modes of action of theophylline at high-altitude (phosphodiesterase inhibition, increase of central respiratory drive, reduction of cerebral blood flow, prevention of leakage of cerebral vascular endothelium, *etc.*).

Since RÖGGLA *et al.* [1] did not study any of these mechanisms it seems speculative to derive any far reaching conclusions concerning the effect of theophylline from their limited data. We do not feel that our data are really contradicted by their work. However, we agree with them that the issue of improvement of acute mountain sickness by theophylline is of high interest and further investigations are needed to elucidate the effects of theophylline at high-altitude.

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