Obstructive sleep apnea (OSA) is a common disorder characterized by repetitive collapses of the pharyngeal airway during sleep. The prevalence of moderate-severe OSA (AHI > 15) in middle-aged adults is approximately 7% (9% in men, 4% in women), whereas the prevalence of mild OSA is substantially higher.1 OSA is highly prevalent in patients with cardiovascular and metabolic disorders. The current gold standard treatment is continuous positive airway pressure (CPAP) via a mask that splits open the airway against all collapse-inducing forces. The discomfort associated with CPAP reduces compliance so that only 50-70% of the patients with OSA use it in the long run. Therefore, a pharmacological treatment would be highly desirable for those who do not tolerate CPAP or who refuse it because they do not suffer from excessive daytime sleepiness but who may carry a higher cardiovascular risk.

OSA results from an anatomically narrow upper airway (UA) in conjunction with an insufficient neuromuscular activation of the UA dilating muscles during sleep, in absolute terms or only relative to the need for a higher tone that would be required in a narrow airway to compensate for the unfavourable narrow anatomy. Whether effective pharmacological activation of UA dilating muscle activity is possible in patients with OSA remains to be demonstrated because attempts to do so were not convincingly successful despite a number of clinical studies with different pharmacological principles.

Major pharmacological progress in the search for drugs for OSA has been hampered or even precluded by both the lack of appropriate pharmacological models and the lack of innovative pharmacological concepts for anti-OSA drugs. To some extent both flaws were causally related in that it is difficult to establish a new pharmacological model without a positive control (a drug appropriate at least for experimental purposes). Developing new pharmacological concepts often requires testing of numerous diverse pharmacological principles in an appropriate animal model to deduce ideas for more appropriate and more efficacious pharmacological principles. We succeeded in identifying a potent new pharmacological principle that inhibited UA collapsibility in pigs as a functional parameter.

In urethane-α-chloralose-anesthetized spontaneously breathing pigs, continuous application of negative pressure to the UA for a few breaths caused UA occlusion (referred to as collapse). UA collapse was indicated by an interruption of airflow to the negative pressure device and by a subglaryngeal pressure change from atmospheric pressure to a pressure that approximated the device pressure because the collapsed UA was almost airtight toward its oral end. GG EMG increased during the negative pressure challenge but was ineffective in opening the UA under control conditions. Pharmacologically augmented inspiratory phasic activation of UA dilating muscle was able to open the closed airway in case of effective stimulation during the inspiratory phase whereas in most cases the UA collapsed again during the expiratory phase because of an expiratory decline in UA dilating muscle activity. The closed airway then opened again with the rise in UA dilating muscle activity with the next inspiratory phase.

In this article we demonstrate a new potential drug for the treatment of OSA, which we characterized in a newly developed pharmacological pig model for OSA. The potassium channel blocker AVE0118 given via nasal administration sensitized and amplified the NPR as indicated by a shift of the threshold to much higher pressures. Given as a slow-release formulation it showed a complete inhibition of UA collapsibility at 10 mg per nostril for more than 4 h, showing its potential for the treatment of OSA. Topical administration of lidocaine to the UA abolished the effect of AVE0118 in accordance with its peripheral mode of action. Collapsibility returned a few min after lidocaine administration when GG EMG had disappeared.

In summary, we present a new pharmacological model for the investigation of the potential of drugs against OSA in spontaneously breathing urethane-α-chloralose anesthetized pigs that is based on UA collapsibility induced by application of strong negative pressures. In this model we investigated a new effective pharmacological principle, which is based on a pharmacological sensitization of UA mechanoreceptors for negative pressure. By topical administration to the UA, potassium channel blocker AVE0118 demonstrated its potential to treat OSA by sensitizing the mechanoreceptor reflex and abolishing UA collapsibility for more than 4 h.

**Source**

Sensitization of Upper Airway Mechanoreceptors as a New Pharmacologic Principle to Treat Obstructive Sleep Apnea: Investigations with AVE0118 in Anesthetized Pigs

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SLEEP, Vol 36 No. 5 2013