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(54) ALKYLARYL POLYETHER ALCOHOL POLYMERS FOR TREATMENT AND PROPHYLAXIS OF SNORING, SLEEP APNEA, SUDDEN INFANT DEATH SYNDROME AND FOR IMPROVEMENT OF NASAL BREATHING

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(57) **ABSTRACT**

A method and composition for treatment and prophylaxis of snoring, sleep apnea or sudden infant death syndrome and for improvement of nasal breathing in mammals by nasal and/or pharyngeal administration of tyloxapol or a related alkylaryl polyether alcohol polymer. A spray, liquid or solid composition comprising from about 0.01 to about 20% (w/v), equivalent to about 100 μg/ml to about 200 mg/ml, of tyloxapol or another alkylaryl polyether alcohol polymer alone or in admixture with pharmaceutically acceptable excipients and additives. The composition is administered as a spray, liquid, liquid drops, lozenges or powder suitable for nasal and/or pharyngeal application.

FIG 1

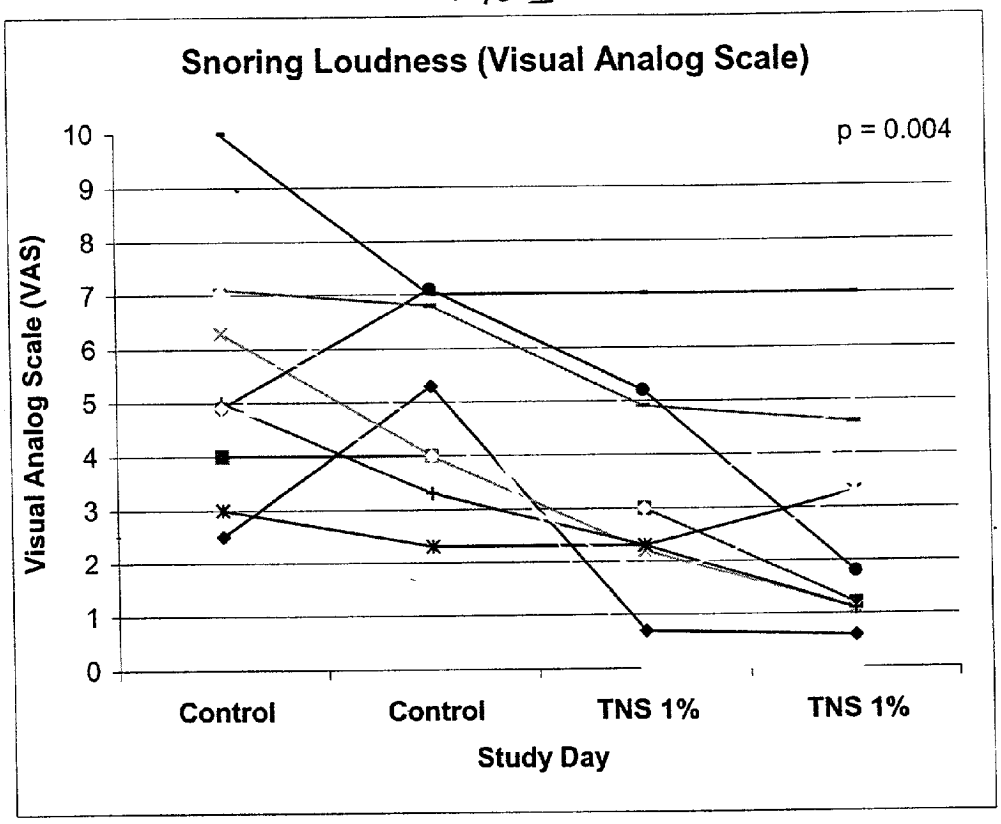

Figure 1: Snoring is rated by the subject's bed partner on a scale of 0-10, and treatment nights (3 + 4, TNS 1%) are compared to control nights (1 + 2, no treatment).

FIG 2

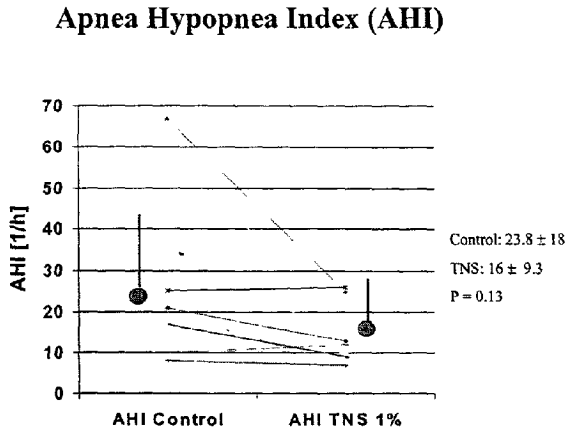

Figure 2: AHI is defined as the number of Apneas and Hypopneas per hour, and is also referred to as "RDI" (Respiratory Distress Index)

FIG. 3

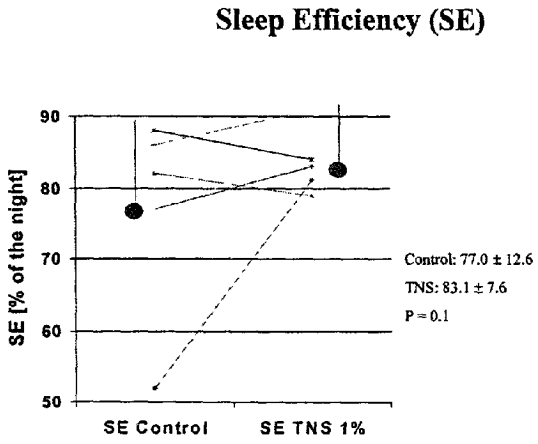

Figure 3: Sleep Efficiency is defined as the time asleep (measured by EEG) as a percentage of the time in bed.

FIG. 4

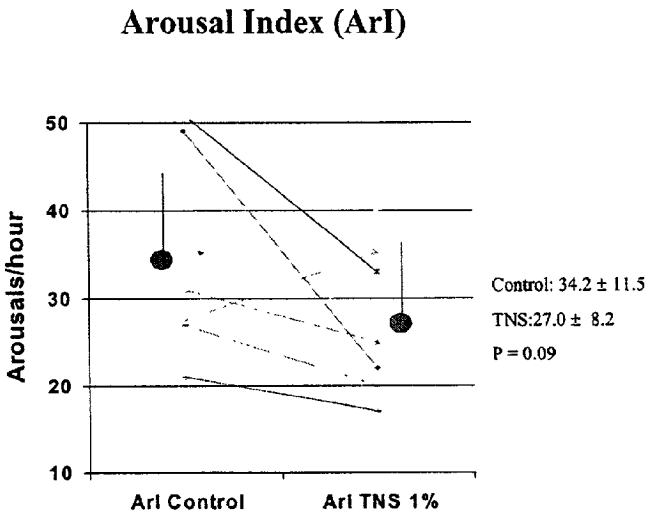

Figure 4: Arousal Index describes the number of (respiratory and EEG-based) arousals per hour.

ALKYLARYL POLYETHER ALCOHOL POLYMERS FOR TREATMENT AND PROPHYLAXIS OF SNORING, SLEEP APNEA, SUDDEN INFANT DEATH SYNDROME AND FOR IMPROVEMENT OF NASAL BREATHING

[0001] This application is based on and claims priority of the provisional application Ser. No. 60/264,166 filed on Jan. 24, 2001.

BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] The current invention concerns a method and composition for treatment and prophylaxis of snoring, sleep apnea or sudden infant death syndrome and for improvement of nasal breathing in mammals by nasal and/or pharyngeal administration of tyloxapol or a related alkylaryl polyether alcohol polymer. In particular, the present invention provides a spray, liquid or solid composition comprising from about 0.01 to about 20% (w/v), equivalent to about 100 μg/ml to about 200 mg/ml, of tyloxapol or another selected alkylaryl polyether alcohol polymer alone, in combination, or in admixture with pharmaceutically acceptable excipients and additives. The composition is administered as a spray, liquid, liquid drops, lozenges or powder suitable for nasal and/or pharyngeal application.

[0004] 2. Background of the Invention

[0005] Snoring and related sleep apnea are amongst the most troublesome sleeping impairments. Snoring is not only a nuisance for other people, but it has been shown, similarly to sleep apnea, to correlate with increased daytime sleepiness and decreased alertness and work performance.

[0006] As a consequence of snoring and sleep apnea, normal sleep rhythm is disturbed and oxygen saturation is decreased ensuing in following tiredness and decrease in alertness and performance. Sleep apnea is characterized by repetitive episodes of upper airway obstruction that occurs during sleep and is usually associated with blood oxygen desaturation, snoring and daytime sleepiness.

[0007] Sleep apnea is defined as cessation of air flow for more than ten seconds, occurring at least ten times per hour at night (*Clinics in Chest Medicine,* 19:1 (1998) and *Diagnostic and Coding Manual, The International Classification System of Sleep Disorders,* Rochester, Minn. (1990)).

[0008] Sleep apnea often leads to increased blood pressure, EKG changes, arrhythmia, neurologic changes, and even to increased risk for stroke (*Clinics in Chest Medicine* 19:1 (1998).

[0009] A milder form of sleep disordered breathing affects many millions of people in the United States. Additionally, several million people suffer from an even more severe form of sleep disordered breathing (*National Commission on Sleep Disorders Research,* Bethesda, Md. (1995).

[0010] Pathophysiologically, snoring and sleep apnea are characterized by a recurrent closure of the pharyngeal airway during sleep. Upper airway patency is influenced by muscle activity, anatomical features, vasomotor tone, mucosal adhesive forces and inflammation (*Clinics in Chest Medicine,* 19:1 (1998)).

[0011] Snoring is an inspiratory sound which arises during a person's sleep. It is believed to be generally caused by the narrowing of the nasopharyngeal airway which is caused by a turbulent airflow during relaxed breathing which vibrates the soft parts of the oropharyngeal passage, such as the soft palate, the posterior faucial pillars of the tonsils and the uvula. While snoring is unpleasant for other people, it is typically not dangerous to the snorer and may cause fatigue. On the other hand, sleep apnea causes disruption in the sleep pattern and can result in daytime tiredness, loss of alertness and productivity. It would thus be advantageous to provide a treatment for both snoring and sleep apnea.

[0012] The current treatments of sleep apnea and snoring are dominated by both pharmacological and non-pharmacological treatments, however, none of these have been found entirely satisfactory.

[0013] Examples of nonpharmacological treatment include positive pressure therapy, such as nocturnal ventilation, continuous positive airway pressure, oral apparatuses, such as tongue retainers and jaw protractors, and surgical management, such as uvulopalatopharyngoplastic surgery comprising removal of accessory pharyngeal tissue. A comprehensive overview of these techniques is given in *Clinics in Chest Medicine,* 19(1):55-68 (1998); *Clinics in Chest Medicine,* 19(1):69-76 (1998); and *Clinics in Chest Medicine,* 19(1):77-86 (1998), among others.

[0014] Numerous other non-pharmaceutical treatment modalities have been proposed and used, however, these treatments, similar to those described above, are not entirely satisfactory and effective. Amongst these modalities are techniques used to manipulate a sleep position by, for example sewing a marble or tennis ball into a pyjama to avoid supine sleeping, visual or electric manipulation triggered by microphones or mild electrical shock devices, or mechanical devices used to manipulate the head position.

[0015] Other treatments utilize such conservative measures as weight loss, reduction of alcohol consumption and avoidance of medications which influence muscular tone.

[0016] Pharmacological treatment modalities include the systemic application of the therapeutic agents, such as tricyclic antidepressants, medroxyprogesterone acetate, tryptophane and other agents. All these agents have been used only with limited success, in part because they can cause undesirable secondary reactions.

[0017] Some attempts were made to treat and prevent snoring and sleep apnea with various topically administered agents. In this regard, to date, the following nasal spray applications have been suggested as possible treatments for snoring.

[0018] Phosphocholinamine as a topical spray (*Am. J. Otolaryngol.:,* 8: 236 (1987)), topical administration of methylsulfonylmethane to the nasal epithelium (U.S. Pat. No. 5,569,679), and a mixture of surface active agents including Polysorbate 80, commercially available under the trade name Sonarex®, were suggested and/or are available as a topical spray for snoring.

[0019] The idea of nasal sprays to treat snoring dates back to 1955, when surface active substances, but not tyloxapol or alkylaryl polyether alcohol polymers, were first proposed for this purpose in U.S. Pat. Nos. 2,989,437 and 4,668,513 and

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