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Yohimbine increases human salivary secretion

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The effect of oral yohimbine (14 mg) on salivary secretion was evaluated in healthy volunteers. Yohimbine significantly increased salivary secretion when compared with placebo. This effect was significant from 60 min until 180 min after administration under our experimental conditions. Yohimbine (or α_2-adrenoceptor blocking agents) could have a potential interest in the treatment of dry mouths.

Keywords yohimbine salivary secretion

Introduction

A common side effect of α_2-adrenoceptor agonists, and especially clonidine, is a reduced salivation resulting in a dry mouth. The mechanism of this side effect remains uncertain but several studies have suggested an action through activation of α_2-adrenoceptors located on parasympathetic neurons in the central nervous system or in the periphery (Langer & Massingham, 1980). Animal studies showed that the inhibitory effect of clonidine on the salivary secretion induced by stimulation of the chorda tympani is suppressed by yohimbine (Green *et al.* 1979). Recent studies from our group showed that yohimbine by itself is able to enhance submaxillary salivary secretion in anaesthetized dogs (Montastruc *et al.*, 1989). Thus, the aim of the present study was to evaluate the effect of yohimbine on salivary secretion in humans.

Methods

Two experimental protocols were performed in healthy volunteers who gave informed consent. Alcohol was prohibited from the 12 h before each experiment and drugs from at least 1 week.

Twenty subjects, aged 25–44 years (14 males, six females) participated in the first randomized cross-over double-blind study of yohimbine against placebo. Salivary secretion was measured using one salivary cotton plug (diameter: 12 mm, length: 4 cm, 0.4 g) weighed before and 2 min after it was placed under the tongue close to the internal gum. Salivary secretion was measured before and 30, 45 and 60 min after administration yohimbine (or placebo). Yohimbine (Yohimbine Houde: yohimbine hydrochloride) was given orally at the dose of 14 mg selected according to our previous study showing that this dose induces an increase in sympathetic tone as estimated by the rise in both plasma noradrenaline and non-esterified fatty acids (Galitzky *et al.*, 1988). Since in this previous study yohimbine failed to modify blood pressure or heart rate, cardiovascular parameters were not measured in the present study. There was a wash-out period of 2 weeks between yohimbine and placebo administration.

The second protocol involved 10 subjects, aged 25–44 years (eight males, two females) drawn among the first 20 volunteers. This second randomized cross-over double-blind study investigated the time course of the effects of yohimbine over 3 h: using the same method we evaluated salivary secretion just before and 30, 60, 90, 120, 150 and 180 min after yohimbine (or placebo) given orally at the same dose than in the protocol 1.

Statistical analysis was made using Student's *t*-test for paired comparison. Mean values ± s.e. mean are given. The level of significance was $P < 0.05$.

Results

In order to test the reproducibility of the method, we measured, in a preliminary experiment, spontaneous salivation in 10 healthy subjects

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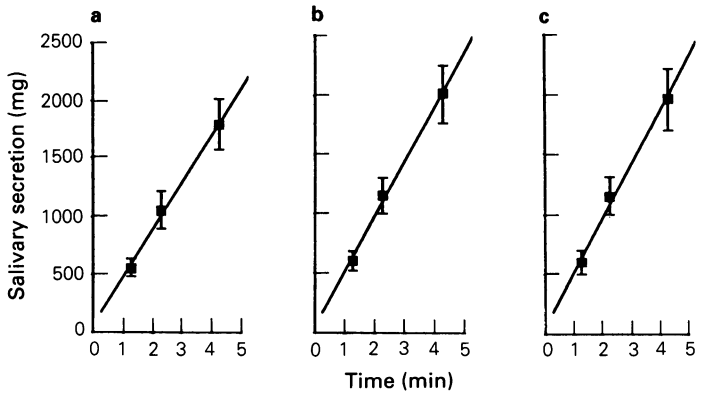

Figure 1 Mean spontaneous salivary secretion in 10 healthy volunteers evaluated at 15 min interval (a, b, c). Cumulative weight of the plug was plotted in function of time (1, 2 and 4 min). There was no significant difference between a, b and c in slope or absolute values at each time. Mean values ± s.e. mean are given.

three times (at 15 min interval) under basal conditions (i.e. without any drug or placebo). At each time, the same plug was weighed at 1, 2 and 4 min, thus allowing us to obtain a cumulative curve. Figure 1 indicates that the values obtained at the different times are similar indicating the validity of the method (at least when the measurements are separated for at least 15 min). We chose to measure the salivary secretion 2 min after the plug was introduced under the tongue (in order to avoid a possible saturation of the plug by excessive salivation with yohimbine): at time 2 min the amount of secreted saliva was around 1045 ± 142 mg under basal conditions.

The results of the protocol 1 clearly indicate that yohimbine increases salivary secretion: 60 min after yohimbine, salivary secretion was 1365 ± 141 mg ($P < 0.05$ when compared with 873 ± 95 mg with placebo). There was no order effect.

Figure 2 shows the time course of the effects of yohimbine when compared with placebo (protocol 2). Yohimbine-induced salivation was significant from 60 min until 3 h. Placebo was ineffective.

Few side effects were observed. With yohimbine, one subject complained of shivers and another of headache, whereas with placebo another volunteer suffered from headache. These side effects lasted around 60 min.

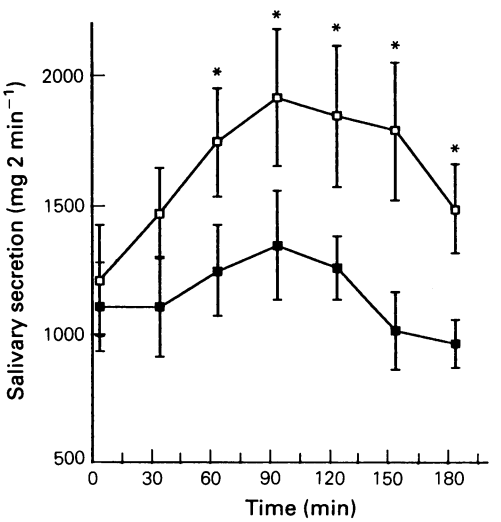

Figure 2 Effect of yohimbine (14 mg orally) on salivary secretion (mg 2 min^{-1}) in 10 healthy volunteers during the 3 h following its administration. Statistical evaluation was made using paired Student's *t*-test when yohimbine (□) was compared with placebo (■). mean values ± s.e. mean are given. * $P < 0.05$.

Discussion

This study clearly demonstrates that acute oral administration of yohimbine produces an increase in spontaneous salivary secretion in healthy man. This conclusion agrees with previous observations in conscious dogs (Taouis *et al.*, 1988). Moreover, in chloralose plus urethane anaesthetized dogs, yohimbine (0.5 mg kg^{-1} i.v.) increased spontaneous submaxillary salivary secretion and potentiated the effect of electrical stimulation of the chorda tympani (but not sympathetic) nerve (Montastruc *et al.*, 1989). These results suggest the existence of a tonic inhibition of salivary secretion by α_2-adrenoceptor stimulation in man.

Another interesting point of the present study is that the effect of yohimbine was observed during the 3 h following administration. This duration of action does not agree with the half-life of yohimbine observed in humans of around

0.6 h (Owen *et al.*, 1987). However, it is in accordance with recent data from our group indicating that yohimbine increases plasma catecholamines and non esterified fatty acids during 4 h (unpublished results). Until now, we have no explanation for this unexpected result. However, it could be suggested that this relatively long lasting effect could be attributed to active metabolite(s) (as proposed by Owen *et al.*, 1987). Another possibility is that the plasma pharmacokinetics of yohimbine in man (Diquet *et al.*, 1985; Owen *et al.*, 1987) do not reflect its tissue pharmacokinetics: for example, it was shown that the half-life of yohimbine in the brain was 3 h in mice (Ho *et al.*, 1971) and 7.7 h in rats (Hubbard *et al.*, 1988).

From a therapeutic point of view, this clinical study suggests the potential interest of yohimbine (and other α_2-adrenoceptor blocking agents) in the treatment of dry mouths. However, according to our previous results in dogs, demonstrating that yohimbine acts by inhibition of presynaptic α_2-adrenoceptors located on the chorda tympani (Montastruc *et al.*, 1989), one can suggest that this drug will be only active when the nerve is intact or functional.

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