An Alternative Method of Assessing Changes in Salivary Flow: Comparison of the Effects of Clonidine and Tiamenidine (HOE 440)

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Summary. An established method for collecting uncontaminated parotid saliva has been applied to assessment of salivary flow rate. Following single doses of 0.3 mg clonidine and 1.0 mg tiamenidine (HOE 440) changes in blood pressure, heart rate, sedation (assessed by a self-rating scale) and salivary flow were followed in nine normal subjects. Both drugs produced a fall in systolic and diastolic blood pressure, sedation, depression of salivary flow and a lowering of heart rate. These changes were maximal between 2 and 6 h and were more marked after clonidine than after tiamenidine. As tiamenidine 1.0 mg did not produce a hypotensive effect equivalent to clonidine 0.3 mg direct comparison of side-effects attributable to these agents proved difficult. The evidence suggests, however, that tiamenidine would cause sedation and reduction in salivary flow comparable to clonidine if given in an equivalent hypotensive dose.

Key words: Clonidine, tiamenidine, salivary flow, blood pressure, sedation.

Tiamenidine [(2-chloro-4-methyl-3- (2'-imidazoline-2'-yl amino)thiophene hydrochloride)] is a new hypotensive agent whose effects resemble clonidine in experimental animals. The structure of this compound closely resembles that of clonidine (Fig. 1). Lindner and Kaiser (1974) showed that like clonidine, tiamenidine produced a transient rise followed by a prolonged fall in blood pressure after intravenous injection in animals. These authors demonstrated that tiamenidine also resembles clonidine in producing a prompt hypotensive effect following intracisternal administration to dogs. This favours a central site of action for the hypotensive effect of the compound. A major difference between tiamenidine and clonidine revealed by the basic pharmacological work was the lower potency of tiamenidine on a weight-for-weight basis.

Recently published evidence (Ashton and Rawlins, 1978) suggested that it might be possible to separate the therapeutic and sedative actions of clonidine and related compounds. Sedation and dry mouth are consistent, often troublesome, side-effects during clonidine therapy (Putzeys and Hoobler, 1972), so that clonidine-like compounds less prone to produce these effects would have a useful place in the treatment of hypertension. The object of the study reported here was to compare sedation and reduction in salivary flow produced by clonidine and

Fig. 1. Structural formulae of tiamenidine and clonidine
tiamenidine while assessing the hypotensive action of single doses of these drugs in healthy volunteers. As unpublished work* suggested that in man 1.0 mg of tiamenidine was equivalent to 0.3 mg of clonidine in producing a fall in blood pressure, these were the doses used in this experiment. Salivary flow was assessed by a method not extensively used previously to study drug effects.

Methods

Subjects and Study Design

Nine healthy male volunteers, aged 19–38 years, took part in the study. The experiment was conducted double blind, subjects being treated with single oral doses of clonidine 0.3 mg, tiamenidine 1.0 mg or placebo in random order. Treatment periods were at one week intervals. Standard caffeine-free meals were taken at breakfast and lunch on study days. No other medication was permitted over the three-week study period.

Measurements

Observations were made before dosing and hourly until 8 h after oral administration of clonidine, tiamenidine or placebo. Supine blood pressure, pulse rate, self-assessed sedation and salivary flow were recorded on each occasion as outlined below.

1. After 30 min rest in a supine position, blood pressure was measured using a standard clinical sphygmomanometer. The systolic pressure was recorded as the point of appearance of continuous rhythmic sounds (Korotkoff 1: K1) and K5 was taken as the diastolic point. These measurements were made by two observers, each unaware of the other's reading, on every occasion. Blood pressure levels quoted are derived from the mean of these readings.

2. Heart rate was monitored by counting the radial pulse over 60 s after the 30 min rest period.

3. Following each 30 min period of recumbency subjects rated themselves using a 100 mm linear scale on which 0 mm represented "wide awake" and 100 mm represented "almost asleep".

4. Salivary flow was determined by measurement of the output from the parotid gland. This was achieved by means of a small suction cup (Stephen and Spiers, 1976) with an inner chamber placed over the parotid duct orifice. In the collecting system used suction was applied not only to maintain the position of the parotid cup, as described by Stephen and Spiers (1976) but also to facilitate collection of saliva, negative pressure (a constant 7 cm Hg) being applied to the inner chamber via a pre-weighed collecting tube. Salivary flow was quantitated by the weight of saliva accumulated over a timed collection period. Collecting vessels were weighed before and after use by a separate observer blind to both subjects and treatment.

Stimulated and unstimulated salivary flow were assessed at the time of each measurement as follows. At 30 min before dosing the collecting cup was applied to the buccal mucosa over the parotid duct (the right side in every case). Saliva was collected for 5 min after the application of a standard stimulus (0.5 ml 5% citric acid solution) to the dorsum of the tongue. Thereafter, when the collecting tube had been changed, saliva was collected for a further 25 min continuously without further citric acid stimulation. At the end of this continuous collection period blood pressure, heart rate and sedation were measured as described above. This sequence – starting with assessment of stimulated salivary flow at 30 min after dosing – was repeated eight times after administration of placebo or active drug. Salivary flow is quoted as a mean over the collection time under consideration in terms of mg · min⁻¹.

Statistical Analysis

Blood pressure measurements, pulse rates and sedation scores following tiamenidine and clonidine were compared with observations made at an equivalent time after placebo by means of the Students paired 't' test. As evidenced by the large errors on measures of salivary flow their distribution was not "normal" so a Wilcoxon matched pairs signed ranks test (Siegel, 1956) was used to compare salivary flow on drug and placebo days.

Results

Blood Pressure, Heart Rate and Sedation

Both drugs produced a significant fall in systolic blood pressure from 1 h (clonidine) or 2 h (tiamenidine) after dosing until the end of the study (Fig. 2). Clonidine in a dose of 0.3 mg produced a significantly greater fall in systolic pressure between 2 and 7 h (p < 0.01 in every case) after dosing than 1.0 mg tiamenidine. In the case of clonidine a significant fall in diastolic pressure (K5) was evident at 1 h and persisted until 7 h after dosing. The effect of tiamenidine