Br J Clin Pharmacol 1996; **41**: 269–275

Comparison of the effects of clonidine on tyramine- and methoxamine-evoked mydriasis in man

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1 It has been reported previously that clonidine can potentiate tyramine-evoked mydriasis on the pain-free side of cluster headache patients. We examined whether a single oral dose of clonidine (200 μg) can also potentiate tyramine-evoked mydriasis in healthy subjects, using mydriasis to methoxamine, a directly acting sympathomimetic amine, as a control.

2 Eight healthy male volunteers participated in four weekly sessions. In the first two sessions (Experiment 1) the effect of clonidine or placebo on the mydriasis to tyramine hydrochloride eyedrops (75 mM; 2×10 μl), and in the last two sessions (Experiment 2) the effect of clonidine or placebo on the mydriasis to methoxamine hydrochloride eyedrops (20 mM; 2×10 μl) was examined. In both experiments subjects were allocated to drugs and sessions according to a double-blind balanced design. In both experiments, pupil diameter of both the treated and the untreated eyes was recorded in standard ambient light and in the dark, before, and 2 h after clonidine/placebo, via binocular infrared television pupillometry. Salivation (dental roll technique), systolic and diastolic blood pressure (sitting), heart rate, and self-ratings of mood and feelings (visual analogue scales), were also measured before, and 2 h after the ingestion of clonidine or placebo.

3 Both tyramine and methoxamine produced a significant mydriasis, which was more prominent in the light condition (change in resting pupil size; mm $\pm$ s.e.mean: tyramine/light 1.05 ± 0.28; tyramine/dark: 0.73 ± 0.15; methoxamine/light: 1.65 ± 0.28; methoxamine/dark: 0.85 ± 0.15). Clonidine produced a significant miosis in the untreated eye which was more prominent in the light condition (change in resting pupil size; mm $\pm$ s.e.mean: Experiment 1, light: -1.34 ± 0.19; Experiment 1, dark: -0.46 ± 0.1; Experiment 2, light -0.97 ± 0.18; Experiment 2, dark: -0.29 ± 0.17). Clonidine had no significant effect on either tyramine- or methoxamine-evoked mydriasis.

4 In agreement with previous reports, clonidine significantly reduced salivation (g, mean $\pm$ s.e.mean; Experiment 1: -0.84 ± 0.22; Experiment 2: -0.55 ± 0.11), systolic blood pressure (mm Hg; Experiment 1: -17.5 ± 3.76; Experiment 2: -23.38 ± 4.67), diastolic blood pressure (mm Hg; Experiment 2: -12.38 ± 2.05), alertness (mm; Experiment 2: -24.19 ± 5.40), and anxiety (mm; Experiment 1: -13.82 ± 4.60), indicating the presence of pharmacodynamically effective tissue levels of the drug.

5 These results show that a single oral dose (200 μg) of clonidine causes significant miosis in human subjects, and fails to potentiate tyramine-evoked mydriasis. This indicates that the pupil on the asymptomatic side of cluster headache patients is affected differently from the pupils of healthy volunteers by tyramine and/or clonidine.

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Keywords clonidine tyramine methoxamine pupil cluster headache

Introduction

Tyramine is an indirectly acting sympathomimetic amine: it exerts its pharmacological actions via noradrenaline released from storage sites in sympathetic nerve endings [1]. Tyramine eyedrops have been used successfully in ophthalmic pharmacology as a diagnostic tool in Horner's syndrome [2] and in cluster headache patients [3,4]. In both clinical syndromes, indirectly acting sympathomimetic amines such as tyramine and hydroxyamphetamine may have a reduced effectiveness in evoking mydriasis. The reduced effectiveness of the indirectly acting sympathomimetic amines is attributed to an impairment of the uptake and/or noradrenaline storage mechanisms in the terminals of the peripheral sympathetic neurones innervating the dilator muscle of the iris [2,3,5]. Furthermore, in Horner's syndrome the reduced effectiveness of tyramine is regarded as evidence for a postganglionic lesion.

Clonidine is an α_2-adrenoceptor agonist with both central and peripheral actions. The central action of clonidine leads to a decrease in sympathetic outflow; this is attributed to the stimulation of inhibitory α_2-adrenoceptors on central noradrenergic neurones [6]. Clonidine affects resting pupil size differently in different species: in rats and cats it causes mydriasis [7,8]. In rabbits [11] and in humans [12,13,14] clonidine causes miosis which is reversed by the α_2-adrenoceptor antagonist idazoxan [12,13]. Whereas the mydriatic effect of clonidine in rats and cats has been attributed to the stimulation of inhibitory postsynaptic α_2-adrenoceptors in the third nerve nucleus in the midbrain [9,10], the miotic effect of clonidine in humans is more likely to be due to stimulation of presynaptic inhibitory α_2-adrenoceptors on central noradrenergic neurones resulting in a reduction in sympathetic outflow.

More recently, Fanciullacci *et al.* [14] examined the effects of systemically administered clonidine on tyramine-evoked mydriasis in cluster headache patients. These authors found that, in agreement with previous reports, tyramine was less effective as a mydriatic on the pain-side pupil. Furthermore, clonidine potentiated tyramine-evoked mydriasis on the pain-free side, without affecting the response on the pain side. The authors postulated that the potentiation of the tyramine-evoked mydriasis on the pain-free side was due to a reduction in sympathetic outflow caused by clonidine, resulting in the accumulation of noradrenaline in the noradrenergic nerve terminals innervating the iris, leading to the release of more noradrenaline in response to tyramine. In this context, it is of interest that it has been suggested by other authors [15,16] that the variability of the mydriatic response to indirectly acting sympathomimetic amines, such as hydroxy-amphetamine and tyramine, might reflect changes in the level of sympathetic activity and thus in the degree of repleteness of the prejunctional noradrenaline stores.

Since apart from the study of Fanciullacci *et al.* [14] on cluster headache patients there is no information on a possible interaction between clonidine and indirectly acting sympathomimetic amines, in the present experiment we examined the effects of clonidine on tyramine-evoked mydriasis in healthy subjects. We used methoxamine-evoked mydriasis as a control: methoxamine is a directly acting α_1-adrenoceptor agonist whose effect is not dependent on the size of the presynaptic noradrenaline store [17]. Some of these results have been communicated to the British Pharmacological Society [18].

Methods

Ethical considerations

The study protocol was approved by the University of Nottingham Medical School Ethics Committee. All volunteers gave their written informed consent following a verbal explanation of the study and after reading a detailed information sheet.

Subjects

Eight healthy male volunteers aged 18–22 years (mean $\pm$ s.d., 19.0 ± 1.2), body weight 68–81 kg (mean $\pm$ s.d., 75.1 ± 4.5) participated in the study. Each subject completed a brief medical history and underwent a complete physical examination. Subjects had not participated in drug studies within 3 months of the start of the present study and had not used any drug within the 14 days preceding the study. They were requested to stop smoking and to avoid drinking alcohol, coffee and other caffeine-containing beverages for at least 12 h before each experimental session. All subjects indicated compliance with these requests.

Drugs

Clonidine hydrochloride 200 μg and placebo were administered orally, and tyramine HCl (75 mM, 2×10 μl) and methoxamine HCl (20 mM, 2×10 μl) were instilled in the left conjuctival sac.

Apparatus and tests

Pupillometry An infrared binocular television pupillometer (TVP 1015B Applied Sciences Laboratory, Waltham, MA, USA) was used for the recording of the resting pupil size in darkness after previous dark adaptation, and in ambient light (32 Cd m^{-2}). Pupil diameter measures were recorded both in dark and light

in order to control for possible errors associated with the measurement of the effects of mydriatic drugs, such as a 'ceiling effect' in the dark [19] and interaction between the two eyes in the light [20] (for details, see Discussion). The recordings took place in a sound attenuated room and the subjects fixed their gaze on a dim red spot of light positioned approximately 2.5 m in front of them. Pupillary measures were digitized and stored on a floppy-disk for off-line analysis. Resting pupil diameter was calculated as the mean of three consecutive recordings of 15 s separated by 5 s intervals.

Salivation Salivation was measured using the dental roll technique [21]. Three cotton-wool dental rolls (size 2) were placed in the mouth for 1 min, two buccally and one sublingually, and the increase in weight was measured. The mean of three measurements, taken at 5 min intervals was used for analysis. Salivary output was measured before and after treatment and the change in mean salivary output was taken as the response.

Cardiovascular measures Systolic and diastolic blood pressure and heart rate (sitting) were measured with an electroaneroid sphygmomanometer (Bosch, Gojo-Prestige). Measurements were taken before and after treatment with the systemically administered drug; the pre-post treatment change was taken as the effect of the drug.

Visual analogue mood rating scale A 16-item scale [22,23] was administered before and after treatment. For the evaluation of the pre-treatment levels of mood and feelings the pre-treatment raw scores on each item were multiplied with the factor loadings derived from a factor analysis, and the 16 items were divided into three groups: factor 1 ('alertness'; 9 items); factor 2 ('contentment'; 5 items); factor 3 ('anxiety'; 2 items) [24]. The mean value (mm) was calculated for each factor, for each subject on each occasion, and the mean value was calculated for the whole group of experimental subjects. For the assessment of the effects of treatment on mood and feelings, the post-pre treatment differences were taken for each item, and each subject in every session, and these were multiplied by the factor loadings. Thereafter, the calculation was as described for the pre-treatment values.

Experimental design

All subjects participated in two separate, but consecutive experiments (Experiment 1 and Experiment 2) at a weekly interval.

In Experiment 1 subjects participated in two weekly sessions, one of which was associated with tyramine/clonidine and the other one with tyramine/placebo. Subjects were allocated to drugs and sessions according to a double-blind balanced design. At the beginning of each session, after a 10 min rest period, the subjects underwent the pre-treatment tests (salivation, cardiovascular measures, pupillometry, mood ratings) after which they ingested the capsule. Identical post-treatment tests were carried out 120 min after ingestion. Tyramine hydrochloride eyedrops (75 mM; 2×10 µl) were instilled into their left conjuctival sacs 40 min prior to the post-treatment tests.

In Experiment 2 the same procedures were followed except that 50 min prior to the post-treatment tests methoxamine hydrochloride eyedrops (20 mM; 2×10 µl) were instilled into their left conjuctival sacs.

The timing of the post-drug tests was based on the single-dose pharmacokinetics of clonidine. It has been reported that peak autonomic and behavioural changes are obtained 2 h after oral administration of a single 200 µg dose [25]. The timing of the instillation of tyramine and methoxamine eyedrops was based on previous pilot studies in our laboratory showing that 40 and 50 min, respectively, are required to attain peak responses.

Data analysis

Student's *t*-test (paired comparisons) was used to compare the effects of treatment on the resting pupil size in darkness and ambient light (clonidine or placebo for the untreated eye, clonidine-tyramine and clonidine-methoxamine for the treated eye), salivation, cardiovascular measures and visual analogue scales.

Results

Resting pupil diameter

The pre-treatment pupil sizes (right eye; absolute diameters in mm) are shown in Table 1. The effect of clonidine on resting pupil diameter (right untreated eye) is shown in Figure 1. Clonidine had a miotic effect in both light and darkness, in both experiments. Change in resting pupil size (mm: mean $\pm$s.e.mean): Experiment 1, light: -1.34 ± 0.19 ($P < 0.01$); Experiment 1, dark: -0.46 ± 0.10 ($P < 0.005$); Experiment 2, light: -0.97 ± 0.18 ($P < 0.05$); Experiment 2, dark: -0.21 ± 0.17 (not significant, $0.1 > P > 0.05$). In both experiments the effect of clonidine was greater in the light than in the dark (Experiment 1: $P < 0.01$; Experiment 2: $P < 0.02$).

Table 1 Pre-treatment pupil sizes (right eye; mm; mean $\pm$ s.e. mean)

	Session 1		*Session 2*	
	Light	*Darkness*	*Light*	*Darkness*
Experiment 1	5.65 ± 0.29	8.40 ± 0.22	5.38 ± 0.26	8.45 ± 0.22
Experiment 2	4.79 ± 0.22	8.29 ± 0.22	4.56 ± 0.24	8.31 ± 0.24

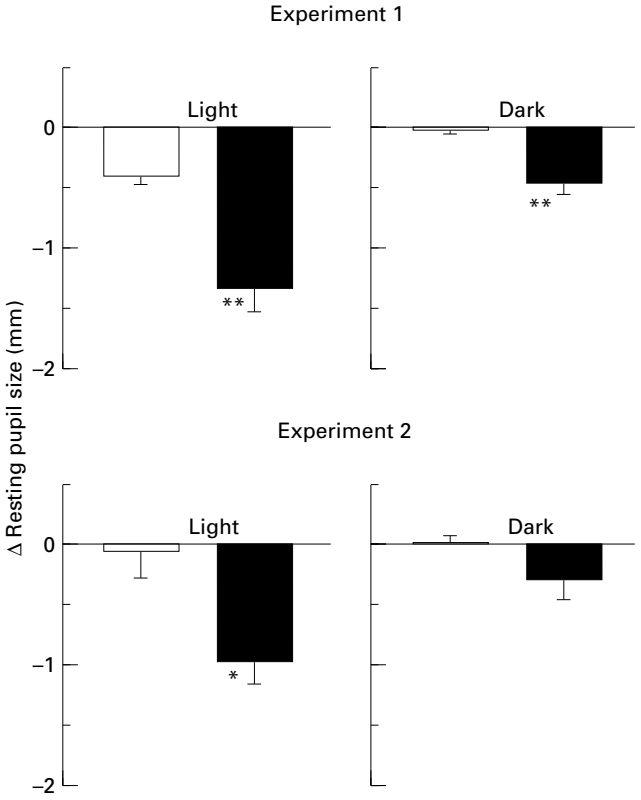

Figure 1 Change in resting pupil size 2 h after the administration of clonidine hydrochloride 200 μg (closed columns) or placebo (open columns). Right eye, mm; mean ± s.e. mean. Student's *t*-test: * $P<0.05$; ** $P<0.01$. Mean differences (95% CI) were as follows: Experiment 1/light: −0.94 (−1.41, −0.47); Experiment 1/dark: 0.45 (−0.68, −0.21). Experiment 2/light: 0.92 (−1.72, −0.11); Experiment 2/dark: 0.3 (−0.69, 0.09).

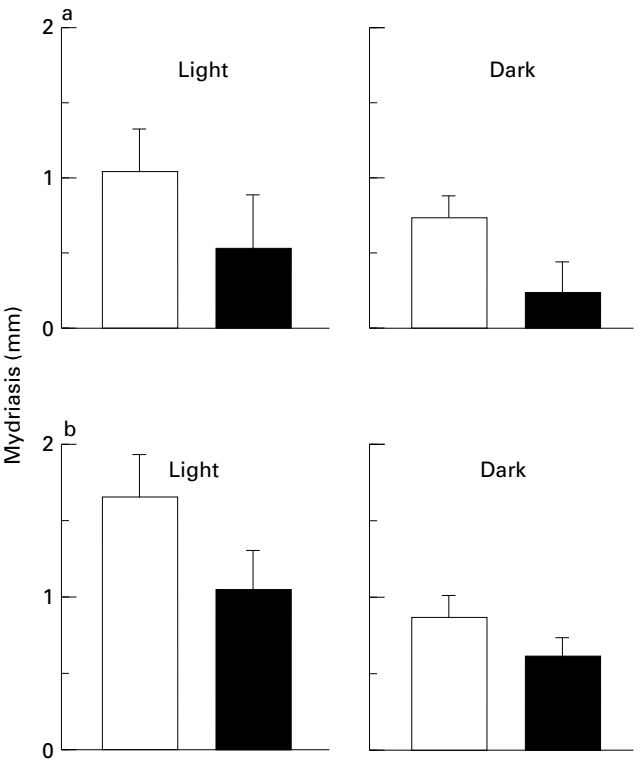

Figure 2 Mydriatic response to tyramine hydrochloride (a) and methoxamine hydrochloride (b) 2 h after the administration of clonidine hydrochloride 200 μg (closed columns) or placebo (open columns). Left eye, mm; mean ± s.e. mean. Mean differences (95% CI) were as follows: Tyramine/light: 0.52 (−1.56, 0.51); Tyramine/dark: 0.51 (−1.12, 0.11). Methoxamine/light: 0.61 (−1.57, 0.34); Methoxamine/dark: 0.25 (−0.69, 0.19).

Tyramine-evoked mydriasis

The effect of clonidine on tyramine-evoked mydriasis is shown in Figure 2. Tyramine caused a significant mydriasis both in light and in the dark. Change in resting pupil size (mm; mean ± s.e.mean): light: 1.05 ± 0.28 ($P<0.008$); dark: 0.73 ± 0.15 ($P<0.002$). Tyramine-evoked mydriasis was greater in the light than in the dark but this difference was not significant ($0.1>P>0.05$).

Methoxamine-evoked mydriasis

The effect of clonidine on methoxamine-evoked mydriasis is shown in Figure 2. Methoxamine caused a significant mydriasis both in the light and in the dark. Change in resting pupil size (mm; mean ± s.e.mean) was: light: 1.65 ± 0.28 ($P<0.001$); dark: 0.85 ± 0.15 ($P<0.002$). However, this response was not significantly affected by clonidine. The methoxamine-evoked mydriasis was greater in light than in the dark ($P<0.02$).

Salivation

The effect of clonidine on salivary output is shown in Table 2. Clonidine reduced salivation in both experiments (Experiment 1: $P<0.02$, Experiment 2: $P<0.05$).

Cardiovascular measures

The effects of clonidine on heart rate, systolic and diastolic blood pressure are shown in Table 2. Clonidine reduced systolic blood pressure in both experiments (Experiment 1: $P<0.02$, Experiment 2: $P<0.002$), and diastolic blood pressure in Experiment 2: $P<0.02$). Clonidine had no significant effect on heart rate.

Rating of mood and feelings

The effects of clonidine on the 'alertness', 'anxiety' and 'contentment' factors derived from the 16 visual analogue scales used, are shown in Table 2. Clonidine reduced 'anxiety' in Experiment 1 ($P<0.05$), and 'alertness' in Experiment 2 ($P<0.01$). The contentment factor was not affected significantly.

Discussion

The effects of two locally instilled mydriatic drugs (tyramine hydrochloride and methoxamine hydro-

Table 2 Autonomic and psychological measures (changes from pre-treatment level)

	Placebo mean ± s.e. mean	*Clonidine* mean ± s.e. mean	*Mean difference (95% CI)*
Experiment 1			
Salivation (g)	0.14 ± 0.11	−0.84 ± 0.22*	−0.98 (−1.72, −0.24)
Heart rate (beats min $^{-1}$)	−8.25 ± 3.64	−1.88 ± 1.85	6.38 (−4.03, 16.78)
Systolic blood pressure (mm Hg)	−1.50 ± 5.10	−17.50 ± 3.76*	−16.00 (−26.96, −5.04)
Diastolic blood pressure (mm Hg)	0.50 ± 2.35	0.88 ± 4.27	−1.38 (−12.69, 9.94)
'Alertness' (mm)	−1.84 ± 4.20	−12.98 ± 4.60	−11.14 (−27.95, 5.70)
'Anxiety' (mm)	0.11 ± 2.80	−13.82 ± 4.60*	−13.93 (−27.10, 0.80)
'Contentment' (mm)	−1.97 ± 2.90	−6.10 ± 3.90	−4.09 (−18.5, 9.90)
Experiment 2			
Salivation (g)	0.02 ± 0.15	−0.55 ± 0.11*	−0.52 (−0.99, −0.06)
Heart rate (beats min $^{-1}$)	−8.13 ± 1.73	−8.50 ± 2.18	0.38 (−6.05, 5.30)
Systolic blood pressure (mm Hg)	−2.88 ± 2.50	−23.38 ± 4.67**	−20.50 (−29.88, −11.12)
Diastolic blood pressure (mm Hg)	2.25 ± 4.64	−12.38 ± 2.05*	−14.63 (−25.95, −3.30)
'Alertness' (mm)	−3.63 ± 2.20	−24.19 ± 5.40**	−20.55 (−32.71, −8.39)
'Anxiety' (mm)	4.68 ± 3.50	−7.74 ± 4.00*	−3.06 (−15.25, 9.11)
'Contentment' (mm)	−1.29 ± 1.20	−1.56 ± 1.60	−0.27 (−4.82, 5.36)

Student's *t*-test: * $P < 0.05$, ** $P < 0.01$

chloride) and of systemically administered clonidine on pupil diameter were studied, both in the dark and in the light under standard illumination conditions. The reason for comparing the effects of the drugs under two illumination conditions was that it is difficult to study mydriatic drugs in the dark, where the initial pupil diameter is large and the size of the mydriasis may be limited by a ceiling effect [19]. In the light, however, a possible source of error could be an interaction between the two eyes: mydriasis in one eye can be accompanied by a consensual miosis in the fellow eye [20]. In the present experiment, as expected, the pupil diameter was consistently smaller under the light than under the dark condition. The effects of both the locally instilled mydriatics and of systemically administered clonidine were qualitatively similar under the two illumination conditions.

In agreement with previous reports, both tyramine hydrochloride [26,27], and methoxamine hydrochloride [28,26] evoked consistent mydriatic responses. Furthermore, the mydriasis to either drug was greater in the light than in the dark, presumably due to the curtailment of the mydriasis in the dark by the operation of a ceiling effect [19]. It is important to note that the doses of both mydriatic drugs used in these experiments were clearly submaximal in the light, both drugs dilating the pupil to a diameter of approximately 6.3 mm. However, in the dark both drugs dilated the pupil to a size of just over 9 mm, which corresponds to the 'ceiling' [29].

Clonidine had a miotic effect in both experiments. This observation is consistent with some previous reports [12–14], although other authors [30] could not detect a miotic effect of clonidine. Since pupil size reflects the balance between parasympathetically mediated pupil constriction and sympathetically mediated pupil dilatation, the miotic effect of clonidine may reflect the central sympatholytic effect of the drug. Interestingly, the miotic effect of clonidine was light-dependent: the clonidine induced miosis was more pronounced in the light than in the dark. This observation may explain why some previous studies carried out in the dark [30] failed to detect the miotic effect of clonidine. The light-dependency of the miotic effect of clonidine suggests that the relationship between the opposing sympathetic and parasympathetic innervations of the iris changes depending on the lighting conditions: not only the parasympathetic but also the sympathetic impulse flow may be greater in the light than in the dark. Therefore, the removal of the sympathetic influence by clonidine may result in an enhanced miotic effect in the light. It should be noted, however, that the synergistic interaction between light and clonidine may be observable only under tonic conditions since clonidine failed to modify the amplitudes of a series of pupillary light reflex responses evoked by brief (200 ms) light pulses [30]. Furthermore, electrophysiological studies indicate that a phasic light stimulus has an inhibitory effect on on-going sympathetic activity recorded in the dark [31].

Apart from affecting resting pupil diameter, clonidine had other significant autonomic effects, such as reductions in salivary flow, and systolic and diastolic blood pressures. These effects of clonidine are well-documented in the literature [6]. The cardiovascular effects of clonidine are usually attributed to the central sympatholytic effect of the drug [6]. The reduction in salivation is more difficult to interpret: the activation of release-modulating α_2-adrenoceptors on cholinergic nerve endings in the salivary glands has been proposed as a possible mechanism in the dog [32]. However, a central mechanism may also be involved since the

peripherally acting α_2-adrenoceptor antagonist MK-467 fails to abolish the clonidine-induced reduction in salivation in healthy subjects [33].

Clonidine also affected the ratings of mood and feelings. There was a reduction in subjectively-rated anxiety and alertness, consistent with the well-documented sedative property of the drug [6]. The observation of characteristic autonomic and psychological effects of clonidine in our experiment indicates that the single oral dose used resulted in pharmacodynamically effective tissue levels of the drug.

Clonidine failed to affect the mydriatic response to either tyramine or methoxamine. The failure of clonidine to potentiate tyramine-evoked mydriasis could not have been due to the operation of a ceiling effect since the dose of tyramine in our experiment (i.e. 20 μl of a 75 mM solution corresponding to 205 μg tyramine) is clearly submaximal [27]. In fact, there was a small, non-significant reduction in the sizes of the responses, possibly reflecting the physiological antagonism between the sympathomimetic amine-evoked mydriasis and the clonidine-induced miosis. This is a surprising finding, since it could be predicted on the basis of the observations of Fanciullacci *et al.* [14] that the response to tyramine would be potentiated, whereas the response to methoxamine would remain unaffected. It is unlikely that the difference between our results and those of Fanciullacci *et al.* [14] are due to the fact that we used orally and those authors intravenously administered clonidine, since in our study some well-known pharmacodynamic effects of clonidine (i.e. reduction in systolic and diastolic blood pressure, salivation, and alertness) could be observed. Therefore, our findings indicate that the pupil on the pain-free side in cluster headache patients is affected differently from the pupils of healthy volunteers by tyramine and/or clonidine.

P.B. was supported by the State Scholarship Foundation of Greece (I.K.Y.).

References

1 Trendelenburg U. Classification of sympathomimetic amines. In *Handbook of Experimental Pharmacology vol 33: Catecholamines*, 336–362, eds Blanschko H, Muscholl E, Berlin Heidelberg New York: Springer, 1972.

2 Thompson HS, Mensher JH. Adrenergic mydriasis in Horner's syndrome. Hydroxyamphetamine test for diagnosis of post- ganglionic defects. *Am J Ophthalmol* 1971; **72**: 472.

3 Fanciullacci M. Iris adrenergic impairment in idiopathic headache. *Headache* 1979; **19**: 8–13.

4 Fanciullacci M, Pietrini U, Gatto G, Boccuni M, Sicuteri F. Latent dysautonomic pupillary lateralization in cluster headache. A pupillometric study. *Cephalalgia* 1982; **2**: 135–144.

5 Cremer SA, Thompson HS, Digre KB, Kardon RH. Hydroxyamphetamine mydriasis in Horner's syndrome. *Am J Ophthalmol* 1990; **110**: 71–76.

6 Glue P, Nutt D. Clonidine challenge testing of alpha-2-adrenoceptor function in man: the effects of mental illness and psychotropic medication. *J Psychopharmacol* 1988; **2**: 119–137.

7 Koss MC. Clonidine mydriasis in the cat. Further evidence for a CNS postsynaptic action. *Naunyn-Schmiedeberg's Arch Pharmacol* 1979; **309**: 235–239.

8 Berridge TL, Gadie B, Roach AG, Tulloch IF. α_2-Adrenoceptor agonists induce mydriasis in the rat by an action within the central nervous system. *Br J Pharmacol* 1983; **78**: 507–515.

9 Koss MC, Gherezghiher T, Nomura A. CNS adrenergic inhibition of parasympathetic oculomotor tone. *J Autonom Nerv Sys* 1984; **10**: 55–68.

10 Hey JA, Gherezghiher T, Koss MC. Studies on the mechanism of clonidine-induced mydriasis in the rat. *Eur J Pharmacol* 1985; **328**: 258–263.

11 Allen RC, Langman ME. The intra-occular pressure response of conscious rabbits to clonidine. *Invest Ophthalmol* 1976; **15**: 815–823.

12 Clifford JM, Day MD, Orwin JM. Reversal of clonidine induced miosis by the α_2-adrenoceptor antagonist RX 781094. *Br J Clin Pharmacol* 1982; **14**: 99–101.

13 Clifford JM. The effects of clonidine and idazoxan (an α_2-adrenoceptor antagonist) on pupil size, and their interaction in healthy volunteers. In *Pharmacology of adrenoceptors*, 343–344, eds Szabadi E, Bradshaw CM, Nahorski SR, London: Macmillan 1985.

14 Fanciullacci M, Pietrini BM, Fusco M, Alessandri S, Marabini S, Sicuteri F. Does anisocoria by clonidine reflect a central sympathetic dysfunction in cluster headache? *Clin Neuropharmacol* 1988; **11**: 56–62.

15 Gillum WN. Sympathetic stimulators and blockers. *Ophthalmic Semin* 1977; **2**: 283

16 Cremer SA, Thompson HS, Digre KB, Kardon RH. Hydroxyamphetamine mydriasis in normal subjects. *Am J Ophthalmol* 1990; **110**: 66–70.

17 Trendelenburg U, Maxwell RA, Pluchino S. Methoxamine as a tool to assess the importance of intraneuronal uptake of l-norepinephrine in the cat's nictitating membrane. *J Pharmac Exp Ther* 1970; **172**: 91–99.

18 Bitsios P, Langley RW, Szabadi E, Bradshaw CM. Modification of the mydriatic response to tyramine and methoxamine by clonidine. *Br J Clin Pharmacol* 1995; **39**: 575P.

19 Longmore J, Theofilopoulos N, Szabadi E, Bradshaw CM. Modification of the pupillary light reflex by miotic and mydriatic drugs: applicability of model of functional interaction. *Br J Clin Pharmacol* 1987; **23**: 610–611P.

20 Theofilopoulos N, Longmore J, Kerr FA, Szabadi E, Bradshaw CM. Consensual pupillary responses to mydriatic and miotic drugs. *Br J Clin Pharmacol* 1988; **26**: 697–702.

21 Peck RE. The SHP test: an aid in the detection and measurement of depression. *Arch Gen Psychiat* 1959; **1**: 35–40.

22 Aitken RCB. Measurement of feelings using visual analogue scales. *Proc R Soc Med* 1969; **62**: 989–993.

23 Norris H. The action of sedatives on brain-stem oculomotor systems in man. *Neuropharmacol* 1971; **10**: 181–191.

24 Bond A, Lader M. The use of analogue scales in rating subjective feelings. *Br J Med Psychol* 1974; **47**: 211–218.

25 Reid J. The clinical pharmacology of clonidine and related central antihypertensive agents. *Br J Clin Pharmacol* 1981; **12**: 295–302.

26 Kerr FA, Szabadi E. Comparison of the effects of chronic administration of ciclazindol and desipramine on pupillary responses to tyramine, methoxamine and pilocarpine in healthy volunteers. *Br J Clin Pharmacol* 1985; **19**: 639–647.

27 Peet M, Yates RA, Shields AG. Dose-response relationship

for mydriasis produced by topical ocular tyramine in man. *Br J Clin Pharmacol* 1980; **9**: 96–99.

28 Szabadi E, Gaszner P, Bradshaw CM. Interaction of desipramine and amitriptyline with adrenergic mechanisms in the human iris *in vivo*. *Eur J Clin Pharmacol* 1981; **19**: 403–408.

29 Loewenfeld IE. In *The Pupil*, 408, Detroit: Iowa State University Press/Amos Wayne State University Press, 1993.

30 Morley MJ, Bradshaw CM, Szabadi E. Effects of clonidine and yohimbine on the pupillary light reflex and carbachol-evoked sweating in healthy volunteers. *Br J Clin Pharmacol* 1991; **31**: 90–101.

31 Nisida I, Ocada H, Nacano O. The activity of the cilio-spinal centers and their inhibition in pupillary light reflex. *Jap J Physiol* 1960; **10**: 73–84.

32 Montastruc P, Berlan M, Montastruc J-L. Effects of yohimbine on submaxillary salivation in dogs. *Br J Pharmacol* 1989; **98**: 101–104.

33 Warren JB, Dollery CT, Sciberras D, Goldberg MR. Assessment of MK-467, a peripheral α_2-adrenergic receptor antagonist, with intravenous clonidine. *Clin Pharmacol Ther* 1991; **50**: 71–77.

(*Received 7 July 1995, accepted 12 December 1995*)