Noradrenergic Modulation of Pupillary Function: Comparison of Modafinil and Clonidine

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INTRODUCTION: Noradrenergic neurones located in the lower brain stem, mainly in the locus coeruleus, project to most parts of the neuraxis. The ascending projection plays a prominent role in arousal and maintenance of wakefulness, whereas projections to preganglionic sympathetic and parasympathetic neurones modulate autonomic activity. The alpha-2 adrenoceptor agonist clonidine can "switch off" the activity of the locus coeruleus, thereby leading to sedation, and to a sympatholytic/parasympathomimetic effect[1]. Modafinil is a novel wakefulness-promoting agent licensed for the treatment of narcolepsy[2]. The mode of action of modafinil is not known: one possibility is that it may activate the central noradrenergic system. We have examined the effects of modafinil on pupillary function and compared them with those of clonidine. We have also investigated the possible interaction between the two drugs on the pupil.

METHODS: Sixteen healthy male volunteers participated in four experimental sessions at weekly intervals in which they received (i) modafinil 200 mg, (ii) clonidine 0.2 mg, (iii) modafinil 200 mg and clonidine 0.2 mg, (iv) placebo. The four treatments were administered in a balanced order according to a double-blind protocol. Pupil diameter was measured with a binocular pupillometer (Procyon, UK) under four light intensities (darkness, 6, 91, 360 Cd m^{-2}). Light reflex responses were evoked by green (peak wavelength 565 nm) light flashes (200 ms; 8.5 x 10^{-3}, 7.0 x 10^{-2} and 0.43 mW cm^{-2}), and darkness reflex responses by switching off the background illumination of 1700 Cd m^{-2}. Recordings were made with a binocular infrared television pupillometer (TVP 1015B, Applied Science Laboratories Waltham, MA, USA). Spontaneous pupillary fluctuations in darkness were measured by the Pupillographic Sleepiness Test (AmTech, Weinheim, Germany). The level of alertness of the subjects was assessed using both subjective self-ratings, and measurement of critical flicker fusion frequency. Cardiovascular parameters (systolic and diastolic blood pressure, heart rate) and salivary output were also recorded.

RESULTS: The effects of the treatments are shown in the table:-

	Clonidine	Modafinil	Clonidine + Modafinil
Resting pupil diameter	- -	+	-
Light reflex amplitude	0	0	0
Light reflex recovery time	++	0	++
Darkness reflex initial velocity	- -	++	- -
Darkness reflex amplitude	- -	0	- -
Pupillary unrest index	++	-	+
Critical flicker fusion frequency	- -	++	- -
Alertness	- -	0	- -
Systolic blood pressure	- -	0	- -
Diastolic blood pressure	- -	0	- -
Heart rate	0	0	0
Salivary output	- -	0	- -

+: increase; -: decrease; 0: no effect. (Double symbols denote strong effects).

DISCUSSION: Clonidine exerted effects consistent with its central sympatholytic and sedative properties. In contrast, modafinil had relatively little effect on most of the measures used: it increased resting pupil diameter and the initial velocity of the darkness reflex, indicating an increase in the sympathetic output to the iris. It reduced the pupillary unrest index and critical flicker fusion frequency consistent with its alerting effect; however, it failed to affect subjective alertness. Modafinil was unable to counteract the effects of clonidine on almost all the measures used. These results argue against an action of modafinil via the central noradrenergic system.

REFERENCE(S):

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2. Broughton, R.J. *et al*. (1997). *Neurology* **49**:444-451.