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REVERSAL OF CLONIDINE INDUCED MIOSIS BY THE α_2-ADRENORECEPTOR ANTAGONIST RX 781094

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Clonidine given i.v. at a dose of 0.1 mg and 0.2 mg was found to cause miosis in a placebo controlled double-blind study in six healthy volunteers. In a further single-blind placebo controlled study in three of these volunteers, the α_2-adrenoreceptor antagonist RX 781094 at a dose of 0.1 mg/kg i.v. reversed the miosis induced by i.v. clonidine 0.2 mg. At a dose of 0.05 mg/kg the miosis was partially reversed.

Introduction

The systematic measurement of pupil size in man at fixed time intervals after intravenous doses of clonidine does not appear to have been reported. Studies in the rat (Gherezghiher & Koss, 1979) and the cat (Koss, 1979) showed that clonidine caused a dose-dependent mydriasis. However, in man overdoses of clonidine have been reported to cause miosis (Stein & Volans, 1978) although in a series of three young children who ingested between 0.25 mg and 0.75 mg of clonidine one showed mydriasis (Mathew *et al.*, 1981). Clonidine (0.25%) instilled locally into the eye caused mydriasis in patients suffering from glaucoma (Jahnke & Thumm, 1972). RX 781094 is a new α_2-adrenoreceptor antagonist which has been shown to reverse behavioural depression and hypothermia induced by clonidine in mice (Dettmar *et al.*, 1981). It was therefore of interest to record the pupillary response, in two separate studies in healthy volunteers, to i.v. clonidine and the effect on such response when RX 781094 was administered shortly after clonidine.

Method

In the first study six volunteers, who had given written informed consent, received either saline, clonidine 0.10 mg or clonidine 0.20 mg by the i.v. route using a randomised double-blind crossover design. In the second single-blind study three volunteers received by the i.v. route either saline followed 0.25 h later by a further saline injection, clonidine 0.20 mg i.v. followed by saline, clonidine 0.20 mg i.v. followed by RX 781094 0.05 mg kg^{-1} i.v. or clonidine 0.20 mg i.v. followed by RX 71094 0.10 mg kg^{-1} i.v. Vital signs were monitored in the recumbent subjects for 9 h from the first injection and pupil size was measured by a photographic method (Clifford, 1980) at fixed time intervals for 5.75 h in the first experiment and 9 h in the second.

Results

Both doses of clonidine caused a reduction in pupil size which was not dose-related. After 0.10 mg the mean peak reduction to 77% of control size occurred at 1.25 h and after 0.20 mg reduction to 80% of control was observed at 0.75 h and 1.75 h (Table 1). In the second study 0.20 mg clonidine i.v. produced a mean reduction of pupil size to less than 70% mean control between 0.25 h and 2.25 h with a maximum reduction to 64% control size occurring at 2.25 h.

Both doses of RX 781094 produced a rapid reversal of this effect in the period 30 min after i.v. injection. Following the higher dose of RX 781094 the mean pupil size increased from 65% to 97% of control within 30 min and pupil sizes no less than 83% of control were measured during the remainder of that round of medication (Figure 1). The lower dose of RX 781094 reversed the effect of clonidine from a reduction of 69% of control to 84% of control over a similar period. Saline produced no such reversal and the clonidine induced miosis persisted for approximately 3 h followed by a slow return to control levels which was still not complete at 9 h.

Discussion

RX 781094 had previously been given alone by the i.v. route, in an open study, to five volunteers who received a single dose of 0.3 mg/kg. Pupil size was

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Table 1 Mean pupil size measurements (mm) ± s.d. occurring after saline, clonidine and clonidine followed 0.25 h later by RX 781094, dose regimens in healthy volunteers.

			Pupil size (mm) *Experiment 1* *Time after dose (h)*				
Dose regimen	*Control*	*+0.3*	*+0.75*	*1.25*	*1.75*	*2.75*	*5.75*
Saline (n=6)	6.2 ±1.4	6.2 ±1.1	5.8 ±1.3	5.8 ±1.3	5.9 ±1.5	6.0 ±1.4	6.2 ±1.3
Clonidine (0.10 mg) (n=6)	6.5 ±0.8	5.2 ±1.3	5.5 ±1.2	5.0 ±1.4	5.1 ±1.3	5.4 ±1.0	6.1 ±0.9
Clonidine (0.20 mg) (n=5)	6.5 ±1.5	5.4 ±1.4	5.2 ±1.4	5.3 ±1.5	5.2 ±1.1	5.7 ±1.3	6.4 ±0.9

				Experiment 2					
Dose regimen	*Control*	*0.25*	*0.75*	*1.25*	*1.75*	*2.25*	*3*	*6*	*9*
Saline/saline	6.2 ±1.9	6.0 ±1.7	6.4 ±2.4	6.4 ±1.4	6.0 ±1.9	6.2 ±1.7	5.8 ±1.7	6.3 ±1.6	6.8 ±1.7
Clonidine/saline (0.20 mg)	6.6 ±1.2	4.5 ±1.6	4.9 ±1.3	4.8 ±1.6	4.5 ±1.7	4.2 ±0.8	5.6 ±1.4	5.4 ±1.5	5.8 ±1.5
Clonidine/RX 781094 (0.05 mg/kg)	6.9 ±1.4	4.1 ±1.2	5.8 ±2.5	6.0 ±2.3	5.8 ±2.0	5.7 ±2.0	5.9 ±1.5	5.4 ±1.6	6.3 ±1.4
Clonidine/RX 781094 (0.10 mg/kg)	6.3 ±1.5	4.1 ±1.2	6.1 ±1.8	5.7 ±1.5	5.2 ±1.4	5.8 ±1.5	6.0 ±1.3	5.9 ±1.9	6.7 ±0.9

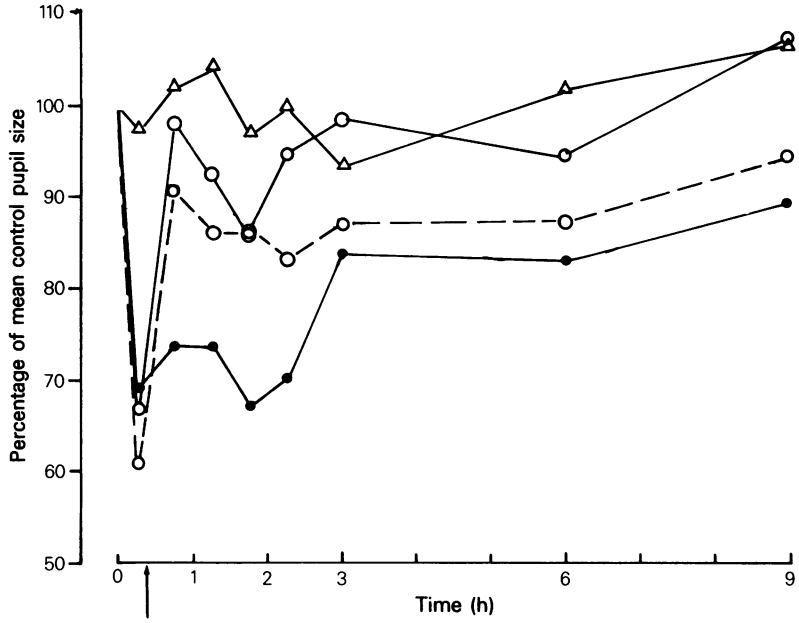

Figure 1 Pupil size changes following the intravenous administration of normal saline (△————△), 0.2 mg clonidine followed 15 min later by saline (●————●), 0.2 mg clonidine followed by 0.05 mg/kg RX 781094 (○- - - -○) and 0.2 mg clonidine followed by 0.1 mg/kg RX 781094 (○————○). The arrow indicates the time of administration of the second injection.

only slightly changed. Percentage values of mean control size at the 20 min, 0.75 h, 1.25 h, 2.25 h, 3 h, 4.5 h, 6 h and 8 h measurement time intervals were 94, 95, 97, 94, 100, 100, 103 and 107. The effect of i.v. clonidine in reducing pupil diameter in man reported here conflicts with previous results obtained in laboratory species. Clonidine by the intravenous route has been reported to produce mydriasis in conscious rats (Walland & Kobinger, 1971) and in chloralose-anaesthetised cats (Koss, 1979). However, in both of these animal experiments relatively much higher doses of clonidine were used than in the human experiments reported here. Thus Walland & Kobinger (1971) used 300 μg/kg clonidine by the intravenous route and 1000 μg/kg orally, whilst Koss (1979) used cumulative intravenous doses up to 100 μg/kg. It is likely that at these dose levels clonidine is behaving as a non-selective α-adrenoceptor agonist and is causing mydriasis by a direct action on α-adrenoceptors in the smooth muscle of the iris. With the low doses used in our human experiments (up to approximately 3 μg/kg maximum dose) it is likely that clonidine is acting centrally to reduce sympathetic tone to the iris thus producing parasympathetic predominance and pupillary constriction. Such a mechanism is consistent with the observation that clonidine as a 0.25% w/v solution applied directly to the cornea induced mydriasis in human subjects (Jahnke & Thumm, 1972). It is likely that the antagonism of the miotic action of clonidine by RX 781094 in these experiments is occurring at α_2-adrenoceptors situated within the central nervous system.

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