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Cinnarizine — a labyrinthine sedative

By G. Towse (Marlow)

Introduction

Cinnarizine (E)-1-(diphenylmethyl)-4-(3 phenyl-2 propenyl) piperazine is a non-competitive antagonist of histamine, noradrenaline, nicotine and angiotensin (Van Nueten and Janssen, 1972; Godfraind, 1968; Schaper *et al.*, 1963). Its direct actions all involve an antagonism of the stimulated influx of extracellular calcium ($Ca(Ca^{++})$ ions (Emanuel, 1979). As a consequence cinnarizine modifies the intracellular calcium A.T.P. balance in erythrocytes, increasing their flexibility and reducing whole blood viscosity (Di Perri *et al.*, 1977). It antagonizes the constriction of vascular smooth muscle (Godfraind and Morel, 1977) and has inhibitory actions on vestibular sensory nuclei in the ear (Philipszoon, 1962).

Cinnarizine first became widely used as a specific anti-vertigo agent. More recently it has also been prescribed to control motion sickness.

This paper reviews the role of cinnarizine in the management of these two conditions.

Experimental Studies

1. *Animal Studies*

The inhibitory effects of cinnarizine on the vestibular nuclei of rabbits was initially demonstrated by Jongkees and Philipszoon (1960). In 1963, a pathophysiological link between nystagmus (involuntary twitching of the eyeball) and motion sickness and vertigo, was established (De Witt, 1963). This concept has been exploited in the development of experimental models of labyrinthine disorders.

Richards *et al.* (1963) compared the efficacy of cinnarizine (10 mg/kg i.p.) with that of dimenhydrinate (25 mg/kg i.p.), meclizine (10 mg/kg i.p.) and cyclizine (10 mg/kg i.p.) by recording changes of intensity, frequency and duration of horizontal nystagmus induced in guinea pigs by caloric irrigations of their ear canals with iced water (4–10°C). Cinnarizine was superior to the other agents in reducing both the duration and intensity of post-caloric nystagmus, and its duration of action was longer.

Cinnarizine also reduced the frequency of caloric-induced nystagmus but was less effective in this respect than both meclizine and cyclizine. In a global comparison of the effects of the four drugs cinnarizine was ranked the most potent.

2. *Human Studies*

In view of the encouraging results from animal experiments Philips-

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zoon (1962) set up a double-blind placebo controlled study in 38 healthy volunteers to investigate the inhibitory actions of cinnarizine on labyrinthine stimulation in man. In these studies subjects with their heads angled 30 degrees forward, were spun on a revolving seat.

When a constant velocity of 20, 36 or 60 degrees per second was reached they were brought swiftly to rest. The eye movements, resulting from these graded stimulations of their horizontal semi-circular canals, were measured by electronystagmography before and three hours after treatment with either placebo or 250 mg cinnarizine. The duration of post-rotationa nystagmus and post-rotational turning sensation were both statistically significantly reduced by cinnarizine ($p < 0{\cdot}01$ Wilcoxon matched pairs signed ranks test). A non-significant placebo effect was recorded in the control experiments performed on the same subjects one week prior to the cinnarizine tests.

A subsequent cross-over study in 12 healthy volunteers confirmed these preliminary findings and demonstrated that a three day regime of cinnarizine (25 mg t.i.d.) was statistically significantly superior to placebo ($p < 0{\cdot}05$) at reducing the amplitude, duration and speed of the slow phase of post-rotational nystagmus, and the total number of beats (Cobb *et al.*, 1976).

Thus cinnarizine appears to exert a significant depressant effect on the vestibular nuclei of healthy volunteers. This action may be attributed to a reduced influx of Ca^{++} ions into the vestibular sensory cells (Van Nueten and Janssen, 1973) and is thought to be responsible for its therapeutic effect in balance disorders. In accordance with this hypothesis, Philipszoon (1962) failed to demonstrate any statistically significant inhibition of eye movements during a parallel swing linear acceleration test designed to stimulate the vestibular otoliths of 28 volunteers.

Clinical Studies

1. *Vertigo*

An initial double-blind placebo controlled study of cinnarizine in the treatment of vestibular vertigo was set up in 48 patients, including 30 with Menières disease, nine with spontaneous nystagmus and nine who had recently undergone ear operations (Philipszoon, 1962). Sixty-five per cent of the cinnarizine-treated patients (30 mg/day) compared with only 24 per cent of placebo-treated subjects were judged by audiography, spontaneous and positional nystagmus tests, caloric tests and E.N.T. examinations to have improved following one week's treatment. This difference was stiatistically significant ($p < 0{\cdot}0005$ Fischer exact test, one-tailed probability). Furthermore, prolonged treatment resulted in a reduction in severity or a complete elimination of vestibular vertigo in 30 out of 39 patients and early administration of cinnarizine supressed vertigo attacks. Similar response rates have been reported in a double-blind study involving

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103 patients in which 87 per cent of the cinnarizine-treated patients experienced relief from dizziness and vertigo compared with only 16 per cent of the placebo group (Albernaz *et al.*, 1968).

In an additional study 49 vertiginous patients with hypoglycaemia, postural vertigo, vestibular neuronitis, vascular insufficiency and labyrinthine ischaemia were assigned to an initial single-blind, two week placebo schedule followed by a four week double-blind regime of either cinnarizine (25 mg t.i.d.) or placebo (Owens, 1974).

The frequency and severity of vertigo attacks were recorded daily by the patients. Cinnarizine was statistically significantly superior to placebo ($p < 0{\cdot}05$ Chi-squared test) at reducing the frequency of mild attacks of vertigo. This difference mainly reflected the smaller number of cinnarizine-treated patients who deteriorated during the study—the numbers who improved were similar in both groups (cinnarizine 14 patients, placebo 12). Inter-group differences in the frequency of severe attacks were not statistically significant.

The vestibular effects of cinnarizine (50 mg t.i.d.) have recently been compared to those of flunarizine (20 mg t.i.d.) in 58 patients with peripheral labyrinthine disorders using the reduction of the average velocity of the slow phase of post-caloric nystagmus, before and after treatment, as a measure of efficacy (Albernaz *et al.*, 1978).

Both cinnarizine and flunarizine exerted a statistically significant depressant effect on the vestibular apparatus, flunarizine being marginally more effective despite being administered at a lower dosage. Flunarizine was statistically significantly superior to placebo ($p < 0{\cdot}05$ Mann Whitney U-test) but there were no inter-group differences between flunarizine and cinnarizine or between cinnarizine and placebo.

In a three month, open, multicentre evaluation in 82 aged patients with dizziness and unsteadiness secondary to cerebral atherosclerosis more definitive results were obtained (Amery and Oosterveld, 1975).

Following one week's treatment with cinnarizine (25 mg t.i.d.) symptoms associated with vertigo (dizziness, unsteady gait, tinnitus and headache) as well as those related to cerebral atherosclerosis (loss of memory and concentration, inactivity, listlessness, lack of interest and insomnia) were statistically significantly improved ($p < 0{\cdot}05$ Wilcoxon matched pairs signed ranks test). Drug efficacy increased throughout the trial and by the end of the study statistically significant improvements in all ten symptoms were observed in even the most severely affected patients ($p < 0{\cdot}001$ McNemar test, two-tailed probability).

The investigators rated 18·3 per cent of the patients as being 'markedly improved, 40·3 per cent as 'clearly improved' and 25·6 per cent as 'slightly improved'. This high level of efficacy has recently been confirmed by Cott and Davidovitch (1976) following the administration of cinnarizine (25 mg t.i.d.) for four days to 14 patients with vertebro-basilar insufficiency.

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2. *Motion Sickness*

a. *Experimental Motion Sickness*

The slow revolving room test was used by Wood and Graybiel (1968) to evaluate the efficacy of 28 anti-motion sickness drugs, including cinnarizine, under controlled laboratory conditions. In this test susceptible subjects experienced motion sickness when they moved their head and upper body out of the plane of the room's rotation. The resulting Cariolis accelerations were standardized by asking the volunteers to set the needles of five dials according to taped instructions.

As the severity of stress increased as a function of the room's speed of rotation (r.p.m.), the number of head movements at a given r.p.m. which induced a level of motion sickness defined as 'severe malaise' (Gabriel *et al.*, 1968) was investigated before, and between one and two hours after, drug or placebo administration. Cinnarizine (150 mg) increased the number of tolerated head movements by 40, when compared to placebo levels, and was 15th in the ranking order. Following the administration of the most potent medication—a mixture of scopolamine and amphetamine—tolerance was increased by about 180 head movements.

In an additional comparative study (Deane *et al.*, 1967) of seven drugs and three independent placebos cinnarizine (50 mg) was ranked third in the slow revolving room test but was eighth when compared by the same volunteers against the same medications during aerobatic manouevres in fighter aircraft.

b. *Seasickness*

The efficacy of cinnarizine in the prevention of seasickness was initially reported by a military study comparing cinnarizine with 14 other motion sickness drugs (including anti-histamines, nialamide and atropine) and with placebo (Trumbull *et al.*, 1960). One hundred and forty-eight of the volunteers were assigned to cinnarizine (7·5 mg t.i.d.) and 122 to placebo.

During a crossing from New York to Bremenhaven vomiting occurred in only 9 per cent of cinnarizine-treated subjects compared with 22 per cent of those receiving placebo. This difference was statistically significant ($p < 0{\cdot}02$). Doubling the dosage of cinnarizine to 15 mg t.i.d. in 138 other volunteers did not increase its effect.

More recently excellent results have been obtained from an open study involving 500 yachtsmen (Heald and Tristram, 1979) in which cinnarizine prevented seasickness in over 90 per cent of the subjects and was rated as being 'good or excellent' by 86 per cent of them. A similar percentage considered cinnarizine to be superior to previous medications (which included hyoscine and promethazine) and 94 per cent said that they would use cinnarizine again. The majority of patients commenced

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treatment 24 hours before casting off but others found the drug effective even if taken when malaise had commenced. Similarly, dosages varied considerably between the subjects, some requiring only a quarter of a tablet whilst others took eleven 15 mg tablets within two days. The overall results from this trial suggest that the optimum regime is 15 mg three times daily for adults and half this dosage for children between five and twelve years old, to be commenced one day before sailing.

Safety

The results from a number of studies have demonstrated that cinnarizine can be administered for the long-term control of labyrinthine disorders without the complications of serious side-effects.

In a double-blind placebo controlled safety evaluation, cinnarizine was administered at more than twice the recommended daily dose (i.e. 75 mg t.i.d.) for eight weeks without evidence of blood or urinary abnormality (Janssen Pharmaceutica, 1971). An additional toxicity study involving 176 patients with an average age of 76 years failed to demonstrate statistically significant changes in blood pressure, erythrocyte or leucocyte counts or blood biochemistry following six months of treatment. By contrast, Owens (1974) reported a statistically significant increase ($p < 0{\cdot}025$) in the mean serum S.G.O.T. concentration of patients treated for six weeks with cinnarizine (25 mg t.i.d.), but elevated L.D.H. and bilirubin levels were also observed in the placebo-treated group ($p < 0{\cdot}05$). These changes were judged not to be clinically important.

The most frequently encountered side-effect of cinnarizine appears to be drowsiness. This has been reported by 20 per cent of the subjects in the open seasickness trial (Heald and Tristram, 1979), and by 50 per cent of the volunteers from a preliminary experimental study who received a single oral dose of cinnarizine (250 mg) far in excess of that clinically recommended (Philipszoon, 1962). Cinnarizine was particularly well tolerated in a three-month study involving 82 aged vertiginous patients. Only nineteen complained of side-effects; these included drowsiness (7 patients), gastrointestinal upset (15), unsteadiness (3), and headache (2). Malaise, dry mouth and marked weight gains were each reported by one patient. These symptoms frequently subsided with continued use of the drug and were mild complaints that are often encountered in elderly people not undergoing drug therapy.

Discussion

In summary, cinnarizine has been shown to suppress the excitability of the vestibular nuclei of normal subjects and of those with vertiginous complaints, possibly by antagonizing the stimulated influx of Ca^{++}ions from the endolymph into the vestibular sensory cells. It has proven therapeutic

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efficacy in the treatment of vertigo and Menières syndrome, and in the prevention of seasickness. Cinnarizine is free from severe side-effects but drowsiness is sometimes encountered.

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