The effects of the "Vestibular Sedative" drug, Flunarizine upon the vestibular and oculomotor systems

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SUMMARY The effects of the "vestibular sedative" drug Flunarizine upon the oculomotor functions of pursuit and voluntary saccades and upon the vestibular response (to rotational stimuli) were assessed in twenty volunteer subjects. The study was then extended to three patients with chronic imbalance of central origin who had reported a beneficial symptomatic response to the drug. Three of the volunteer subjects were found to have a directional preponderance (presumed to arise from peripheral dysfunction). In the remaining seventeen normal subjects Flunarizine was found to reduce the amplitudes of fast phases of vestibular nystagmus. The directional preponderance in the other three subjects was redressed through production of fast phases which were of lower and more uniform amplitude. In the patients, in addition to a reduction in fast phase amplitude, there was a reduction or abolition of after nystagmus. In no case was any reduction in slow phase velocity observed. Pursuit and voluntary saccades were unaffected by the drug. It was concluded, on the basis that the fast phases of nystagmus are centrally generated, that Flunarizine has a central action rather than a depressant effect upon the vestibular end organ. In view of known oculomotor physiology and pharmacology it is proposed that vestibular sedatives act by depression of Type II vestibular neurons, and modification of the functional relationships between the vestibular nuclei, the perihypoglossal nuclei and the flocculus of the cerebellum. A trial of vestibular active drug is indicated particularly in patients in whom asymmetry of the vestibular response and/or abnormal after nystagmus is demonstrated.

The mainstay of treatment of states of disequilibrium of various causes, both peripheral and central, remains the so-called "vestibular sedative" drugs. No rationale exists for the application of these drugs in individual cases so, not surprisingly, response to treatment is often disappointing. Several criticisms may be levelled at previous investigations into vestibular sedatives. Acute dose studies have attempted to define the mode of action of such drugs upon the vestibular system, both in animals and man, by employing objective measurements of the vestibular response. Chronic dose studies have relied upon psychophysical rating scale assessments of subjective experiences. All reports have ignored the contribution of drowsiness (drug induced or otherwise) to modification of the vestibular response. There is a common (and unwarranted) assumption that vestibular sedatives act upon the vestibular end organ. Little consideration has been given to possible actions upon central vestibular connections and this has biased the interpretation of data. In addition there has been a total disregard of the possibility that vestibular sedatives may influence oculomotor function, despite the fact that vision and eye movements contribute equally with the vestibular system to the maintenance of equilibrium.

The purpose of this present study was to examine the effects of a vestibular sedative on a range of objective tests of vestibular and oculomotor functions in a chronic, double blind crossover, placebo controlled trial in normal volunteers. The drug selected for assessment was Flunarizine,
"Vestibular Sedatives"

[(E)-1-{bis(4-fluorophenyl)methyl}-4-(3-phenyl-2-propenyl)piperazine dihydrochloride], on the grounds that our clinical experience suggested that it was helpful in disorders of equilibrium of central origin. The study was extended to selected patients who had reported a positive beneficial response to treatment with the drug. Flunarizine is a difluorinated derivative of Cinnarizine, [(E)-1-(di-phenylmethyl)-4-(3-phenyl-2-propenyl) piperazine], which is more potent on a weight for weight basis and has a longer half life. It is principally protein bound in the serum [99%] and is detectable 20 minutes after oral ingestion. Maximal concentrations are achieved between two and four hours after dosing. Sleepiness has been reported four to six hours after ingestion. Plasma levels have shown considerable individual differences on chronic dose studies. Side effects have been reported as dose related rather than related to plasma levels. Rationale for the use of Flunarizine is at most speculative and its administration is ad hoc, as with all vestibular sedatives.

Subjects and methods

Twenty control subjects (10 male, 10 female), age range 24 to 40 years with no previous history of vertigo or imbalance were assessed. Informed consent after a full explanation of the trial was obtained from each subject.

At the commencement of the trial each subject underwent a baseline assessment of vestibular and oculomotor functions as detailed below. The subjects then took placebo or Flunarizine 5 mg twice daily for one week and then had a second assessment. Following a seven day washout period they then took placebo or Flunarizine, issued on a double blind cross-over design, for a further week at the end of which they were tested for a third time. The subjects were instructed to refrain from smoking and ingestion of alcoholic beverages during the 24 hours prior to each test session.

Each test session consisted of the following standardised tasks. (1) Assessment of saccade velocity and latency evoked by target jumps which were randomised with a rectangular distribution in both time and amplitude. The target jumps ranged from 5 to 40°. The minimum inter-jump interval was 1.5 seconds and the maximum was 3.5 seconds. (2) Smooth pursuit was assessed using a deterministic, sinusoidal target motion the frequency of which ramped linearly up and down in frequency from starting rightwards up to 0-8 Hz down to stopping leftwards. Pursuit was tested both with and without background illumination. (3) The subjects were oscillated in yaw in a rotating chair in darkness using a sinusoidal motion ramped linearly up and down in frequency from starting rightwards up to 1-0 Hz down to stopping leftwards. A constant peak velocity of 80°/s was maintained and the duration of the stimulus was two minutes.

Eye movements were measured using DC coupled electro-oculography and stored on magnetic tape for off line computer analysis. An electrostatic ink jet recorder print out was used for qualitative assessments and manual measurements.

Serum Flunarizine levels were measured with high performance liquid chromatography, using 254 nm UV detection, as described by Woestenborghs et al.

Computer analysis was made of saccade latency and peak velocity in relationship to amplitude of target jumps and of accuracy of pursuit using proportion of the eye movement occupied by saccadic intrusions plotted against peak target velocity as an index of performance. Details of the method of analysis have been published previously.

The target used for the pursuit and saccade tests was the projected beam of a helium-neon laser reflected from a servo-controlled rotating mirror on to a tangent screen. The target subtended 0.002 radians at a distance from the subject of 3 metres.

Following analysis of the results from normal controls, the study was extended to an examination of the effects of Flunarizine in three patients who had previously reported a positive symptomatic response to that drug. As a consequence of the findings in normal subjects the test procedure was modified. The patients were examined using EOG for the presence of gaze-evoked nystagmus in the light and dark. Full field optokinetic stimulation for two minutes to the right and left was given. Following each direction of stimulation they were observed in darkness for the presence of optokinetic after nystagmus (OKAN). They were also given rapid acceleration to and deceleration from 40°/s constant angular velocity rotation in a rotating chair in addition to the ramped sinusoidal stimuli described previously.

Each patient was given a baseline assessment and then took Flunarizine 10 mg nocte for four weeks after which they were reassessed.

Results

FINDINGS IN NORMAL SUBJECTS

The relevant negative findings were that as assessed with placebo Flunarizine had no effect on saccade velocity or latency in response to random target jumps; pursuit was neither impaired nor improved; there was no difference between pursuit with and without background both within and between test sessions.

In baseline testing, three of the normal subjects were found to have an asymmetry in the pattern of nystagmus they produced to rightwards and leftwards rotational stimuli. In all 20 subjects the velocity of the slow phase of vestibular nystagmus was unaffected by Flunarizine. In the 17 subjects with symmetrical responses, however, a significant reduction in the amplitudes of fast phases of nystagmus was found. Results of statistical analysis of saccade amplitudes sampled at each peak of chair velocity are given in the table. A highly significant difference between saccade amplitudes during both the control and placebo test sessions and the on-drug session was demonstrated. Frequency of saccades during the
on-drug sessions could not be accurately measured as the saccades were often of such low amplitude that they were at the limit of resolution of the EOG.

The nature of the asymmetries in the three subjects mentioned above were complex but followed a similar pattern both for placebo and baseline testing sessions (fig 1). Although the velocities of the slow phase components of nystagmus for each direction of rotation were not significantly different, the frequencies and amplitudes of fast phases of nystagmus were unequal for the two directions of motion. A further consequence of the asymmetries was that there could be a directional bias of deviation of the eyes from the primary position.

Under the influence of the drug the directional preponderance of vestibular nystagmus in these subjects was wholly or partly redressed (fig 1). In addition, the amplitude of saccades generated during vestibular stimulation was reduced.

Plasma levels of Flunarizine showed great variation, with values ranging from 4-8 ng/ml to 38-2 ng/ml (mean = 15-7 ng/ml). Three subjects experienced unacceptable drowsiness during the first three to four days of ingestion of the drug. The drowsiness was no longer noted by the time of the on-drug assessment. Plasma levels in these subjects were 9-8, 17-6 and 19-8 ng/ml. However, three other subjects reported a significant degree of psychomotor retardation whilst taking placebo! Plasma levels in the three subjects in whom directional preponderance was redressed were 15-2, 19-8 and 20-1 ng/ml. The remaining subjects were unaware as to whether they were taking the drug or not. No additional side effects were encountered.

**FINDINGS IN PATIENTS WITH CENTRAL VESTIBULAR DYSFUNCTION**

Three patients successfully completed the testing regime. Each had a different disorder and the nystagmographic findings in each were different and so are treated separately.

**Patient number 1** A 63-year-old male began to experience giddy attacks following a fall five years previously. The attacks could be spontaneous or precipitated by head movement. When walking he tended to veer to the right. Examination two years after the accident revealed benign positional nystagmus with the right ear dependent. This resolved subsequently. On examination, he had an essential tremor. There was a mild slurring dysarthria. Following eye movements were broken up in all planes. No spontaneous nystagmus was seen on direct inspection of the eyes.

**EOG findings on and off the drug** EOG showed first degree nystagmus to the left in the dark only. This was absent whilst on drug. Pursuit was impaired but better in the presence of background illumination. Pursuit was not altered on drug. Optokinetic responses were symmetrical. OKAN to right 35 s, (on drug, 8 s), OKAN to the left 15 s, (on drug, 19 s). Responses to rotational vestibular stimuli were as
follows: starting right 43 s, (on drug, 50 s); starting left 44 s, (on drug, 10 s), with spontaneous reversal of nystagmus lasting 31 s, (abolished on drug). Stopping from right 64 s, (on drug, 18 s); stopping from left 35 s, (on drug, 38 s).

Responses to oscillatory vestibular stimulation both on and off drug are illustrated in fig 2. Off drug the responses were asymmetrical against the left as determined by frequency of saccadic intrusions. On drug the record was virtually devoid of large amplitude fast phases of nystagmus, consisting almost entirely of sinusoidal modulation of eye position. On close examination however the overall modulation is determined by runs of small amplitude saccades at very high frequencies. These, unfortunately, are at the limit of resolution of the EOG. Asymmetry is still present in the record and arises from a hyperactive response to the right with respect to the left.

**Patient number 2** A 45-year-old male, in 1980, became aware that on executing a left hand turn in his car it felt as though he were about to overturn. Symptoms of mild, intermittent imbalance persisted up to the time of assessment. On examination he veered to the left when walking with his eyes closed; Romberg’s test was positive.

**EOG findings on and off the drug** EOG showed first degree nystagmus to the left with prolongation of the slow phase durations in darkness which was abolished on eye closure. Pursuit was impaired. Neither the spontaneous nystagmus nor the deranged pursuit was affected by the administration of Flunarizine and there was no symptomatic relief on this occasion. Optokinetic stimuli produced symmetrical responses. Before the drug, optokinetic after nystagmus (OKAN) to the right lasted for 23 s and to the left 22 s. On Flunarizine OKAN to the right lasted for 29 s, OKAN left for 12 s. Responses to rotational vestibular stimulation were as follows: duration of post rotatory nystagmus starting right, 40 s (on drug, 19 s); starting left, 24 s (on drug, 32 s), with spontaneous reversal lasting 22 s which was abolished on drug; stopping from right, 50 s (on drug, 16 s) and stopping from left 30 s (on drug, 17 s).

Responses to oscillatory vestibular stimulation both on and off drug are illustrated in fig 2. The records show that the response off treatment comprised nystagmus which was abnormal in that the pattern of saccadic intrusion throughout the entire trace was highly irregular. For cycles of stimulus with similar periods, at times saccade amplitudes were very large and at others quite small. Within any given cycle the nystagmus to right and left could be dissimilar, as could the responses to adjacent cycles to stimulus. In contrast, the responses whilst on drug were symmetrical in direction at all frequencies of stimulation; the response to stimuli at similar frequencies were of uniform appearance which, on inspection, was due to relative uniformity of the amplitudes of the fast phase of nystagmus.

**Patient number 3** A 48-year-old woman suddenly, in 1978, developed nausea, vomiting, loss of taste, paraesthesia of the arms and a tendency to veer to the right when walking. These all settled rapidly, but she was left with residual sensations of mild imbalance particularly on moving the head rapidly or when decelerating in the car. On examination, apart from mild impairment of pursuit, there were no abnormalities.

**EOG findings on and off the drug** Off drug there was a first degree nystagmus to the right in the dark only. Pursuit movements were impaired. Neither the nystagmus nor the pursuit was altered by the drug. Optokinetic responses were symmetrical. OKAN to the right lasted 47 s (on drug, 69 s); to the left 36 s (on drug, 40 s). Responses to rotational vestibular stimuli; Starting right, 55 s (on drug, 55 s); with spontaneous reversal lasting 150 s, (on drug, 25 s). Starting left, 43 s (on drug, 36 s); with spontaneous reversal lasting 70 s (on drug, 10 s). Stopping from
right 54 s (on drug, 42 s); with spontaneous reversal lasting 75 s (abolished on drug); stopping from left 80 s (on drug, 45 s); with spontaneous reversal lasting 42 s (abolished on drug).

Responses to oscillatory stimulation are illustrated in fig 2. The off drug trace is probably within normal limits. On drug, the amplitude of saccades is reduced. At certain points in the record slow phase generation is impaired with respect to gain and phase. In addition there is distortion of the slow phase which should, ideally, be sinusoidal. Maximum saccade amplitude is reduced and saccade amplitude is more uniform.

A histogram displaying the reduction in saccade amplitude over five equally spaced epochs of three and a half cycles each in patients Nos. 2 and 3 is shown in fig 3. It can be seen that the degree of asymmetry of saccade amplitude, right versus left, has also been lessened.

**Discussion**

The results of this chronic dose study demonstrate that, in normal subjects, Flunarizine exerts no measurable effect on the pursuit system or upon the generation of voluntary saccades. In normal subjects a reduction in the amplitudes of fast phases of vestibular nystagmus was found. In asymptomatic subjects in whom there was evidence of asymmetry of vestibular function (of probable peripheral origin) the drug redressed or partially redressed the asymmetry by an overall reduction of saccade amplitude, so rendering saccades more uniform in amplitude and frequency. In patients with imbalance of central origin who had reported a beneficial effect, Flunarizine lessened asymmetries of vestibular function by modification of the pattern and amplitude of fast phases of vestibular nystagmus and reduction of the duration of after nystagmus. In no instance was any effect upon the generation of the slow phases of vestibular nystagmus noted. We shall argue that these results indicate that Flunarizine has a central site of action.

Other studies have concluded that Flunarizine and related drugs have a peripheral action on the basis that effects on slow phase velocity were noted. A review of the background physiology and pharmacology of the vestibular system will show that this is not necessarily the case.

In a caloric induced vestibular nystagmus in a normal subject the maximum velocity of the slow phase of nystagmus induced by an ampullopetal stimulus is an appropriate measure of (peripheral) vestibular function.14 Duration of nystagmus is very
much influenced by the phenomenon of adaptation. This is mediated mainly through the central nervous system,
though some experimental evidence from responses to prolonged rotation suggest a peripheral contribution by direction specific receptors. The elementary, three neuron vestibulo-ocular reflex arc traverses the median longitudinal fasciculus (MLF). This is the pathway responsible for generation of the slow phases of vestibular nystagmus. The polysynaptic second pathway (implicated in the generation of fast phases of nystagmus) passes to the oculomotor nuclei via brainstem accessory nuclei and nuclei of the reticular formation. Anderson et al. have described the effect of amylobarbitone on the vestibular response: increasing doses first cause a fall in the number of nystagmic beats and later abolition of saccadic intrusions. Rashbass and Russell found no decrease in slow phase velocity with amylobarbitone and this finding was confirmed by Haciska. She postulated that barbiturates exerted a depressant action specifically upon polysynaptic vestibular pathways, sparing the MLF and thereby having no effect upon slow phase velocity. In view of the fact that internuclear ophthalmoplegia can occasionally be observed in the context of barbiturate intoxication, it is more probable that amylobarbitone in low concentrations inhibits conduction in polysynaptic pathways, sparing the MLF only until higher drug levels are attained.

Studies of the effects of administration of d-amphetamine upon vestibular nystagmus also showed no effect on slow phase velocity. Haciska found an improvement in the regularity of both frequency and amplitude of nystagmus during eye closure. Importantly, Collins noted that level of arousal was far more important a factor in determining variation in slow phase velocity, though the alerting action of amphetamine did smooth out individual variations in the amount of mental activity required to avert onset of a state of reverie. He stressed that this fact had to be borne in mind in the evaluation of drug effects. Barbiturates have a direct depressant action on the reticular activating system; amphetamines have an excitant action. By inference, one can assert that the effects of the vestibular responses described above reflect these actions.

The studies in man by Phillipszoon on Cinnarizine and those by Oosterveld on Flunarizine have been acute dose studies. In the latter study, a significant reduction in both slow phase velocity and duration of nystagmus was found. This effect may well have been due to temporary decrease in level of arousal. The chronic dose study of Flunarizine by Oosterveld suggests that the drug is symptomatically beneficial, but objective assessments of vestibular function were not undertaken. Both these workers imply that these drugs act by depression of either peripheral labyrinthine tonic discharge rate or sensitivity to cupular deflection.

If “vestibular sedatives” redress tonus imbalance by any inhibitory effect, either upon tonic or phasic discharges, then the only means by which they could be effective would be by reducing resting or phasic firing rates bilaterally to near zero. This is not the case. Two findings were common to all our subjects. In no case was slow phase velocity altered. Fast (saccadic) components were modified in amplitude and degree of variability of amplitude and, in some cases, the degree of asymmetry of insertion of saccades was diminished. Because saccade amplitude was often reduced to near (or very likely) below the limit of resolution of the EOG we could not obtain accurate saccade counts. However, naked eye inspection of the records indicated that, overall, the frequency of insertion of saccades was increased. Such an increase in saccade frequency along with the decrease in saccade amplitude would be in keeping with the finding of no alteration in slow phase velocity. The three patients described in this present study all had definitive evidence of a balance disorder of central origin. In the three volunteer subjects who fortuitously showed objective evidence of vestibular imbalance there were no additional abnormalities that would indicate a central nervous disturbance and we assume that their asymmetrical responses were of peripheral origin. There was a definite effect of Flunarizine in all six cases, though not exactly the same modifications were found in each subject. We believe that the absence of any effect on slow phase velocity in the present trial is attributable to the fact that our subjects had developed tolerance of the sedative effects of the drug and that the previously reported effects upon slow phase velocity reflect drowsiness following acute dosage. Our findings indicate that the drug acts centrally. The reasons underlying this conclusion shall now be outlined and discussed.

A striking effect in the patients described above was the abolition, or near abolition, of spontaneous reversal of nystagmus both from accelerative and decelerative stimuli. In view of our understanding of the mechanisms underlying the production of after nystagmus, this observation lends strong support to the hypothesis of a central site of action. Cells of the vestibular nuclei are termed Type I (“on” response) or Type II (“off” response). Secondary nystagmus arises from after discharge in antagonistic neurons. Since these antagonistic neurons are mainly of Type II it follows that secondary nystagmus is in the opposite direction to the initial nystagmus. In general, the greater the adaptation during stimulation in the “on” direction, the greater the rebound following an
“off” stimulation. A velocity-storage integrator/system has been identified and characterised which is involved in the generation of after nystagmus following both vestibular and optokinetic stimulation. The anatomical location of this system had not been absolutely established, but it is probably situated in the nucleus prepositus hypoglossi and is under the influence of the cerebellum.

A second effect, seen both in subjects and patients, was a general reduction in the amplitudes of the fast phases of vestibular nystagmus. Groups of neurons located to the fast phases of vestibular nystagmus have been identified and extensively investigated in the cat. Premotor neurons participating in the activation or suppression of abducens motor activity during angular acceleration in yaw have been termed excitatory burst neurons (EBNs) and inhibitory burst neurons (IBNs). EBNs are located in the dorsomedial reticular formation immediately rostral to and projecting to the ipsilateral abducens nucleus. IBNs are located just caudal to the abducens nucleus and project to the contralateral abducens nucleus. The so-called pause cells of the pontine paramedian reticular formation exert a direct effect upon the IBNs. Discharge of the EBNs causes inhibition of Type I vestibular neurons and excitation of both Type II vestibular neurons and IBNs. In addition, it is known that stimulation of reticulospinal neurons located rostroventral to the abducens nucleus can augment frequency and amplitude of nystagmus related discharges, probably through facilitation of nearby centres rather than direct input. A schematic representation of these centres is shown in fig 4.

To take a simplistic view of the system, the net result of this neuronal circuitry is to effect efficient inactivation of the generation of the slow phases of vestibular nystagmus (mediated by Type I neurons) and to reset eye position by generation of the fast phases of nystagmus. It can readily be appreciated that a synchronous generation of burst activity in EBNs, IBNs, and Type II cells is necessary for well coordinated saccadic activity to occur. The threshold of EBN discharge rate necessary for initiation of a fast phase must be determined by an interreaction of these three cell types, with, of course, a contribution from equivalent contralateral structures. What determines saccade amplitude is as yet unknown. Amplitude may either be preceded at the time of initiation of the fast phase or be simply a function of the duration of EBN discharge (and Type I cell inhibition) versus pause cell activity. In the case of nystagmus generated with the subject in darkness the latter option seems more likely as no retinal error information is available.

If one accepts that adaptation occurs primarily through central mechanisms, then the abolition of spontaneous reversal of nystagmus induced by starting and stopping stimuli (trapezoidal wave form) seen in the three patients must indicate a central site of action. It is not clear which structures or pathways may be affected by such drugs but, in view of our knowledge of the inhibitory influence of the cerebellum on the vestibulo-ocular reflex, we suspect that the connections between vestibular nuclei and the cerebellar flocculus are involved. In addition, we suggest that the function characteristics of the velocity-storage integrators situated in the nucleus prepositus hypoglossi (perihypoglossal nucleus in man) are also altered by the drug.

The effect of administration of Flunarizine upon saccade amplitude suggests an action on the reticular burst neurons or their connections. As the drug has sedative effects in higher doses, an excitatory action seems unlikely. We postulate that it acts neurochemically through suppression of Type II (inhibitory) vestibular neurons. This results in the lowering of the threshold for the insertion of saccades during vestibular nystagmus. Smaller amplitude, more frequent saccades are produced and
asymmetry is diminished through a relative decrease in the degree of direction-related amplitude asymmetry. In conclusion, considering the effects of Flunarizine observed, we propose that the term "vestibular sedative" is a misnomer. "Vestibular isostatic" would be more apt a description. In general neurological practice the "dizzy" patient presents a spectrum of symptomatology ranging from intense rotational vertigo through to mild unsteadiness. Sensations of imbalance may arise from disorder of the visual, proprioceptive and vestibular systems, the cerebellum or any combination of these. Unless asymmetry of vestibular function had been demonstrated by objective tests (such as caloric and rotational tests and ENG), and the abnormalities detected are compatible with the patient's symptoms it is unreasonable to expect a positive response to treatment with a vestibular active drug. A trial of Flunarizine (or any similar drug), is worthwhile in patients with objective evidence of asymmetry of the vestibular response (whether of peripheral or central origin), or with abnormal spontaneous reversal of rotational induced nystagmus.

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