Improvement of vestibular compensation by Levo-Sulpiride in acute unilateral labyrinthine dysfunction

Facilitazione del compenso vestibolare indotto da Levosulpiride nelle lesioni vestibolari acute periferiche

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Key words

Vertigo • Treatment • Levosulpiride • Vestibular compensation

Parole chiave

Vertigini • Terapia • Levosulpiride • Compenso vestibolare

Summary

L-sulpiride is the levorotatory enantiomer of sulpiride, a neuroleptic of the family of benzamide derivatives; it has a characteristic antagonist effect on central DA2 dopaminergic receptors and dopamine DA1 "autoreceptors". Its efficacy in the symptomatic control of acute vertigo spells has been recognized, apart from its well-known antiemetic, antidyspeptic and anti-depressant properties, at high dosages. To establish objective parameters of the results of its clinical application, a randomized prospective study was started comparing the effects of the drug in a group of 87 patients with vertigo of peripheral origin, with those in a control group treated with other vestibular suppressants. The drug was administered via the intravenous route, 25 mg t.i.d., for the first 3 days, then by oral administration, with the same schedule and dosage, for a further 7 days. After clinical evaluation of vestibular signs and symptoms, electronystagmographic recordings of rotatory tests were obtained, at admission and were then controlled after 6 months. A subjective Visual Analogue Scale was also delivered daily to the patients in order to monitor symptomatic improvements. When compared to conventional treatments, L-sulpiride appeared to induce a statistically significant faster recovery in unilateral vestibular lesions. An unexpected favourable outcome of treatment was the facilitation of spontaneous vestibular compensation, in terms of lesser residual labyrinthine dysfunction and reduction of recurrent vertigo attacks during the 6 months follow-up. The mechanisms of action of the drug and its interaction with the vestibular system are discussed.

Riassunto

La Levo-sulpiride è l'enantiomero levogiro della Sulpiride, un neurolettico della famiglia delle benzamidi; ha un caratteristico effetto anatgonista sui recettori DA2 e sugli autorecettori dopaminergici centrali DA1. La sua efficacia nel controllo sintomatico della vertigine acuta è già stata documentata, oltre alle ben note proprietà antiemetiche, antidispeptiche e antidepressive agli alti dosaggi. Per stabilire dei parametri obiettivi dei risultati della sua applicazione clinica, gli Autori hanno iniziato uno studio prospettico randomizzato per confrontare gli effetti della somministrazione del farmaco in un gruppo di 87 pazienti ricoverati per una crisi vertiginosa di origine periferica, con quelli ottenuti in gruppo di controllo trattato con altri soppressori vestibilari. La L-sulpiride è stata somministrata alla dose di 25 mg x 3/die per via endovenosa per i primi 3 giorni, quindi per via orale con lo stesso dosaggio per ulteriori 7 giorni. Oltre alla valutazione clinica dei segni e dei sintomi vestibolari, sono state ottenute le registrazioni elettronistagmografiche delle prove rotatorie all'ammissione e sono state controllate controllate dopo 6 mesi. Una scala analogica visiva soggettiva è stata sottoposta quotidianamente ai pazienti per monitorare il miglioramento sintomatico. Rispetto ai trattamenti convenzionali, la L-sulpiride ha indotto un recupero più veloce in lesioni vestibolari unilaterali, raggiungendo la significatività statistica. Un risultato favorevole inatteso del trattamento è consistito nella facilitazione del compenso vestiobolare spontaneo, in termini di ridotta disfunzione labirintica residua e riduzione delle recidive vertiginose durante i sei mesi di follow-up. I meccanismi di azione del farmaco e le sue interazioni con il sistema vestibolare sono discussi.

Introduction

Vertigo and dizziness are common complaints in patients attending the General Practitioner's office, second only to headaches and asthenia. Whenever possible, medical treatment of vertigo attacks should be directed at the underlying cause; since diagnosis is not always evident at onset, the use of antivertiginous and antiemetic agents is particularly useful in suppressing acute symptoms, while waiting for the outcome of an appropriate diagnostic workup. Suitable drugs for symptomatic relief should, if possible, not interfere with the physiological or induced compensation processes [1-3]. Clinical observations on the use of sulpiride in dyspeptic syndromes indicated a positive influence of this dopaminergic antagonist on the associated vestibular disturbances, with faster attenuation of acute vertigo and better long-term recovery [4-8]. Levo-sulpiride (L-sulpiride) is the levorotatory enantiomer of sulpiride, an "atypical" neuroleptic agent of the family of benzamide derivatives; it has a characteristic antagonist effect on central DA1 dopaminer-

gic receptors and on DA2 pre-synaptic "autoreceptors". Experimental demonstration of suppression of the vestibular response has been explained with facilitation of the inhibitory GABAergic transmission to medial vestibular nuclei (MVN) neurons.
In order to establish the clinical efficacy of the L-enantiomer in the treatment of vertiginous patients, a randomized prospective study has been carried out comparing the effects of low-dose L-sulpiride (25 mg t.i.d) in a group of 87 patients with vertigo of peripheral origin, with those obtained in an analogous control group of 56 subjects, treated with vestibular suppressants.
A thorough clinical vestibular evaluation, blood tests and ENG recording of rotatory tests were performed at admission and controlled after 6 months. A subjective scale was also developed in order to monitor daily improvements in symptoms. When compared to conventional treatments, L-sulpiride appeared to induce a faster recovery, being statistically significant, in unilateral vestibular lesions. The interactions of the drug with the vestibular system are discussed.

Materials and methods

Of 772 patients evaluated at the Otolaryngology Dept. of the University of Brescia for vestibular disorders, in 2000, 143 were admitted to the Clinic on account of acute vertigo attacks. Of these, 87 randomly selected patients were treated, upon admission, with an intra-venous infusion of L-sulpiride, 25 mg t.i.d for 3 days, followed by oral administration of the same dose of the drug for another 7 days, and included in the "active" group of the study. Another 56 patients, treated with other vestibular suppressants (metoclopramide, tiethylperazine, diazepam), served as a control group. Inclusion criteria included the admission within 48 hours from the onset of the vertigo attack; exclusion factors were: use of other vestibular suppressants prior to admission and a diagnosis of benign positional paroxysmal vertigo.
Before starting treatment, all patients underwent complete otoneurologic assessment including:

- thorough clinical history;
- blood tests (full blood count, erythrocyte sedimentation rate, serum proteins and immunoglobulin fractions, total haemolytic activity, serum electrolytes, metabolites, minerals and enzymes) and urinalysis;
- neurologic, vascular, stomatognathic, physiatric consultation and imaging (when needed for diagnostic purposes);
- pure tone audiometry; middle ear impedance testing; brainstem auditory evoked responses;
- vestibulo-spinal reflexes testing (Romberg, indication, stretched arms, stepping test and marching test of Unterberger);
- detection of spontaneous, positional (Rose, right and left lateral decubitus) and positioning nystagmus (Dix-Hallpike's and McClure's manoeuvre) with Frenzel's glasses; head shaking test (HST);
- electronystagmographic (ENG) recording of saccades, smooth pursuit, optokinetic nystagmus and vestibulo-ocular reflexes (VOR), visuo-vestibular interactions (VVOR) and vestibular suppression by fixation (VST).

Saccades were considered pathologic when metric disorders and abnormal latencies were present; alterations in morphology and gain were abnormal findings of the smooth pursuit tracking; asymmetry of ≥ 20% of the VOR tests was considered significant.
Asymmetry of vestibular responses has been calculated by comparing measurements of slow-phase angular velocity (mean ± SD) of nystagmus induced by pendular chair rotation (0.5 Hz, period 20, angle 180°, damped sinusoidal rotation) [9].
All patients were followed up for a period of at least 6 months and tests were repeated at that time.
A restricted group of patients were identified from the initial pool of selected candidates, as better matching its "control" counterpart; thus, the two groups resulted homogeneous (Fisher and Mantel-Haenszel tests, $p>0.5$) according to age and sex, type of onset of the balance disorder, subjective sensation, provocative mechanism, association with otologic, neurologic and neurovegetative symptoms and signs.
A subjective report of daily variations in intensity of the vertigo has been recorded on a five-step Visual Analogue Scale (VAS): none → mild → moderate → intense → debilitating.
The final statistical analysis has been performed comparing the results of L-sulpiride treatment in 50 patients with those in a control group of 40 subjects. It has been conducted using different parametric and non-parametric tests, each being the best fit to the variables considered (Student t, Fisher, Mantel-Haenszel, U Mann-Whitney, Kruskall-Wallis, analysis of variance – ANOVA –, analysis of covariance – ANCOVA –, Dunnett). The group comprised 29 females and 21 males, mean age 52.1 ± 15.2 years, range 18-87.

Results

The vestibular disorders were peripheral in 42/50 and mixed (peripheral + central) in 8/50 in the active group; associated disturbances of the postural control were detected in 12 patients by stabilometry. The diagnosis was Ménière's disease in 35/50, labyrinthitis in 7/50, vestibular neuronitis in 5/50 and not defined in 3/50. Similar proportions were obtained in the control group. Presence of segmental tonic deviations and spontaneous nystagmus, at admission, and

Table I. Incidence of positive findings according to clinical vestibular examination.

	Control group		Active group		
	Admission	6 months	Admission	6 months	Statistical analysis
Romberg	10/40 (25%)	8/40 (20%)	5/50 (10%)	3/50 (6%)	Fisher p = 0.129
Stretched arms	10/40 (25%)	3/40 (7.5%)	10/50 (20%)	1/50 (2%)	Fisher p = 0.167
Indication (Barany)	2/40 (5%)	13/40 (32.5%)	15/50 (30%)	5/50 (12.5%)	Fisher p = 0.091
Stepping test	13/40 (32.5%)	7/40 (17.5%)	15/50 (30%)	7/50 (14%)	Fisher p = 0.084
Marching (Unterberger)	3/40 (7.5%)	3/40 (7.5%)	1/50 (2%)	1/50 (2%)	Fisher p = 0.319
HST	20/40 (50%)	12/40 (30%)	29/50 (58%)	6/50 (12%)	Fisher p = 0.052
Spontaneous nystagmus	29/40 (72.5%)	26/40 (65%)	37/50 (74%)	24/50 (74%)	Fisher p = 0.003 Mantel-Haenszel p = 0.003

HST: Head shaking test

6 months after the therapeutic trial, are reported in Table I, both for the active and control groups.

When judged on the basis of clinical findings, the outcome of L-sulpiride treatment vs vestibular suppressants is not significantly different in the medium term (6 months' observation), except for a very consistent decrease in the number of patients who showed spontaneous or head-shaking nystagmus. This agrees with the significantly different recurrence rate of vertigo spells in the 2 groups: 23/40 (57.5%) of the controls complained of one or more episodes of vertigo during the follow-up period, vs only 16/50 (32%) in the "active" group (Fisher p=0.002, Mantel-Haenszel p=0.003). In the latter, 15/16 with recurrent symptoms were patients with active Ménière disease, i.e., 42.8% of the 35 affected individuals, a much lower figure than in the control group, in which vertigo spells recurred in 19/23 (82.6%) of Ménière patients and 4/12 (33.3%) in non-Ménière patients (Fisher p=0.001, Mantel-Haenszel p=0.002).

ENG recordings of rotatory tests obtained within 48 hours of admission and at 6 months after treatment are summarized in Table II. All selected patients and controls showed some degree of asymmetry of labyrinthine response; irrespective of quantification of vestibular function (i.e., some patients had unilateral hypofunction, others had hyperreflexivity or a vestibular response within normal limits but with significant asymmetry). Absolute values of slow phase angular velocity of nystagmus have not been considered in this study.

A significant decrease in the asymmetry has been achieved in the group treated with L-sulpiride, as confirmed by ANCOVA when the basal value is employed as the covariate, and by Student t test for independent variables. The same statistical test excluded a significant impact of the underlying pathology (Ménière vs other diseases) on the outcome assessed by ENG.

The long-term efficacy of L-sulpiride treatment in

Table II. Degree of vestibular response asymmetry by ENG recording of pendular chair rotation tests. Significant differences were observed between controls and treated group, but not between Ménière's and non-Ménière's patients in the two groups.

	Control group			L-sulpiride			Statistical analysis
	Overall	Ménière	Non-Ménière	Overall	Ménière	Non-Ménière	Control vs L-sulpiride
Admission	19.7 ± 17.5	19.9 ± 11.3	19.6 ± 20.1	17.5 ± 13.5	18.8 ± 11.7	16.7 ± 14.8	ANCOVA p=0.0379 *Student t* p=0.042
6 months	14.6 ± 12	18.1 ± 14.9	13.5± 7.8	9.7 ± 9.8	10.2 ± 7.9	9.4 ± 11.1	U Mann-Whitney p=0.082

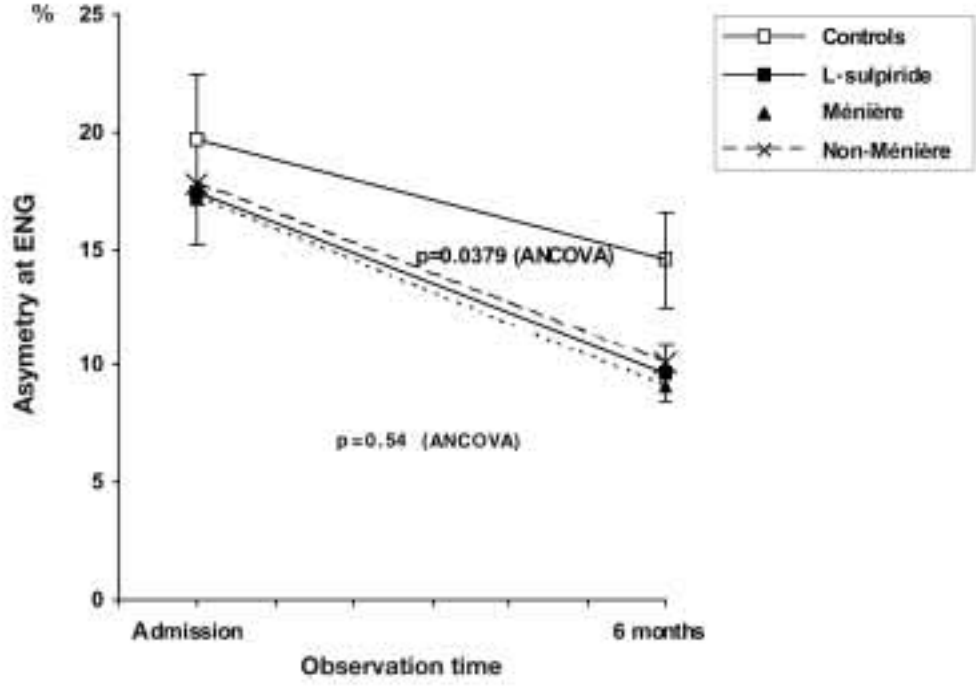

Fig. 1. Effect of treatment on vestibular response recorded by ENG in the two groups of patients. Study group treated with L-sulpiride has been further differentiated between Ménière and non-Ménière patients (no statistical difference in outcome).

the control of vertigo, taking the decrease in asymmetry of the vestibular response as the parameter, is shown in Figure 1.

Statistical analysis of the daily variations in the subjective intensity of vertigo after the beginning of treatment has been performed both with parametric (ANOVA with two fixed factors and one random) and non-parametric tests (Kruskall-Wallis, U Mann-Whitney). Homogeneity of variances has been confirmed with Levene's test; significant variations compared to basal judgment have been identified by Dunnett's test. The various statistical approaches to the analysis of the VAS confirm that both treatments reduce the symptoms in a comparable fashion up to the 2nd day; from the 4th day on, L-sulpiride control of vertigo is significantly better than that with other drugs (Kruskall-Wallis Chi-square = 104.38 vs 47.50, p = 0.0001). VAS scores over time in the two treatment groups are shown in Figure 2.

Application of the 1995 AAOO guidelines [10] for the reporting of results is not suitable for the present study as the follow-up period is limited to 6 months; moreover, transferring the AAOO categories to the overall outcome of L-sulpiride therapy, in our patients, it appears that, in the time period of the observation, cure or improvement was observed in a considerable proportion of them (Table III).

Finally, Figure 3 outlines the overall outcome of the therapeutic trial in terms of residual vestibular dysfunction at 6 months (percentage of patients showing asymmetry of VOR testing by ENG recording of pendular chair rotation, exceeding 20%): a distinct improvement is observed in the L-sulpiride treated group (Fisher Chi-square p = 0.003), while no significant differences are detectable between Ménière and non-Ménière patients.

Discussion

L-sulpiride is the levorotatory enantiomer of sulpiride, a substituted benzamide. It is the biologically active form, effective at lower doses and with fewer adverse effects than the racemic mixture. The main action of L-sulpiride is DA2 dopaminergic receptor blockade; in particular, at low doses, those located on the presynaptic membrane (autoreceptors) in the dopaminergic pathways in the central nervous system and gastrointestinal tract. L-sulpiride has anti-psychotic, antidepressant, anti-emetic and anti-dyspeptic activity [4 11-16].

It has some characteristics (stimulating activity, at low doses and sedation effects, at very high doses, lower D2/D3 affinity ratio) that distinguish it as the

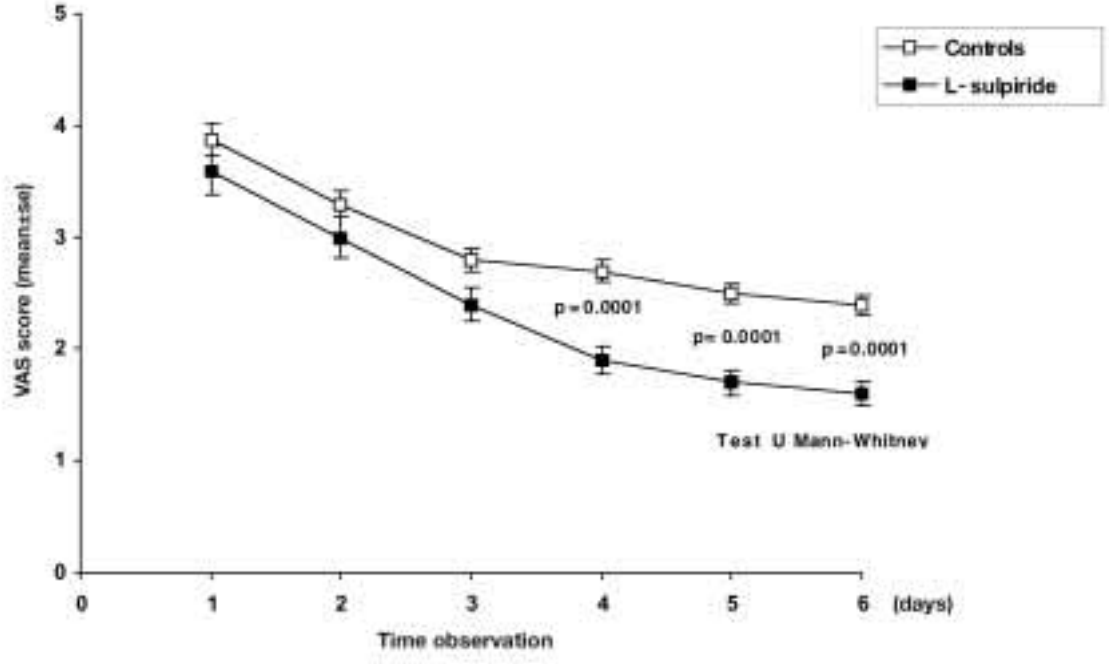

Fig. 2. Visual Analogue Scale scores of subjective intensity of vertigo during treatment.

Tab. III. Outcome of L-sulpiride treatment vs conventional vestibular suppressants. See text.

	Control group			L-sulpiride			Statistical analysis
	Overall	Ménière	Non-Ménière	Overall	Ménière	Non-Ménière	Control vs L-sulpiride
Cured/ Significant improvement	11/40 (27.5%)	8/28 (28.7%)	3/12 (25%)	29/50 (59.2%)	22/35 (62.8%)	7/15 (46.7%)	Mantel-Haenszel p = 0.007
Modest improvement	12/40 (30%)	7/28 (25%)	4/12 (33.3%)	4/50 (8.2%)	3/35 (8.6%)	1/15 (6.7%)	
Unchanged	13/40 (32.5%)	8/28 (28.7)	5/12 (41.6%)	16/50 (32.7%)	10/35 (28.6%)	6/15 (40%)	
Worsened	4/40 (10%)	2/28 (7.1%)	2/12 (16.6%)	0	0	0	

principal compound of the so-called "atypical neuroleptic agents" [17]. The drug was found to be effective in the prevention of chemotherapy-induced and post-operative vomiting as well as in the treatment of nausea and vomiting during hepatic, biliary and gastro-duodenal disorders, organic and functional dyspepsia, travel sickness and vertigo. L-sulpiride is at least as effective as domperidone, antihistamines and neuroleptic agents. Compared with the latter drugs and with d-sulpiride and the racemus, L-sulpiride is much better tolerated. Drowsiness is reported only at high doses, and only few clinical signs of hyperprolactinaemia have been observed, at low doses, even after prolonged administration [18].

There is no consensus regarding the effects of L-sulpiride on norepinephrine, acetylcholine, serotonin, histamine or gamma-aminobutyric acid (GABA) receptors: some Authors, using sulpiride, reported no effects, whereas others report a possible action on noradrenergic and acetylcholinergic pathways, at higher doses.

Giardino et al. [3 19] provided evidence for the involve-

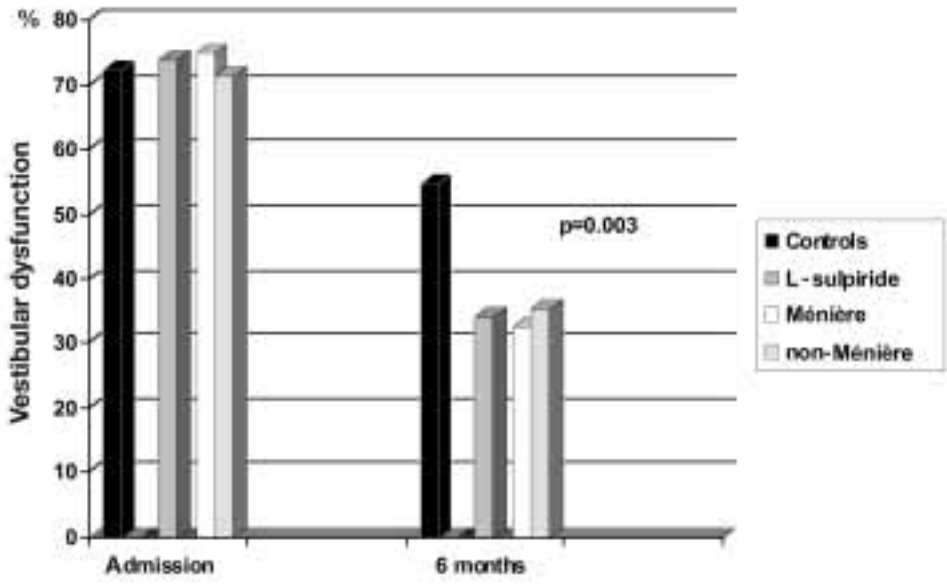

Fig. 3. Overall outcome of therapeutic trial.

ment of the DAergic system during vestibular compensation in young and old hemi-labyrinthectomized rats, since a bilateral increase (20-30%) of DA1 receptors and a two-fold increase in DA2 receptors were found in the striatum of old rats. Since the mesostriatal dopaminergic system is known to serve as a supravestibular centre in posture and locomotion control, their results indicate marked biochemical plasticity of the remaining DA receptors and an active role in compensation of vestibular lesions.

In humans, the effectiveness on vertigo resulting from peripheral and central causes is well-documented [2]. In elderly patients, although remarkably well-tolerated, high daily doses (150 to 200 mg) for 4 to 6 weeks can lead to side-effects of the extrapyramidal type [20]. The low dosage employed in the present study (75 mg/day in 3 divided doses) avoided side-effects, irrespective of the patient's age.

Commonly used anti-vertiginous and anti-emetic drugs include anti-histamines, anti-cholinergics, mono-aminergic agents, calcium entry blockers with anti-histamine, benzodiazepines, phenothiazines and substituted benzamide derivatives [21-25].

In most instances, the exact mechanism of action of these drugs has not been well characterized, with the exception of anti-H1 and anti-cholinergic drugs. The former agents block the effects of the excess histamine release from various brain areas (hypothalamus, thalamus and cortex) and the medial vestibular nucleus (MVN) during vertigo and travel sickness episodes [26 27], while the latter agents probably inhibit the function of the afferent vestibular nerve to the lateral vestibular nucleus (LVN), which is known to contain acetylcholine as a transmitter candidate [28]. Apart from histamine and acetylcholine, it is unlikely that other substances such as dopamine, noradrenaline and serotonin have a transmitter role in the vestibular neurons, since cell bodies and nerve terminals containing the nonoamines have not, so far, been detected in the vestibular nuclei. On the other hand, dopamine has been shown to regulate the glutamatergic inner hair cell activity in the guinea pig cochlea [29], following common pathways within the cochleo-vestibular nerve.

While phenothiazines and benzamide derivatives can effectively suppress emetic episodes associated with dizziness through blockade of dopamine D2 receptors in the chemoreceptor trigger zone of the area postrema [30-32], their anti-vertiginous action exerted at the level of vestibular apparatus is less clear, but should not involve a dopaminergic pathway, which is apparently absent in the vestibular nuclei. For example, the anti-vertiginous action of the benzamide derivative sulpiride (a racemic drug containing L-sulpiride as the active isomer with antagonistic properties at dopamine D2 receptors) has been well known, in clinical practice, for a long time [20].

Experimentally, an increase in central dopamine levels (i.e., in the anterior caudate nucleus), such as that associated with the "high pressure neurological syndrome", results in vertigo, nausea, tremors, myoclonus, electroencephalography (EEG) modifications and convulsions [33]. Therefore, based on the results of this study, a direct relationship between an

enhanced dopamine synthesis in the brain and the occurrence of vertigo can be established. Furthermore, a number of studies have indicated a possible interaction between dopamine and the vestibular system. Dopamine, and the selective D2 receptor agonists levo-quinpirole and piribedil, were found to depolarize the guinea-pig MVN neurons *in vitro* through an action antagonized by L-sulpiride [19]. The depolarizing responses to dopamine were explained as a consequence of a presynaptic inhibitory action of the drug on nerve terminals that normally release GABA on MVN neurons and tonically maintain them in a state of hyperpolarization.

Based on these findings, the therapeutic efficacy of L-sulpiride in the control of vertigo could depend on the blockade of presynaptic dopamine D2 receptors on GABAergic pathways, which cause a negative feedback mechanism on GABA release to MVN. Therefore, the vestibular suppressant action of L-sulpiride might ultimately derive from a facilitation of the inhibitory GABAergic transmission to MVN neurons.

Another study conducted on the rat striatum may shed some light on the potential mechanism of action of L-sulpiride as an anti-vertiginous agent [16]. In the striatum, acute or repeated administrations of methamphetamine were found to be associated with marked histamine release [34]. Pretreatment with the dopamine D2 antagonists sulpiride and haloperidol blocked the methamphetamine-induced increase in histamine release, whereas pretreatment with SCH23390 (a selective D1 receptor antagonist) did not [35 36]. These findings suggest that methamphetamine-induced histamine release in the striatum is controlled by D2 dopamine receptors. If this mechanism occurs also in the MVN and in other brain regions, including the thalamus and cortex, which are innervated by the hypothalamic histaminergic system [20], the blockade of D2 receptors by L-sulpiride should cause a decrease in the central (and vestibular) histaminergic function such as that caused by anti-histamines, which have long since been considered the drugs of choice for the control of vertigo.

Both the above-mentioned mechanisms of L-sulpiride action, at vestibular nuclei level (Fig. 4), can act synergistically or independently to achieve the facilitation of the stable and faster compensation of unilateral labyrinthine disturbances observed in the present clinical study.

Conclusions

In this study, L-sulpiride has been found to exert a significant anti-vertiginous action in clinical practice. This action may be derived from enhancement of the inhibitory GABAergic transmission to the MVN, from suppression of the histaminergic trans-

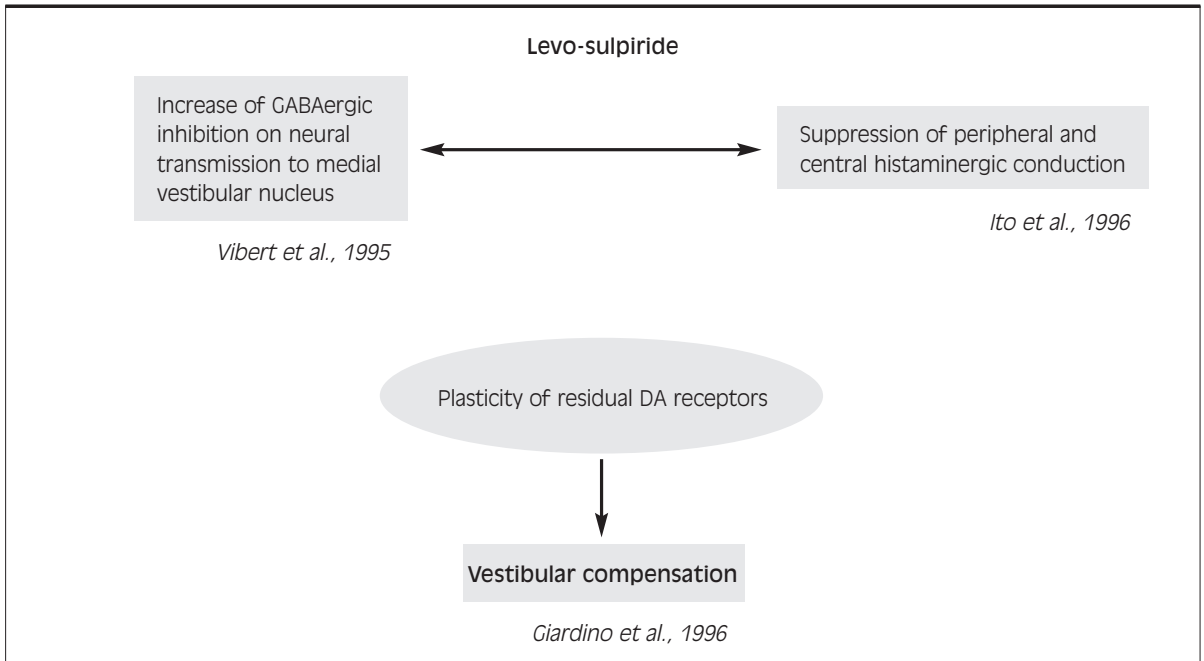

Fig. 4. Mechanisms of action of L-sulpiride in vestibular system.

mission at central and vestibular level or from both mechanisms.
Absence of side-effects, at the low doses employed (25 mg t.i.d.), and the induction of fast and steady vestibular compensation strongly recommend its use as the drug of choice for the control of acute vertigo attacks, being more effective than the routinely employed vestibular suppressants, which usually delay spontaneous compensation.

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