

*Short report*

## The use of lisuride in the treatment of multiple system atrophy with autonomic failure (Shy-Drager syndrome)

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**SUMMARY** In a controlled trial lisuride, an ergolene derivative with dopamine receptor agonist properties was given in maximum tolerated doses (2.4 mg/day) to seven patients with multiple system atrophy with autonomic failure (Shy-Drager syndrome). Improvement in Parkinsonian features occurred in only one patient and another patient who had been deriving marked benefit from levodopa treatment before the study began failed to respond to large doses of lisuride. Psychiatric side effects (including nightmares, isolated visual hallucinations and toxic confusional states) were the dose-limiting factor in six patients. A modest reduction in orthostatic hypotension occurred in two patients, one of whom had experienced an aggravation of this disturbance on levodopa and bromocriptine. Destruction of post-synaptic dopamine receptors and damage to central noradrenergic systems may offer an explanation for the lack of therapeutic effects of lisuride.

The Shy-Drager syndrome, also known as multiple system atrophy with autonomic failure, is a degenerative disorder of the nervous system which affects the central pathways involved in normal voluntary movement and the autonomic nervous system.<sup>1</sup> There are no distinctive biochemical disturbances but a severe depletion of the brain catecholamines, dopamine and noradrenaline, occurs and central cholinergic systems are also affected.<sup>2</sup> In contrast to Parkinson's disease, however, where similar abnormalities occur, dopamine replacement therapy has proved disappointing. Temporary improvement has been reported in a few patients with both levodopa and the dopaminergic agonist, bromocriptine, but unresponsiveness even to large doses is more common. A more complete destruction of dopaminergic neurones in the substantia nigra might offer one explanation for this disparity as both levodopa and bromocriptine require an intact presynaptic neuronal apparatus to produce their pharmacological effects.

Lisuride hydrogen maleate is a semi-synthetic ergolene derived from d-isolysergic acid. It is a

powerful antagonist of 5-hydroxytryptamine and in common with some other ergot alkaloids, it possesses dopamine receptor stimulating properties. For example, it provokes stereotypy in rodents, reverses reserpine-induced catalepsy and hypothermia<sup>3</sup> and causes contralateral rotation in rats with unilateral destruction of the nigro-striatal dopaminergic pathway.<sup>4</sup> Lisuride increases brain dopamine concentration, reduces brain dopamine turnover<sup>5</sup> and is a potent suppressor of prolactin release in animals and man.<sup>6</sup> One important difference between lisuride and the structurally related bromocriptine is that the former's behavioural and biochemical effects are not abolished by inhibition of tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of dopamine.<sup>3</sup> This suggests that lisuride acts as a direct post-synaptic dopaminergic agonist and it could, therefore, have beneficial effects even in the total absence of dopaminergic neurones. This justified a trial of lisuride in patients with multisystem degeneration and autonomic failure.

### **Patients and methods**

Seven patients with multi-system degeneration and autonomic failure agreed to participate in a controlled

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Table The therapeutic effects of levodopa on histologically proven cases of striato-nigral degeneration ( $\pm$  autonomic failure) (all patients had severe rigidity and bradykinesia)

	Sex	Age at onset (yr)	Duration of disease (yr)	Clinical features				Levodopa treatment				Adverse effects		
				Tremor	Dysarthria	Pyramidal signs	Cerebellar signs	Postural hypotension	Sphincter dysfunction	Duration at onset (yr)	Max dosage (mg/day)		Results	
Izumi <i>et al</i> 1971	M	51	2			+					1	6400	No effect	None
	F	53	3								2	2600	No effect	None
Greer <i>et al</i> 1971	F	73	4	+							3	1200	Marked benefit for 6 mths	None
Bannister and Oppenheimer 1972	F	48	6		+	+			+		3	3000	No effect	Severe postural hypotension
Rajput <i>et al</i> 1972	F	56	7	+	+	+				+	7	5000	No effect	None
	F	63	7	+	+	+	+				7	5000	No effect	Severe postural hypotension
Trotter 1973	F	66	8		+	+					4	8000	Modest benefit for 3 mths	Severe postural hypotension
Sharpe <i>et al</i> 1973	F	41	6	+	+	+					5	6000	Modest benefit for 2 mths	Orofacial dyskinesia
Takeji and Mirra 1973	F	66	2	+	+	+					1	3000	No effect	Nausea
Schober <i>et al</i> 1975	F	53	3	+	+	+					1	2000*	Modest benefit for 6 mths	None
	M	61	3	+	+	+					2	3000	No effect	Rise in erect blood pressure
	F	61	2	+	+	+					1	600*	No effect	None
	F	59	7	+	+	+					3	3000	No effect	None
	F	56	4	+	+	+					2	5000	No effect	None
	F	56	4	+	+	+					2	800*	No effect	None
	F	56	4	+	+	+					2	4000	Modest benefit for 6 mths	Orofacial dyskinesia.
Delean and Deck 1976	M	54	6	+	+	+					4	1000	Modest benefit for 3 mths	Rise in erect blood pressure
Rajput and Kozlisky 1976	M	46	5	+	+	+					4	750*	No effect	Severe postural hypotension
Feve <i>et al</i> 1977	F	61	4	+	+	+					1	2000	Marked benefit for 3 yrs	Dyskinesias
	M	70	9	+	+	+					1	3000	Marked benefit for 3 yrs	Dyskinesias
Spokes <i>et al</i> 1980	M	49	9	+	+	+					1	3000	Marked benefit for 3 yrs	Dyskinesias
	M	49	9	+	+	+					1	3000	Marked benefit for 3 yrs	Dyskinesias
	M	51	4	+	+	+					1	3000	Marked benefit for 3 yrs	Dyskinesias
	F	53	3	+	+	+					3	300*	No effect	Severe postural hypotension
Present living cases 1980	M	57	3	+	+	+					3	300*	No effect	Severe postural hypotension
	F	49	6	+	+	+					6	750*	No effect	Severe post hypotension
	M	59	7	+	+	+					7	750*	Mild benefit for 3 mths	Somnolence; severe post hypotension
	M	59	5	+	+	+					5	500*	No effect	None
	F	57	2	+	+	+					2	750*	No effect	None
	M	41	6	+	+	+					6	600*	Marked	Dyskinesias; wearing off effects
	F	69	8	+	+	+					8	200*	Marked	Severe postural hypotension; syncope

\* In combination with a peripheral dopa decarboxylase inhibitor.

trial of lisuride hydrogen maleate to be carried out in hospital. All of them had Parkinsonian features and postural hypotension with abnormalities of their cardiovascular reflexes. Severe bradykinesia and rigidity were present in patients Nos 1, 2, 3, 5, 6, and 7 and three of the patients also had a coarse (4–7 Hz) tremor at rest (patients Nos 1, 2, 7). The results of levodopa therapy in combination with a peripheral dopa decarboxylase inhibitor in the patients are shown in the table. After informed consent all levodopa preparations were withdrawn; only one of the three patients still receiving them deteriorated appreciably (patient No 6). Patients Nos 1, 5 and 7 had also taken bromocriptine without benefit and profound aggravation of orthostatic hypotension had occurred in two (patients Nos 5 and 7).

For ethical reasons patient No 6 was given lisuride in an open fashion as he became severely incapacitated on withdrawal of levodopa. The remainder of the patients took part in a randomised double-blind cross-over trial using a placebo indistinguishable from lisuride. Treatment was begun with an initial dose of 0.2 mg a day after supper and after three days this was increased to 0.2 mg every 8 hours following meals. After this daily increments of 0.6 mg in divided dosage were made every three days up to optimum tolerated levels or an arbitrary maximum daily dosage of 5 mg. The patients were maintained on maximum doses for a minimum of 7 days and each phase of the trial lasted for 6 weeks. If toxic side-effects occurred the daily dose was reduced by 0.6 mg and the patients were kept at that level of drug intake until the end of the trial.

Patients were evaluated twice a week by the same assessor using a modified Columbia University scale (4-point disability rating system).<sup>7</sup> Fifteen parameters were used to give a maximum total disability score of 60. Erect and supine blood pressure recordings were made at six-hourly intervals. For statistical analysis the last three disability scores on active and placebo medication, were used together with mean lying and standing blood pressures taken over the last three days of each phase of the trial.

## Results

The mean dose of lisuride was 2.4 mg (0.6–5.0 mg) daily but only patient No 4 who had relatively mild Parkinsonian features tolerated 5.0 mg/day. No statistically significant improvement in disability occurred and only patient No 7 showed any benefit. The overall scores for each individual are shown in the figure. A separate analysis of individual parameters failed to reveal any selective benefits. No statistically significant effects on orthostatic hypotension occurred, although a modest elevation in erect blood pressure in patients Nos 4 and 7 was seen.

Psychiatric side-effects were the limiting factor in six patients and the dosage was reduced promptly when they occurred; the effects subsided rapidly and did not recur. Visual hallucinations occurred in five patients and in two they were accompanied by a toxic confusional state. Patient No 1 complained of soldiers charging down the ward on horseback in the

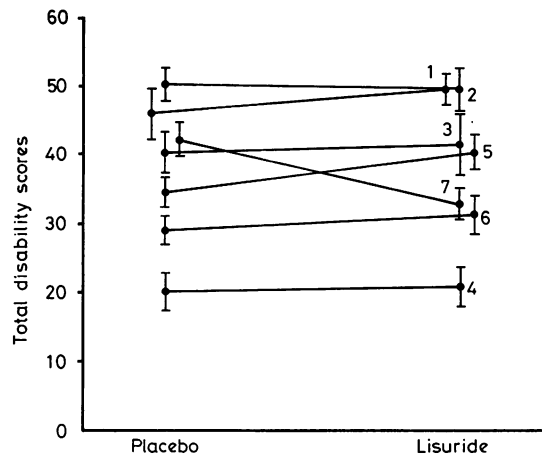


Figure 1 Therapeutic effects of lisuride

early evening. Patient No 2 reported neighbours and relatives peering out of her bath water. Patient No 3 became unable to recognise his fellow patients in the hospital ward and saw armed guards arresting other patients and opening surgical equipment. On other occasions this patient became convinced that he was to be charged with the murder of a young girl. Patient No 5 noticed giant rats and hideous beasts at her bedside and patient No 6 had a panoramic nightmare in vivid colours involving macabre occult-rituals. Patient No 7 described the most alarming visions of all: diseased putrefying faces, grotesque monsters imprinted on personal possessions like her handbag, threatening bandits, and her bed being transformed into a huge sweet jar. Finally she became convinced that a member of the Royal Family was having a miscarriage in the bed next to her. None of these patients had experienced any psychiatric complications on levodopa or bromocriptine. Other adverse reactions were insignificant and included mild nausea (two patients) and severe dizziness without an increase in orthostatic hypotension (patient No 5).

## Discussion

At least two distinct neurological diseases cause loss of preganglionic sympathetic fibres in the central nervous system. The first is a multi-system degeneration affecting corticospinal and cerebellar pathways as well as the basal ganglia. Striato-nigral degeneration and olivo-ponto-cerebellar atrophy have so far not been distinguishable pathologically from this condition and it is only the additional involvement of the sympathetic fibres in the intermediolateral column of the spinal cord which justify

the eponymous title the Shy-Drager syndrome. In the second group of patients autonomic failure occurs either alone or in association with bradykinesia, rigidity and tremor indistinguishable clinically from idiopathic Parkinson's disease. Here the histological findings include the presence of Lewy-type inclusion bodies in the degenerating pigmented brain stem nuclei and the sympathetic ganglia.<sup>8,9</sup> It is possible that patient No 7 was suffering from Parkinsonism with autonomic failure rather than the Shy-Drager syndrome and it is of interest that she was one of the two patients who derived marked initial benefit from levodopa.

The effects of levodopa therapy on the 21 patients in the medical literature with bradykinetic-rigid syndromes found at necropsy to be due to striato-nigral degeneration are shown in the table.<sup>2,10-22</sup> Only one patient<sup>22</sup> had derived sustained worthwhile improvement and at the price of dyskinesias, but initial benefit lasting up to 6 months occurred in a further six. Eight of these 21 patients also had autonomic failure (Shy-Drager syndrome)<sup>2,12,17,20,21</sup> and in only two of these<sup>17,20</sup> did transient benefit in extrapyramidal features occur. Clinical studies also confirm the poor response of the Shy-Drager syndrome to levodopa,<sup>23</sup> although two patients with olivo-ponto-cerebellar degeneration improved.<sup>24</sup> Results with bromocriptine have been similar<sup>25-27</sup> with temporary benefit occurring in occasional patients. There is only one histologically confirmed case of Parkinsonism with autonomic failure in the literature who received levodopa.<sup>21</sup> In this patient a dose of 3.0 g levodopa per day produced a marked increase in postural hypotension, as occurred in our patient No 7.

The therapeutic effects of lisuride in this study were extremely disappointing; modest benefit occurring only in patient No 7. Patient No 6 who was the only one benefiting from levodopa, derived no benefit from lisuride at high dosage. Damage to post-synaptic dopamine receptors is known to occur in the Shy-Drager syndrome and this may be the explanation for the lack of improvement.<sup>28</sup>

Lisuride had no significant effects on postural hypotension although in two patients (patients Nos 4 and 7) a modest elevation occurred. It was of interest that patient No 7 had experienced syncopal attacks with levodopa and bromocriptine. A rise in standing blood pressure has also occasionally been reported with levodopa<sup>23,29</sup> and bromocriptine<sup>27</sup> although a severe increase in orthostatic hypotension can also occur. After conversion of levodopa to dopamine, central hypotensive<sup>30</sup> and peripheral pressor effects occur and disconnection between these two pathways in some patients with the Shy-Drager syndrome might lead to paradoxical effects. Further-

more, effects of dopaminergic drugs on blood pressure may be different when there is severe destruction of central autonomic pathways.

Visual hallucinations occur relatively commonly in patients with Parkinson's disease receiving levodopa and bromocriptine but have only occasionally been reported in patients with multiple system atrophy. Vivid dreams and nightmares often occur before the hallucinations which are frequently evaluated by the patients as being fictitious. Excessive stimulation of mesolimbic and mesocortical dopamine pathways have been suggested as a likely cause but the pathological substrate of Parkinson's disease must be a relevant factor as these dopaminergic drugs have not so far produced psychiatric effects in normal people or acromegalics. Structural irritative lesions in the parieto-occipital cortex<sup>31</sup> can produce similar perceptual disturbances and the poorly documented peduncular hallucinations described initially by L'Hermitte<sup>32</sup> also bear some resemblance to these drug-induced effects. Although lisuride and bromocriptine show some structural similarity to the psychedelic drug lysergic acid diethylamide (LSD-25), basic molecular differences make it unlikely that endogenous conversion to this agent occurs.

The high incidence of visual hallucinations with lisuride was surprising. None of the patients had clinical or radiological evidence of cortical atrophy and none had experienced similar phenomena with levodopa or bromocriptine. Psychiatric complications have not constituted a major problem with lisuride in Parkinson's disease as yet although there are only a few published reports.<sup>33</sup>

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