PAPER

Apomorphine in idiopathic restless legs syndrome: an exploratory study

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Background: Dopaminergic and opioidergic drugs have been found to be effective in patients with restless legs syndrome (RLS).

Objectives: To test the effect of apomorphine—a combined opioidergic and dopaminergic agonist—and subsequent selective antagonism by naloxone and metoclopramide on subjective and objective symptoms in patients with idiopathic RLS.

Methods: Nine patients with RLS were pretreated with oral domperidone for three days. A modified suggested immobilisation test (SIT) was carried out between 8 pm and 1 am under the following conditions of intravenous drug administration: baseline–apomorphine–apomorphine plus naloxone–apomorphine plus metoclopramide. Outcome variables were a visual analogue scale (VAS) of subjective RLS symptoms and EMG documented periodic leg movements while awake (PLMW).

Results: Compared with baseline, apomorphine resulted in a rapid and significant improvement in subjective RLS symptoms as measured by VAS (54.5% improvement; $p=0.011$), and an almost immediate cessation of PLMW, measured by PLMW index (98.0% improvement; $p=0.012$). Neither additional naloxone nor metoclopramide blocked this effect significantly. While given apomorphine with metoclopramide, there was a trend to reappearance of PLMW.

Conclusions: Apomorphine may be an effective treatment for idiopathic RLS. Its effectiveness may reflect both to its dopaminergic and its opioidergic activity, and is not diminished significantly by blocking only one of these pathways. The trend to a worsening of the PLMW index with metoclopramide hints at a primarily dopaminergic effect of apomorphine in idiopathic RLS.

The prevalence of the restless legs syndrome (RLS) is around 10% in Western populations.^{1–5} It is defined by four essential diagnostic criteria⁶: an urge to move the legs, usually accompanied by uncomfortable and unpleasant sensations in the legs; worsening during inactivity; improvement with movements; and worsening in the evening or at night. Further clinical features are a positive family history, a response to dopaminergic drugs, periodic limb movements during wakefulness (PLMW) or sleep (PLMS), sleep disturbances, and a normal neurological examination.

Therapeutic effects of L-dopa, dopamine agonists, and different opioidergic substances on RLS symptoms have been demonstrated.⁷ Dopaminergic treatment is considered to be most effective.⁸ A reduction in PLMS has been documented in RLS patients during dopaminergic treatment.^{9–12}

Involvement of the opioidergic and dopaminergic systems in RLS has been demonstrated. Naloxone, an opioid antagonist, which acts at all three types of opioid receptors (μ , κ , and σ), antagonised the treatment effects of propoxyphene and methadone in two patients^{13 14}; pimizide, a D2 receptor antagonist, partially antagonised the treatment effect of codeine sulphate in a further patient.¹⁵ D2 receptor antagonists such as olanzapine¹⁶ and risperidone¹⁷ are suspected to provoke RLS. However, in untreated patients, intravenous administration of the opioid antagonist naloxone and the D2 receptor antagonist metoclopramide failed to cause deterioration in the sensory or motor symptoms of RLS.¹⁸

Apomorphine (10,11-dihydroxyaporphine), a derivative of morphine, acts as a dopamine and opioid agonist. It has a good D2, D3, and D4 receptor affinity and much less affinity for D1 and D5 receptors.¹⁹ The ratio of its affinity for D2 to its affinity for D1 is about 10:1. Metoclopramide can antagonise apomorphine induced stereotypy in rats.²⁰ Naloxone is known

to reverse the opioidergic effects of high doses of apomorphine, such as central nervous system and respiratory depression.²¹

There are only a few case reports on apomorphine in RLS. In one patient with idiopathic RLS and another with Parkinson's disease and RLS, an overnight infusion of apomorphine improved nocturnal discomfort and leg movements. Periodic limb movements were not assessed.²² Another patient with paraspastic symptoms and a vitamin B-12 deficiency induced PLM disorder had an EMG documented response to subcutaneous apomorphine.²³ In nine patients with a periodic limb movement disorder, 0.5 mg of subcutaneous apomorphine at bedtime resulted a significant reduction of PLMS during the first four hours of sleep compared with two control nights.²⁴ Eight patients from that study were reported also to have RLS; however, the RLS was not clinically characterised nor were apomorphine effects measured.²⁴ In a sample of 12 parkinsonian patients, one night's treatment with apomorphine improved akinesia, rigidity, and sleep indices,²⁵ including a 15% reduction in the periodic limb movement index. RLS symptoms were not documented.

As data are scarce, we carried out this study in order to document the effects of apomorphine in idiopathic RLS. We hypothesised that apomorphine might be effective in people suffering from this condition. We also investigated whether the effects of apomorphine on subjective and objective RLS

Abbreviations: IRLSSG, International RLS Study Group; PET, positron emission tomography; PLMS, periodic limb movements during sleep; PLMW, periodic limb movements during wakefulness; RLS, restless legs syndrome; SIT, suggested immobilisation test; SPECT, single photon emission computed tomography; VAS, visual analogue scale

symptoms could be reversed by selective opioidergic or dopaminergic antagonism.

METHODS

Subjects

This study was approved by the local ethics committee and written informed consent was obtained from all participants before study entry.

Nine consecutive patients with severe idiopathic RLS (five male/four female; mean (SEM) age, 55.3 (3.1) years; tables 1 and 2) were included in a prospective, open, observational study. Six patients were pretreated and had responded to specific treatment (table 2) but were still suffering from RLS symptoms. Three patients were drug-naïve.

Inclusion criteria were: men or women aged between 30 and 75 years, with severe and almost daily (six or seven days a week) restless leg symptoms according to the definition of the International RLS Study Group (IRLSSG).⁶ There were normal findings in the medical history, physical and neurological examination, and blood analyses, and objective sleep disturbances were documented on whole night polysomnography. The PLMS index was >10 per hour of total sleep time. Subjective sleep and daytime sleepiness were controlled by the Pittsburgh sleep quality index²⁶ and the Epworth sleepiness scale.²⁷

Exclusion criteria were as follows:

- any secondary RLS (for example, from renal insufficiency—excluded by serum creatinine and blood urea nitrogen);
- disorders of iron metabolism (excluded by measurements of iron, ferritin, and transferrin);
- diabetes mellitus (excluded by measurement of serum glucose and HbA1c);
- thyroid dysfunction (excluded by measurements of TSH, T3, and T4);
- anaemia (excluded by blood count);
- deficiency of folic acid, vitamin B-12, or magnesium (all within the normal range);
- pregnancy;
- signs of a severe polyneuropathy on clinical examination or in the nerve conduction velocity studies;
- any other sleep disorder;
- an apnoea index of >5/hour total sleep time or an apnoea–hypopnoea index of >10/hour total sleep time;
- any previous intake of neuroleptic agents or any intake of other psychotropic drugs during the previous six months;
- alcohol abuse.

Table 1 Clinical characteristics of nine patients with idiopathic restless legs syndrome

Variable	Mean (SEM) or n	Range
M/F	5/4	
Age (years)	55.3 (3.1)	(41 to 71)
PSQI	11.9 (1.5)	(4 to 19)
ESS	6.2 (1.2)	(0 to 12)
Duration of RLS (years)	16.3 (3.9)	(3 to 40)
IRLSSG rating scale	27.1 (2.2)	(15 to 37)
PLMS/h TST	32.1 (8.2)	(10.1 to 91.9)
Sleep efficiency (TST/TIB) (%)	72.4 (5.0)	(40.1 to 85.7)

ESS, Epworth sleepiness scale (daytime sleepiness); IRLSSG, International RLS Study Group rating scale; PLMS/h TST, periodic leg movement index per hour total sleep time; PSQI, Pittsburgh sleep quality index; RLS, restless legs syndrome; TST/TIB: total sleep time/time in bed (sleep efficiency).

In the pretreated patients, specific drug treatment was discontinued at least 10 times the plasma half life before the study day. One patient treated with ropinirole (half life 5.8 hours²⁸) could not tolerate the drug withdrawal and discontinued the treatment 48 hours before the study. Apomorphine is known to cause effects such as nausea, drowsiness, sedation, and arterial hypotension.²⁹ To prevent these possible side effects, domperidone (30 mg three times daily)—a potent peripheral dopamine antagonist which does not cross the blood–brain barrier³⁰—was given orally three days before the study.

Study procedure

The patients arrived at the sleep centre for baseline RLS symptom assessments and mounting of electrodes at 7.00 pm. Electrodes for electroencephalography, electro-oculography, and surface electromyography of both mental muscles and both anterior tibial muscles were set up. Non-invasive surface electrodes were placed over the belly of both anterior tibial muscles, 2 to 4 cm apart on the long axis of the muscles. An impedance of less than 10 000 ohm was set. Band pass filter settings of 10 Hz and 90 Hz with a time constant of 0.003 seconds were used. An intravenous cannula was mounted in the cubital vein.

A modified suggested immobilisation test (SIT)^{9, 31, 32} was carried out. The patients lay in bed in the supine position with the upper body slightly raised at a 45° angle. They were advised to limit their voluntary movements for the entire duration of the test and not to fall asleep. If they did so, they were awakened. Every five minutes during the SIT, the patients were asked to rate their subjective leg symptoms (subjective leg dysaesthesias and the need to move the legs) by means of an 11 point (0–10) visual analogue scale (VAS).³³ SIT data were recorded on a personal computer system (Alpha-trace; Grossegger, Vienna, Austria). Periodic limb movement scoring was done automatically and visually. Scoring rules followed international recommendations:

- a “leg movement” is a burst of the anterior tibial muscle activity lasting 0.5 to 5 seconds and with an amplitude greater than 25% of calibration (= toe movement without resistance);
- a “PLM sequence” is a sequence of four or more periodic leg movements separated by at least 4 but not more than 90 seconds.^{34, 35}

According to recent SIT studies, which showed a longer duration of periodic leg movements during wakefulness than in sleep, we used a duration criterion of 0.5 to 10.0 seconds for leg movements.³²

The SIT started at 8 pm. All study drugs were given intravenously. Each of the four conditions (baseline, apomorphine, apomorphine plus naloxone, apomorphine plus metoclopramide) was measured for 30 minutes. Mean values of the five minute VAS values were calculated. The number of PLMW was doubled to determine the PLMW index per hour. Baseline condition was measured after the patients had reached their subjective typical RLS discomfort. Subsequently, apomorphine was given as a bolus of 0.035 mg/kg body weight and continuously as an intravenous infusion in a dose of 0.03 mg/kg/h. According to clinical response, the dose was increased (or decreased) by 0.01 mg/kg/h every 15 minutes until there was a stable clinical effect on RLS symptoms, at which point VAS and PLMW were measured. The dose in the final step was then given continuously for the rest of the SIT. Naloxone was given as a 2 mg bolus in all patients; metoclopramide was administered as a bolus of 2 mg/kg body weight. The effect of naloxone was measured immediately after administration. There was then a 30 minute

Table 2 Clinical details of nine patients with idiopathic restless legs syndrome (RLS)

	Sex	Age (years)	Duration of RLS (years)	Family history*	PNP†	Specific drug treatment (mg/d)	Other drugs (mg/d)
1	F	58	12	+	–	L-dopa 200 mg CR+benserazide 50 mg	Candesartan 4 mg
2	F	56	8	–	–	Gabapentin 900 mg	Indapamide 1.5 mg Diosmin 900 mg
3	M	55	30	–	+	Gabapentin 900 mg	Phenprocoumon Losartan 12.5 mg Doxazosin 1 mg Salbutamol
4	F	41	12	–	–	L-dopa 200 mg L-dopa 200 mg CR +benserazide 100 mg	0
5	M	51	9	–	+	Gabapentin 400 mg Alprazolam 0.25 mg	0
6	M	65	40	+	+	Ropinirole 1 mg	0
7	M	45	16	–	+	Drug-naïve	0
8	M	71	3	–	–	Drug-naïve	Metoprolol 23.8 mg Aspirin 100 mg Oxerutin 300 mg
9	F	56	17	–	–	Drug-naïve	0

*+, positive; –, negative.

†PNP, low grade polyneuropathy, documented by nerve conduction velocity studies.

washout period. After administration of metoclopramide, there was a half hour wait before the clinical effect was measured. The duration of the entire SIT ranged between three hours and four hours, 14 minutes.

Statistical analysis

Expecting a non-normal distribution in the small sample size of nine participants, non-parametric statistics were used. Comparisons of treatment effects were analysed with the Wilcoxon matched pairs test. The Friedman ANOVA (analysis of variance) was used as a test statistic for the treatment effect over time. The level of significance was set at $p < 0.05$. Baseline values are described as mean (SEM), and treatment effects as percentage change from baseline. Because of the exploratory character of the study and the small sample size, even borderline significant results were interpreted.

RESULTS

VAS of subjective leg symptoms

The VAS results for subjective leg symptoms (subjective leg dysaesthesiae and the need to move the legs) are shown in table 3 and fig 1.

The baseline mean (SEM) VAS symptom score was 5.8 (0.7), which was reduced by apomorphine by 54.5% ($p = 0.011$). Compared with baseline, apomorphine plus naloxone reduced mean VAS by 46.4% ($p = 0.015$) and apomorphine plus metoclopramide reduced it by 41.7% ($p = 0.028$). Compared with apomorphine alone, naloxone with apomorphine and metoclopramide with apomorphine increased mean VAS non-significantly (by 8.1% and 12.9%).

PLMW index

The results of the PLMW index (number of periodic leg movements during wakefulness per hour of the SIT) are shown in table 3 and fig 1.

The baseline mean PLMW index was 56.4 (19.2). Apomorphine reduced this by 98.0% ($p = 0.012$). Compared with baseline, apomorphine plus naloxone reduced the index by 98.4% ($p = 0.012$) and apomorphine plus metoclopramide reduced it by 74.8% ($p = 0.058$). Compared with apomorphine alone, naloxone plus apomorphine decreased the index by 0.4% (NS) and metoclopramide plus apomorphine increased it by 23.2% (NS).

Latency, effective dosage, and side effects of apomorphine

The treatment effects of apomorphine were reached very rapidly. The mean latency to reach a stable and significant improvement was 13.1 (3.5) minutes for subjective leg discomfort and 5.1 (1.7) minutes for the PLMW. Effective doses of apomorphine were reached in seven of the nine participants with the initial bolus of 0.035 mg/kg body weight or with a constant infusion rate of up to 0.04 mg/kg/h. One patient (No 5) needed 0.05 mg/kg/h of apomorphine for adequate response. This patient had shown a poor response to previous dopaminergic treatment (L-dopa with benserazide and cabergoline). Another drug-naïve patient (No 9) with a high PLMS index (40.2/h TST) needed 0.07 mg/kg/h of apomorphine for adequate response.

After the initial bolus of apomorphine, side effects were frequent and in a few patients they were marked, as follows (cumulative numbers of affected patients in brackets):

Table 3 Results from nine patients with idiopathic restless legs syndrome

	VAS			PLMW/h		
	Mean (SEM)	Relative reduction of symptoms (%)	p Value (v baseline)	Mean (SEM)	Relative reduction of symptoms (%)	p Value (v baseline)
Baseline	5.8 (0.7)	–	–	56.4 (19.2)	–	–
Apomorphine	2.6 (0.8)	–54.5	0.011	1.1 (1.1)	–98.0	0.012
Apomorphine + naloxone	3.1 (0.8)	–46.4	0.015	0.9 (0.6)	–98.4	0.012
Apomorphine + metoclopramide	3.4 (0.8)	–41.7	0.028	14.2 (8.3)	–74.8	0.058

Values are given as mean (SEM) and relative reduction of symptoms as compared with baseline. Visual analogue scale (VAS) and periodic leg movements per hour (PLMW/h) under the four conditions of baseline, apomorphine, apomorphine + naloxone, and apomorphine + metoclopramide.

Figure 1 Subjective leg symptoms (visual analogue scale) and periodic leg movements during wakefulness per hour (PLMW/h) during the immobilisation test in nine patients with idiopathic restless legs syndrome. * $p < 0.05$ v baseline; ^xNS v baseline.

drowsiness (8), yawning (7), dizziness (6), falling asleep (4), severe nausea (4), coughing (4), sweating (4), nasal congestion (3), lacrimation (2), heat sensation (2), mild nausea (2), hiccup (1), vomiting (1), diarrhoea (1), mild hyperventilation (1), slight hoarseness (1), chills (1). In the steady state of apomorphine administration, side effects were less marked. Naloxone improved CNS side effects such as drowsiness and dizziness to some extent. Metoclopramide improved gastrointestinal side effects rapidly, especially nausea, which was fully reversed.

DISCUSSION

The main finding of this study was that apomorphine caused a rapid and highly significant improvement in subjective symptoms and periodic limb movements during wakefulness, even in this small group of nine patients with idiopathic RLS. Neither naloxone nor metoclopramide antagonised this effect to a significant extent. Given the exploratory character of the study, apomorphine may therefore be considered effective in idiopathic RLS.

Naloxone had no significant impact on the effect of apomorphine. Hence, blocking of μ , κ , or σ receptors of the opioidergic system does not seem to influence the apomorphine effect in idiopathic RLS.

The combined administration of apomorphine plus metoclopramide compared with apomorphine alone and with apomorphine plus naloxone produced no significant difference in the subjective RLS symptoms or the PLMW index. Comparing combined apomorphine plus metoclopramide administration with baseline, the improvement in RLS symptoms was significant, but there was only a trend to improvement of the PLMW index. There could be various reasons for this finding. First, in a previous study it was shown that both subjective symptoms on the VAS and periodic limb movements increased in patients with RLS during the SIT. After 10 minutes of SIT, both variables differed significantly in patients compared with healthy controls.³⁶ In our study, metoclopramide was given after two to three hours of SIT, so an increase in RLS symptoms might reflect the long duration of the SIT. However, at the time of administration of naloxone, after a SIT duration of at least one hour, there was only a slight increase in leg discomfort and no increase in PLMW. Another explanation for our findings might be partial blockade of the apomorphine effect by the D2 receptor antagonist metoclopramide, causing the non-significant reappearance of PLMW. This could be interpreted as a primarily dopaminergic mechanism in idiopathic

RLS.¹⁵ Furthermore, our results support the recommendation to use dopaminergic substances as first line treatment, and opioidergic substances as second line treatment in RLS.⁸ Owing to the small numbers in our sample, the antagonising effect of metoclopramide might not have reached statistical significance, but the results encourage further studies on a possible antagonism of apomorphine and metoclopramide in RLS.

Dopaminergic pathways in the CNS have been examined in different functional imaging studies. SPECT and PET studies of the dopaminergic synapse in the striatum produced equivocal results. Some groups reported presynaptic^{37,38} or postsynaptic^{37,39–41} alterations. However, in all these studies the differences were only small.⁴² In contrast, some studies have shown normal functional conditions at the dopaminergic synapse in RLS.^{43–45} The useful effects of apomorphine in our patients are in accord with many treatment studies with dopaminergic and opioidergic substances,⁷ but the location of action of apomorphine in RLS remains unknown.

In our patients, some side effects of apomorphine were accentuated. In evaluating a possible therapeutic use of apomorphine in RLS, one should bear in mind that our patients were receiving apomorphine for the first time and that the dose escalation was rapid. Seven of the nine patients had good and stable improvement in their symptoms with the initial dose, which encourages trials of lower doses. Generally, effective long term treatment dosages of L-dopa and dopamine agonists are lower in RLS than in Parkinson's disease. In RLS, a slower tapering of apomorphine to a lower therapeutic dose might be better tolerated but still effective.

In the present study we needed an intravenous route for the administration of naloxone and metoclopramide. Apomorphine was also given intravenously, because we did not want to expose the participants to any further unnecessary risk, such as subcutaneous reactions (panniculitis) to apomorphine.⁴⁶ However, apomorphine given subcutaneously in similar doses to those we used intravenously have been reported to be well tolerated in the long term treatment of advanced Parkinson's disease,^{47,48} and this might also be a possible way of giving the drug in RLS. The pharmacokinetics (drug absorption, volume of distribution, plasma clearance, and half life) of intravenously and subcutaneously administered apomorphine are similar.⁴⁹ An equally good effect of subcutaneous apomorphine in RLS may be assumed. Transdermal administration of apomorphine has also been considered in Parkinson's disease with periodic leg movements²⁵ and might be a further option in the treatment of

RLS. Oral dopamine agonists remain the first line treatment in RLS. However, apomorphine could be helpful in severe, treatment refractory, and well selected cases.

Furthermore, a modified "apomorphine test" might be used as a diagnostic tool in RLS. This test is established for the rapid evaluation of the dopaminergic response in parkinsonian syndromes,⁵⁰ and might be used in patients with suspected RLS both for diagnostic purposes and for the evaluation of a possible therapeutic response. Thirty minutes of apomorphine administration under SIT conditions should be sufficient to evaluate an eventual response.

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