Transdermal apomorphine permeation from microemulsions: a new treatment in Parkinson's disease

Transdermal Apomorphine Permeation From Microemulsions: A New Treatment in Parkinson's Disease

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Abstract: **We studied absorption, efficacy, and tolerability in Parkinson's disease (PD) of a new preparation of apomorphine included in a microemulsion and administered by transdermal route (Apo-MTD). Twenty-one PD patients were treated with levodopa plus oral dopamine-agonists (T0), with levodopa alone (T1), finally with levodopa plus Apo-MTD (T2). Apo-MTD provided therapeutic plasma levels for many hours, improved Unified Parkinson's Disease Rating Scale III scores, and reduced total duration of *off* periods compared to T0 and T1. We concluded that Apo-MTD is absorbed and demonstrates clinical efficacy and long action. Therefore, it seems a promising add-on treatment for uncontrolled prolonged *off* phases in PD patients, but chronic tolerability needs further study.** © 2004 Movement Disorder Society

Key words: apomorphine; transdermal; pharmacokinetics; Parkinson's disease; dopamine agonists

Apomorphine (10,11-dihydroxyapomorphine) is a well-known potent short-acting dopamine agonist at D1 and D2 dopamine receptors, and it was proposed as an antiparkinsonian drug more than a century ago. It is potentially a very useful adjunctive medication in parkinsonian patients with refractory motor fluctuations[1,2]; unlike other currently available dopamine agonists, apomorphine is able to reverse bradykinesia when administered alone; thus, it has been used for treatment of *off* periods.[3,4] Despite these favourable characteristics, its clinical use for the treatment of Parkinson's disease is somewhat limited by its pharmacokinetic profile: a short half-life of approximately 30 minutes, rapid clearance from plasma, the absence of storage or retention in brain regions, poor oral bioavailability (5%), and first-pass hepatic metabolism are important limitations to chronic oral treatment.[5–7] Attempts have been made to overcome these limits by using other routes of administration. The subcutaneous route is able to avoid the first-pass hepatic metabolism; by this route, apomorphine is quickly absorbed, with little regional retention, and peak plasma levels achieved in 3 to 10 minutes in most patients; significant variations in peak plasma levels among patients have been described.[5,6] Unfortunately, its short half-life and rapid clearance from plasma are still responsible for a short clinical effect. For these reasons, at present its use is limited to rapidly reversing *off* periods or as a diagnostic tool.[8,9] Subcutaneous administration of apomorphine by means of a microinfusor is able to give constant therapeutic plasma levels of the drug, and it has been successfully used in patients with advanced Parkinson's disease to reduce motor fluctuations or to guarantee a continuous dopaminergic stimulation during the transitory interruption of levodopa (L-dopa) therapy ("drug holiday").[10] Nevertheless, this treatment sometimes cannot be longer than a week due to the occurrence of local subcutaneous nodules or other systemic side effects (nausea, sleepiness, hallucination phenomena).[10] Other routes of administration such as sublingual, intranasal, and rectal, although promising, still remain of limited use. Absorption through the sublingual route is slow, and bioavailability is less than 20%; irritation of the oral mucosa is the most important factor that limits the use of this preparation only to selected patients.[11–13] Similarly, nasal stuffiness and crusting during the intranasal route using a nebulized spray may occur and may limit its use.[6,14–17] The rectal route may provide prolonged effect and so may be a useful treatment in patients with nocturnal impairments refractory to other agonists; nevertheless, this route still remains impractical for most patients.[6,18,19] To exploit the favourable pharmacological characteristics of apomorphine and overcome the pharmacokinetic limits, we studied a new pharmaceutical preparation of apomorphine dissolved in a thickened microemulsion,[20] which may be administered by an epicutaneous–transdermal route (Apo-MTD). Apomorphine was present in the microemulsion as ion-pair complex with octanoate to increase its lipophilicity and to diminish its dissociation. The drug was completely dissolved in the microemulsion,

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and relatively high concentrations could be carried as a consequence of the supersolvent properties of microemulsions. The dispersed phase, also acting as a reservoir, made it possible to maintain an almost constant concentration in the continuous phase. Pseudo–zero-order kinetics, thus, could be achieved. The microemulsion was able to provide in vitro, through hairless mouse skin, a flux of 88 μg/h per cm^2 for 24 hours, with a kinetic release of pseudo–zero-order and was chosen for in vivo study; all the components were biocompatible and safe. The flux gave a first approximation of the feasibility of the transdermal administration in man. After the approval of the ethical committee, we tested this preparation in a group of patients affected by Parkinson's disease and motor fluctuations, to verify (1) primarily the absorption and the achievement of detectable plasma levels of the drug; (2) secondarily its clinical efficacy and tolerability.

PATIENTS AND METHODS

Apomorphine Microemulsion: Components and Characterization

The Apo-MTD preparation consisted of R-apomorphine hydrochloride incorporated in a stable water-in-oil microemulsion. Antioxidants were added to both the oil phase and the aqueous phase to avoid oxidation of the drug. Components of microemulsion were aqueous solution containing 2% ascorbic acid (18.2%), oil phase (isopropylmiristate-decanol 1:1.5 v/v containing 1% of ascorbylpalmitate; 42.1%), R-apomorphine hydrochloride (3.9%), Epikuron 200 (7.3%), benzyl alcohol (7.1%), octanoic acid (4.6%), sodium octanoate (3.5%), sodium taurocholate (5.7%), 1,2-propanediol (7.6%). The average droplet diameter was 74.9 nm, with a polydispersity index of 0.20. The microemulsion was thickened by adding 5.9% (w/w) of Aerosil 200 to the microemulsion. The pH was 6.0. As control, a thickened microemulsion not carrying apomorphine was also prepared to verify the possible local side effects.

Apomorphine Microemulsion Application

Ten grams of Apo-MTD (apomorphine hydrochloride 3.9%) was applied to 100 cm^2 skin area over the anterior part of the chest, delimited by 1-mm-thick biocompatible foam tapes and covered by a polyester-based membrane (3M Scotchpak) and an occlusive membrane (Smith and Nephew OpSite Flexigrid) to prevent evaporation of some components. In these conditions, a single layer of microemulsion (1 mm thick) was directly in contact with the skin surface and acted as a reservoir of apomorphine. The skin of patients was not pretreated.

Patients

Twenty-one consecutive patients affected by idiopathic Parkinson's disease who presented long-term L-dopa syndrome, failure of complete reduction of *off* periods with the optimization of currently available antiparkinsonian drugs, or positive response to apomorphine subcutaneous test without severe side effects were selected for the study. All patients gave informed consent and were evaluated for 5 days in basal conditions (T0 evaluation, with both L-dopa and oral dopamine agonist therapy present). Unified Parkinson's Disease Rating Scale (UPDRS) part III and the tapping and walking test at regular intervals of 1 hour from 8:00 AM until 10:00 PM were performed. Mean scores values in *off* and *on* conditions were calculated and a diary kept. During this time, a dietary regimen was given to minimise possible interference of amino acids on drug absorption. Domperidone was started and maintained for the whole period of study. L-Dopa therapy was not discontinued, while dopamine agonists were gradually suspended at least 10 days before Apo-MTD administration. The other antiparkinsonian drugs, if present, were maintained. For 5 days before Apo-MTD treatment (T1 evaluation, only L-dopa therapy present), patients were re-evaluated as previously described. On day 6, at 8:00 AM, Apo-MTD was applied and left for 12 hours (T2 evaluation, L-dopa and Apo-MTD treatment present). Blood samples were collected at regular intervals from 8:00 AM for 24 hours: every 15 minutes during the 1st hour, every 30 minutes until the 3rd hour, every hour until the 12th hour, again every 30 minutes until the 14th hour, and finally on the 18th and 24th hour. Apomorphine blood concentration was detected by high performance liquid chromatography with electrochemical detection according to the methods described.[21] At the same time of diurnal blood collections, UPDRS part III and the tapping and walking tests were performed and results were obtained for each patient, together with heart rate and blood pressure parameters. UPDRS III and tapping test scores obtained for each patient during Apo-MTD treatment (T2) were compared to scores obtained on T0 and on T1 by using the Wilcoxon rank test. Walking test time scores and duration of *off* periods were compared using a paired *t* test; *P* value less than 0.05 was considered statistically significant. *StatView* software (SAS, Cary, NC) was used for statistical analysis.

Pharmacokinetic Analysis

Plasma drug concentration data of the individual subjects were analyzed by standard noncompartmental methods. The individual Cmaxs and times to Cmax (Tmax) were obtained. The area under the curve (AUC) to the last measurable concentration was calculated with the log–linear trapezoidal rule, and the absorption and

elimination half-life determined. Pharmacokinetic parameters were correlated to UPDRS III scores, walking and tapping test scores, and duration of *off* periods, obtained on T2, using Spearman rank correlation test.

RESULTS

Clinical Characteristics of Patients

Clinical characteristics of parkinsonian patients are summarized in Table 1. Mean age was 59.5 years, mean duration of illness 7.9 years, with a mean Hoehn–Yahr score equal to 3.4; mean L-dopa daily dosage was 645 mg. All patients presented long-term L-dopa syndrome characterized by predictable *off* and "wearing-off" phenomena, but none of them presented unpredictable *off* or hallucinations. Of 21 patients, 7 had peak-dose and plateau-dose dyskinesias, 6 patients presented nocturnal dystonias. All patients, according to inclusion criteria, had a positive apomorphine test (dose range, 1.5–4.5 mg) without severe side effects.

Pharmacokinetic Analysis

Apo-MTD pharmacokinetic analysis is summarized in Table 2. In all patients except 2, apomorphine was detected in blood samples after a variable lag-time from the application of Apo-MTD. Epicutaneous–transdermal apomorphine absorption was demonstrated to be rapid (mean half-life of absorption = 1.03 hours) with a variability among patients (half-life of absorption SD = 1.39 hours). Mean Cmax was above therapeutic range (mean Cmax = 42.81 ± 11.67 ng/ml); pharmacokinetic analysis revealed a mean Tmax of 5.1 ± 2.24 hours and a mean half-life of elimination equal to 10.8 ± 1.93 hours. Figure 1 shows the mean time course of apomorphine plasma levels after Apo-MTD application in 19 patients (excluding the 2 patients with undetectable drug in plasma), compared with apomorphine plasma profile after 3 mg of subcutaneous apomorphine test carried out in 1 patient. It is evident that the increase in the apomorphine plasma level reached therapeutic concentrations after a mean latency of 45 minutes (range, 18–125 minutes). Stable concentrations of apomorphine, above therapeutic range, were obtained until Apo-MTD was maintained. On the 12th hour, Apo-MTD was removed, and during the next hours, apomorphine plasma concentration decreased at a rate comparable to that described for subcutaneous administration.

TABLE 1. *Clinical characteristics of patients*

Patients, N (M/F)	21 (12/9)
Age, mean (yr)	59.5 (range,55–74)
Duration of illness, mean (yr)	7.9 (range,4–15)
L-Dopa dose/24h, mean (mg)	645 (range,250–1100)
Hoehn and Yahr score (mean)	3.4 (range,3–4)
Long-term L-dopa syndrome duration, mean (yr)	3.4 (range,1–9)
Wearing off	21
Predictable *off*	21
Dyskinesias	7
Nocturnal dystonias	6
Unpredictable *off*	0
Hallucinations	0
Use of dopamine oral agonists	21
Use of COMT inhibitors	12
Use of seligiline	3

Values are expressed as number of patients, unless otherwise indicated.

TABLE 2. *Pharmacokinetic analysis*

	Mean	SD	Min	Max
Cmax (ng/ml)	42.81	11.67	33.19	62.75
Tmax (hr)	5.1	2.24	1.2	6.1
AUC (ng/ml × hr)	639.34	115.77	528.91	826.00
Half-life of absorption (hr)	1.03	1.39	0.23	3.49
Half-life of elimination (hr)	10.80	1.93	8.19	13.43

Clinical Evaluation and Pharmacokinetic Correlations

Differences between motor performances during Apo-MTD treatment (T2 evaluation) and motor performances obtained on T1 evaluation and on T0 evaluation are summarized in Table 3 (the 2 patients with undetectable drug in plasma are not included). Cmax and AUC obtained after Apo-MTD administration in each patient showed only a mild correlation, with mean UPDRS III scores in the *on* condition on T2 obtained for each patient ($r = 0.42$; $P = 0.04$ and $r = 0.38$; $P = 0.06$, respectively), and a stronger correlation with mean tapping test scores ($r = 0.52$; $P = 0.03$ and $r = 0.49$; $P = 0.02$, respectively). Moreover, Cmax and AUC showed a good correlation with the reduction of total duration of *off* periods, calculated as the difference between the total duration of *off* periods obtained on T1 and T2 for each

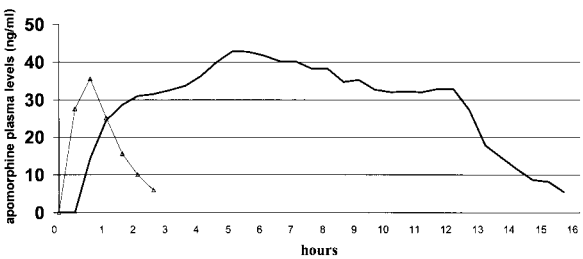

FIG. 1. Comparison of apomorphine plasma concentration–time profile after application of a preparation of apomorphine included in a microemulsion and administered by transdermal route (Apo-MTD) (mean) and after apomorphine 3 mg administered by subcutaneous (s.c.) route [HPLC method]. Time 0, Apo-MTD application; hour 12, Apo-TD removal. Triangles, Apo-MTD; solid line, Apomorphine s.c.

TABLE 3. *Clinical evaluation of patients in* on *and* off *conditions during L-dopa plus Apo-MTD treatment (T2) compared with L-dopa alone (T1) and L-dopa plus oral dopamine agonists therapy (T0)*

	T0		T1		T2	
	On	*Off*	*On*	*Off*	*On*	*Off*
UPDRS-III score	12.6 ± 8.9	32.3 ± 8.4	13.3 ± 5.1	36.6 ± 9.8	11.8 ± 7.6	30.1 ± 10.7[a]
Tapping test score (taps/min)	118.3 ± 32.6	77.2 ± 31.8	113.4 ± 26.5	62.1 ± 23.1	120.1 ± 31.9	78.7 ± 21.5[b]
Walking test (sec)	16.1 ± 3.1	—	15.8 ± 3.1	—	15.4 ± 2.3	—
Total duration of *off* periods (hr)	4.6 ± 2.6		6.6 ± 3.4		3.1 ± 1.2[c,d]	

Values are expressed as mean ± SD.
T0, L-dopa plus oral dopamine agonists therapy; T1, L-dopa alone; T2, L-dopa plus Apo- MTD treatment.
[a]$P = 0.04$ compared to T1 in *off* conditions
[b]$P = 0.02$ compared to T1 in *off* conditions
[c]$P = 0.0001$ compared to T1
[d]$P = 0.02$ compared to T0

patient (r = 0.56; $P = 0.02$ and r = 0.51; $P = 0.04$, respectively). On the contrary, Tmax did not show correlations with UPDRS III scores, walking and tapping test scores, or reduction of *off* periods duration on T2. No relationship between pharmacokinetic parameters with age or sex was found.

Overall Tolerability

In our study, Apo-MTD overall tolerability was good. Considering systemic side effects, 6 patients (28.5%) reported sleepiness during treatment, 1 patient (5%) presented mild orthostatic hypotension, 3 patients (14.2%) had transient nausea easily controlled with domperidone. Only in 1 case (5%) this side effect was not tolerated, and Apo-MTD had to be discontinued. Nausea, but not sleepiness or orthostatic hypotension, was strictly related to the highest plasma level of apomorphine. Among the 7 patients with dyskinesias, 2 showed a moderate worsening of the involuntary movements, but this worsening did not cause excessive trouble for the patients and did not lead to treatment interruption. No hallucination phenomena occurred. Regarding local side effects, 15 patients (71.4%) had a transient mild erythema at the site of Apo-MTD application, with a complete regression within 48 hours; in 2 patients, this erythema lasted more than 3 days and required local therapy. In 7 patients, it appeared to be particularly pronounced along the border of the patch where the foam tapes were in contact with skin. The microemulsion not carrying apomorphine, applied as control to 10 patients for the same time interval used with the apomorphine-loaded microemulsion (12 hours), using the same adhesive system, gave a similar reaction of the skin (erythema along the border of the patch) in 3 patients, but the application of microemulsion not carrying apomorphine on the skin without any delimiting foam tape and occlusive membrane did not produce skin reactions in any patient.

DISCUSSION

The management of motor fluctuations in advanced Parkinson's disease still represents a major problem, and several therapeutic strategies have been proposed: controlled-release preparations of L-dopa, continuous infusion of L-dopa and apomorphine, and additional therapy with COMT inhibitors or dopamine agonists.[1,22–25] Even if apomorphine is a potent dopamine agonist, its practical use for the treatment of motor fluctuations in Parkinson's disease has been limited to date by its short half-life and local side effects.[11,14,15] Apo-MTD seems to overcome some of these limitations. Pharmacokinetic analysis demonstrates that, in most patients, Apo-MTD is absorbed by the epicutaneous–transdermal route. This finding is in contrast with other previous reports, where the transdermal route did not result in detectable plasma levels of apomorphine[6] or no apomorphine could be transported passively through the skin.[26] This difference may be due to the apomorphine dosage, or it may be related to the particular pharmaceutical preparation used in our study: apomorphine was present in the microemulsion as ion-pair complex with octanoate to increase its lipophilicity and to diminish its dissociation. The formation of an ion pair is presumably the main reason for the facilitated transport of apomorphine through the skin. Cmax after Apo-MTD administration (42.81 ± 11.67 ng/ml) proves to be comparable to that of Cmax after administration by the subcutaneous and sublingual routes as reported in the literature (approximately 30 ng/ml for both routes).[6,13] As expected, Tmax for transdermal absorption (5.1 hours) is not as short as described for subcutaneous and sublingual routes (Tmax of approxi-

mately 20 minutes and 45 minutes, respectively, with large variability among patients according to different studies).[6,13] Nevertheless therapeutic concentration after Apo-MTD administration is achieved quite rapidly and much earlier than Tmax (mean latency time for the therapeutic concentration equal to 45 minutes), and after this time, apomorphine concentration remains quite stable and above the therapeutic threshold for several hours (half-life of elimination equal to 10.8 hours). Variability of all the pharmacokinetic parameters is evident as shown by high standard deviations, but it should be noted that significant variations in peak plasma levels among patients and variability of half-life of absorption have also been described for subcutaneous injections and sublingual administration.[6,13] In vitro studies suggested that the internal phase of microemulsion acts as a reservoir and is able to provide through hairless mouse skin a sustained flux of apomorphine for 24 hours with a kinetic release of pseudo–zero-order.[20] In vivo, several variables are involved for transdermal absorption of the drug: steady-state flux through intact skin primarily depends on apomorphine concentration and application area. Moreover, skin temperature and pH, together with local blood flow, may play a role for in vivo apomorphine rate of absorption. These variables may explain the wide range of half-life of absorption found in our study; no relationship between half-life of absorption and age was found. It still remains unclear why two patients did not present detectable apomorphine plasma levels; a further explanation may include alterations of some components due to a not perfectly occlusive patch. Even in the presence of variability of pharmacokinetic parameters, Apo-MTD in our study demonstrates the feasibility of providing therapeutic apomorphine plasma levels for a period of time much longer than any previous apomorphine preparations (several hours), corresponding to the period of time that the Apo-MTD reservoir is maintained on the skin. Regarding clinical evaluation, mean total duration of *off* periods on T2 is by far shorter compared to mean total duration of *off* periods on T1 (3.1 ± 1.2 hours vs. 6.6 ± 3.4 hours; $P = 0.0001$). These findings are somehow expected, because on T1, patients were treated with L-dopa only, whereas on T2, Apo-MTD was added. The two patients presenting undetectable apomorphine plasma levels did not show any amelioration of motor performances on T2. Analysing T2 versus T0 clinical evaluation, Apo-MTD seems to show advantages compared to standard oral dopamine-agonist treatments. In *off* conditions, motor performances evaluated by UPDRS III slightly improve on T2 compared with T0 clinical evaluation. Mean total duration of *off* periods is shorter on T2 compared to T0, this difference being statistically significant. The *off* phases are not completely abolished by Apo-MTD, but no relationship with low apomorphine plasma levels was found. Variability in clinical response to apomorphine is reported for the other routes of administration,[6,13] mainly in patients with more advanced disease under chronic L-dopa therapy. Our group of patients presented severe motor fluctuations, so the pharmacodynamic aspects of dopaminergic stimulation and the degree of nigrostriatal degeneration may play a role in our findings. It should be noted, however, that T0 clinical evaluation is made after having already optimized antiparkinsonian therapy; thus, Apo-MTD seems to be able to reduce *off* periods more than any other adjunctive antiparkinsonian drug previously used for each patient (L-dopa dosage remained unchanged), indicating a longer clinical benefit. That *on* period scores are not further improved with Apo-MTD may be due to an all-or-nothing way of action: therapeutic threshold concentration has to be reached before clinical effect occurs, but no further motor performance improvement occurs after overcoming it.[4,5] This mechanism of action may also explain why apomorphine plasma levels show only a mild correlation with UPDRS III scores obtained in the *on* conditions on T2, whereas Cmax and AUC show a good correlation with the reduction of total duration of *off* periods. Overall tolerability was good in our group of patients, and few and mild systemic side effects have been noted. In the literature, apomorphine side effects are reported to be more frequent,[27,28] but this difference can be partially explained by our inclusion criteria requiring a positive apomorphine test without severe side effects. Local tolerability was good for 1-day therapy (transient local erythema), but further studies are necessary to verify tolerability during chronic treatment.

In conclusion, our pilot study shows that this new preparation of apomorphine administered by an epicutaneous–transdermal route is able to provide a *sustained* release of the drug and therapeutic plasma levels for a prolonged period of time, by far longer than any other dopamine-agonist preparation and comparable to continuous infusion of apomorphine. We used an optimized group of patients, clinical evaluation was not blinded, some findings relied on subjective measures (patient diary records), and the patch was "homemade." Nevertheless, the results are encouraging and Apo-MTD might become of value in some L-dopa–treated patients suffering from uncontrolled "wearing-off" and prolonged *off* phenomena. On the contrary, because of the lag-time of approximately 1 hour needed to reach therapeutic concentrations, Apo-MTD does not seem to be the "ideal"

preparation for the rapid relief of the *off* condition: in this case, apomorphine administered by subcutaneous route, having the most rapid absorption, still remains the best choice. Local side effects are likely to be a major problem in chronic treatment and need to be further investigated. To verify the clinical findings of our pilot study and tolerability in chronic use, we are planning a randomized, double-blind clinical trial over a longer time span with a larger group of patients and comparisons with other selected antiparkinsonian therapies (included repeated apomorphine SC administrations). Future efforts should also be directed toward the arrangement of a specific transdermal delivery system that could permit standardized apomorphine dosages and application areas.

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REFERENCES

1. Olanow CW, Watts RL, Koller W. An algorithm (decision tree) for the management of Parkinson's disease: treatment guidelines. Neurology 2001;56:S1–S88.
2. MacMahon DG. Use of apomorphine in clinical practice. Adv Neurol 1999;80:529–533.
3. Poewe W, Wenning GK. Apomorphine: an underutilized therapy for Parkinson's disease. Mov Disord 2000;15:789–794.
4. Colosimo C, Merello M, Hughes AJ, Sieradzan K, Lees AJ. Motor response to acute dopaminergic challenge with apomorphine and L-dopa in Parkinson's disease: implications for the pathogenesis of the on-off phenomenon. J Neurol Neurosurg Psychiatry 1996;60: 634–637.
5. Gancher S. Pharmacokinetics of apomorphine in Parkinson's disease. J Neural Transm Suppl 1995;45:137–141.
6. Gancher ST, Nutt JG, Woodward WR. Absorption of apomorphine by various routes in parkinsonism. Mov Disord 1991;6:212–216.
7. van der Geest R, van Laar T, Kruger PP, et al. Pharmacokinetics, enantiomer interconversion, and metabolism of R-apomorphine in patients with idiopathic Parkinson's disease. Clin Neuropharmacol 1998;21:159–168.
8. Hughes AJ. Apomorphine test in the assessment of parkinsonian patients: a meta-analysis. Adv Neurol 1999;80:363–368.
9. Dewey RB Jr, Hutton JT, LeWitt PA, Factor SA. A randomized, double-blind, placebo-controlled trial of subcutaneously injected apomorphine for parkinsonian off-state events. Arch Neurol 2001; 58:1385–1392.
10. Colzi A, Turner K, Lees AJ. Continuous subcutaneous waking day apomorphine in the long term treatment of L-dopa induced interdose dyskinesias in Parkinson's disease. J Neurol Neurosurg Psychiatry 1998;64:573–576.
11. Ondo W, Hunter C, Almaguer M, Jankovic J. A novel sublingual apomorphine treatment for patients with fluctuating Parkinson's disease. Mov Disord 1999;14:664–668.
12. Deffond D, Durif F, Tournilhac M. Apomorphine in treatment of Parkinson's disease: comparison between subcutaneous and sublingual routes. J Neurol Neurosurg Psychiatry 1993;56:101–103.
13. Montastruc JL, Rascol O, Senard JM, et al. Sublingual apomorphine in Parkinson's disease: a clinical and pharmacokinetic study. Clin Neuropharmacol 1991;14:432–437.
14. Kapoor R, Turjanski N, Frankel J, et al. Intranasal apomorphine: a new treatment in Parkinson's disease. J Neurol Neurosurg Psychiatry 1990;53:1015.
15. Kleedorfer B, Turjanski N, Ryan R, Lees AJ, Milroy C, Stern GM. Intranasal apomorphine in Parkinson's disease. Neurology 1991; 41:761–762.
16. Dewey RB Jr, Maraganore DM, Ahlskog JE, Matsumoto JY. A double-blind, placebo-controlled study of intranasal apomorphine spray as a rescue agent for off-states in Parkinson's disease. Mov Disord 1998;13:782–787.
17. van Laar T, Jansen EN, Essink AW, Neef C. Intranasal apomorphine in parkinsonian on-off fluctuations. Arch Neurol 1992;49: 482–484.
18. Hughes AJ, Bishop S, Lees AJ, Stern GM, Webster R, Bovingdon M. Rectal apomorphine in Parkinson's disease. Lancet 1991;337: 118.
19. van Laar T, Jansen EN, Neef C, Danhof M, Roos RA. Pharmacokinetics and clinical efficacy of rectal apomorphine in patients with Parkinson's disease: a study of five different suppositories. Mov Disord 1995;10:433–439.
20. Peira E, Scolari P, Gasco MR. Transdermal permeation of apomorphine through hairless mouse skin from microemulsions. Int J Pharm 2001;226:47–51.
21. van der Geest R, Kruger P, Gubbens-Stibbe JM, van Laar T, Bodde HE, Danhof M. Assay of R-apomorphine, S-apomorphine, apocodeine, isoapocodeine and their glucuronide and sulfate conjugates in plasma and urine of patients with Parkinson's disease. J Chromatogr B 1997;702:131–141.
22. Albanese A, Bonuccelli U, Brefel C, et al. Consensus statement on the role of acute dopaminergic challenge in Parkinson's disease. Mov Disord 2001;16:197–201.
23. van Laar T, van der Geest R, Danhof M, Bodde HE, Goossens PH, Roos RA. Stepwise intravenous infusion of apomorphine to determine the therapeutic window in patients with Parkinson's disease. Clin Neuropharmacol 1998;2:152–158.
24. Baas H, Harder S, Demisch L, Burklin F, Stecker K, Fischer PA. Fluctuations in Parkinson's disease. Pathogenetic significance of L-dopa's cerebral pharmacokinetics and pharmacodynamics. J Neural Transm Suppl 1995;46:367–379.
25. Baas H, Harder S, Burklin F, Demisch L, Fischer PA. Pharmacodynamics of L-dopa coadministered with apomorphine in parkinsonian patients with end-of-dose motor fluctuations. Clin Neuropharmacol 1998;21:86–92.
26. van der Geest R, van Laar T, Gubbens-Stibbe JM, Boddé HE, Danhof M. Iontophoretic delivery of R-apomorphine. II. An in vivo study in patients with Parkinson's disease. Pharm Res 1997; 14:1804–1810.
27. Pietz K, Hagell P, Odin P. Subcutaneous apomorphine in late stage Parkinson's disease: a long term follow up. J Neurol Neurosurg Psychiatry 1998;65:709–716.
28. Ondo W, Hunter C, Almaguer M, Gancher S, Jankovic J. Efficacy and tolerability of a novel sublingual apomorphine preparation in patients with fluctuating Parkinson's disease. Clin Neuropharmacol 1999;22:1–4.