

Subcutaneously administered apomorphine

Pharmacokinetics and metabolism

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Article abstract—Apomorphine is a non-narcotic morphine derivative that acts as a potent dopaminergic agonist. Its high first-pass hepatic metabolism prevents effectiveness by the oral route; instead, subcutaneous injection is the usual route, and intranasal, sublingual, rectal, and iontophoretic transdermal delivery has been investigated for the treatment of Parkinson's disease (PD). The rate of uptake after subcutaneous injection is influenced by factors such as location, temperature, depth of injection, and body fat. Studies have shown the latency of onset to clinical effect after s.c. injection ranged from 7.3 to 14 minutes. Cerebrospinal fluid T_{\max} lags behind plasma T_{\max} by 10 to 20 minutes. Considerable intersubject variability is found with pharmacokinetic variables; in some studies there are five- to tenfold differences in C_{\max} and area-under-the-concentration-time-curve seen in PD patients. Apomorphine metabolism occurs through several enzymatic pathways, including N-demethylation, sulfation, glucuronidation, and catechol-O-methyltransferase as well as by nonenzymatic oxidation. The complexities of apomorphine uptake, distribution, and clearance probably contribute to its variability of clinical actions.

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Apomorphine, used for many years because of its potent emetic properties, has become an important option for anti-parkinsonian therapy.¹ Its first use in treating Parkinson's disease (PD) goes back more than 50 years when, on the basis of reports that apomorphine could reverse surgically induced experimental decerebrate rigidity, Schwab et al.² used s.c. doses of apomorphine at 0.5–1.0 mg to treat several PD patients. The result was a brief but unequivocal benefit against tremor and rigidity, despite prominent side effects. At that time, because the recognition of dopamine deficiency as the pathophysiologic hallmark of PD was still years away and the dopaminergic effects of apomorphine were unknown, the clinical effects were largely ignored.

With the later discovery of levodopa's remarkable efficacy at relieving parkinsonian symptomatology, the dopaminergic properties of apomorphine and related compounds generated new interest during the late 1960s. Pioneering clinical studies by George Cotzias³ and others⁴ revealed substantial benefits associated with parenteral administration of apomorphine in the treatment of PD. It is now clear that this drug has the potential to play a major role in treating patients not adequately controlled with levodopa and other oral anti-parkinsonian medications.

Compared with the other dopaminergic compounds used for PD, apomorphine stands out for its potency at overcoming "off" states that can be unresponsive even to continuous levodopa infusion.⁵ Al-

though apomorphine must be given parenterally, this inconvenience in route of administration nevertheless offers some advantages for its most common therapeutic applications. Subcutaneous administration of apomorphine has become a therapeutic option for rapid rescue from disabling "off" states in patients with unpredictable or suboptimal effects from levodopa.⁶ Furthermore, studies in Europe have shown that continuous delivery of apomorphine by s.c. infusion can accomplish a steady-state control of parkinsonism without the excesses of dose-effect that can cause dyskinesias or psychiatric problems.^{7,8} Substantial increases in "on" time with s.c. delivery of apomorphine have been reported in a number of studies.^{9–13}

The pharmacology of apomorphine. Apomorphine is a crystalline aporphine alkaloid of the dibenzoquinoline class. First created in 1869, it can be derived from morphine by heating it in an acidic environment (with sulfuric or hydrochloric acid, or with $ZnCl_2$). Apomorphine can also be synthesized from other starting compounds.¹⁴ Apomorphine lacks the narcotic properties and other opiate effects of its parent compound. Instead, apomorphine's primary pharmacologic actions are derived from its polycyclic and tertiary amine structures that contain a moiety homologous with the dopamine molecule. Presumably on this basis, apomorphine exerts potent dopaminergic activity at dopamine receptors.

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In vitro, it exhibits high binding affinity for the dopamine D4 receptor, moderate affinity for the dopamine D2, D3, and D5 receptors, and low affinity for the dopamine D1 receptor.¹⁸ Other studies have shown similar potency at D2 and D1 (adenylate cyclase-linked) dopamine receptors.¹⁷ In some investigations, apomorphine behaves as a partial agonist at D1 receptors.¹⁹ In addition, it has moderate affinity for adrenergic 1D, 2B, and 2C receptor, and for serotonin 5HT1A, 5HT2A, 5HT2B, and 5HT2C receptors.^{15–19} Although the precise mechanism of action of apomorphine as a treatment for PD is unknown, it is believed to be due to stimulation of postsynaptic dopamine D2-type receptors in the caudate nucleus and putamen. A multivariate analysis of drug binding at these and other subclasses of human and animal dopamine receptors,¹⁷ as well as binding at other monoaminergic¹⁸ and serotonergic receptors,¹⁹ showed apomorphine to have a distinctive profile differing from 10 other dopaminergic compounds that also exert anti-parkinsonian effects.

For clinical practice, apomorphine is formulated as a hydrochloride salt with a molecular weight of 312.79. Its chemical description is 6 α -aporphine-10,11-diol hydrochloride hemihydrate. Although apomorphine has stereoisomers, only the *R* enantiomer has activity against parkinsonism because the *S* form is lacking in dopaminergic actions and may have antagonistic effects at dopamine receptors.¹⁵ Readily soluble in water, apomorphine needs protection against oxidation that is promoted by exposure to air or light. Because most apomorphine used for clinical purposes is derived from natural sources, this drug has the potential for variability in potency and stability among the various marketed products.

Early attempts to use the oral route for administration of apomorphine in PD were unsuccessful because this compound was rapidly metabolized in first-pass metabolism by the liver. Trials of oral apomorphine administration by Cotzias et al.,³ using doses between 150 and 1440 mg/day, achieved some degree of clinical improvement in PD. However, orally administered apomorphine was associated with dose-related nephrotoxicity, possibly as a result of the large intake of this compound necessitated by its high first-pass metabolism. As a result of this experience, alternative routes of drug delivery have been sought to utilize smaller systemic doses of this compound. These have included trials of s.c., sublingual, i.v., rectal, intranasal, and iontophoretic transdermal drug delivery. Each of these routes has shown some potential for clinical effectiveness, although adverse effects and instability of some of the drug preparations have been limiting factors.^{20–22} In addition to s.c. apomorphine, promising future directions for apomorphine administration include transdermal²² and intranasal preparations, which attempt to avoid the problems encountered with earlier trials using these alternative means of drug delivery.^{23,24}

The 10 mg/ml sterile solution of apomorphine hydrochloride can be injected s.c. at locations that differ

in their rate of uptake, e.g., injecting the drug into the abdominal wall leads to more rapid absorption than injection into the thigh.^{25,26} Other local influences include temperature, as shown by experiments demonstrating that slowing of uptake occurs after cooling the injection site.²⁷ One study of 10 PD patients with motor fluctuations found that the onset of motor effects after s.c. injection occurred after an average of 12.3 \pm 4.5 minutes and lasted an average of 61.9 \pm 13.3 minutes.²⁸ Other studies investigating the clinical effect of apomorphine found the average onset of action to be 7.3 minutes²⁹ and 14 minutes.³⁰ The variability of clinical effect after injection may be governed by subcutaneous fat, depth of the injection, and other factors that might be difficult to standardize.

One investigation of s.c. apomorphine examined dose–response characteristics from increasing doses in 10 PD patients evaluated for clinical improvement (defined as percent change from baseline scores using the Columbia University Rating Scale).³¹ The percent change tended to increase as a function of dose. An insignificant response followed injection of 0.5 mg of apomorphine, while 10% improvement occurred after 1 mg, 22% improvement after 2 mg, and 25% after 4 mg s.c. However, even the highest dose led to clinical improvement (20% greater than baseline) for only 6/8 patients tested. These data illustrate the variability in clinical response that even parenteral administration of apomorphine offers for patients with motor fluctuations. In this study, plotting of plasma apomorphine concentration against clinical effect yielded a steep sigmoid concentration–effect relationship, with a mean EC₅₀ determined to be 20 pmol/ml.³¹ A 6-minute equilibrium half-life accounted for the lag between plasma concentration and clinical effect.

In general, the drug's pharmacokinetic properties are the determinants of clinical results achievable in PD patients. This has been demonstrated in a study exploring the relationship between plasma and lumbar CSF apomorphine concentrations and the drug's clinical effect.³² Unlike the plasma concentrations of apomorphine, the CSF appearance of the drug correlated closely with the onset of anti-parkinsonian effect (*r* values of 0.93 and 0.89 in the two patients studied). This investigation found that the central pharmacokinetics of apomorphine, as represented by its CSF concentration, were best described by a two-compartment model. The delay in the time of maximal CSF drug concentration (T_{max}), compared with plasma T_{max} , was 10 and 20 minutes for the two patients studied. Apomorphine in CSF was 3.6% and 2.5% of the concentrations measured in plasma. In another study, the ventricular CSF concentration of apomorphine was measured in six subjects undergoing investigation for normal-pressure hydrocephalus. In this atypical and non-PD population, the maximal drug plasma concentration occurred at 20 minutes and was followed 10 minutes later by the T_{max} for the CSF compartment.³³ In another study of peripheral apomorphine pharmacokinetics after s.c. bolus

administration (20–30 µg/kg) in a group of 15 PD patients, plasma T_{max} was achieved in 7.8 ± 1 minutes.³⁴ Considerable intersubject variability was noted in several pharmacokinetic parameters. There was a 10-fold difference in C_{max} and a five-fold difference in plasma concentration AUC in these patients.

Values for plasma T_{max} after s.c. administration have ranged from 5 to 45 minutes in a number of pharmacokinetic studies.^{26,31,35–37} Most commonly, T_{max} occurs 10–20 minutes after s.c. administration. Another measure of uptake, the drug's absorption half-life, was determined to be 5.8 minutes in one study.³⁶ The pharmacokinetics of apomorphine after s.c. and i.v. administration showed a great deal of interindividual variability in T_{max} , C_{max} , and plasma concentration AUC.^{25,38} There were no correlations between these values and body weight, age, or gender in this or another study of apomorphine clearance in PD patients.²⁹ Total drug clearance varied from 1 to 12 L/kg/hour.²⁵ Other details of apomorphine pharmacokinetics after s.c. administration, as well as delivery by other routes (rectal, intranasal, iontophoretic transdermal, and i.v.), can be found in an extensive review by Neef and van Laar.²⁷

Metabolism of apomorphine. The clearance of apomorphine occurs through several routes. After parenteral administration, the drug measured in the plasma is highly protein-bound. *In vitro* literature has indicated that the potential pathways of metabolism for apomorphine included oxidation, *N*-demethylation, metabolism by catechol-*O*-methyl transferase (COMT), glucuronidation, and sulfation.³⁸ A study by van der Geest et al.³⁸ showed that only 0.3% of an administered dose of apomorphine was excreted unchanged. Several routes of metabolism have been described. Among these are nonenzymatic oxidation reactions in the bloodstream and organs, forming various quinone products and related compounds. An estimate of apomorphine oxidation concluded that more than two-thirds of an administered dose is cleared by this means.³⁶ In the latter study, an *in vitro* evaluation of apomorphine stability showed a 39-minute half-life of auto-oxidation. Another study of apomorphine disposition after i.v. administration to PD patients found that systemic oxidation of apomorphine occurred with a half-life of 142 ± 35 minutes.³⁸ Because the majority of an administered dose of apomorphine could not be detected, extensive systemic oxidation of apomorphine appears to be the explanation, especially since the measured clearance of the drug, 40.4 ± 14.9 ml/min/kg (with a mean volume of distribution at steady state of 1.57 ± 0.50 L/kg) exceeds the rate of hepatic blood flow.

Conclusion. Apomorphine is a potent dopamine agonist with full D2 and partial D1 activity. Its extensive first-pass hepatic metabolism has required only parenteral administration in its current applications for the treatment of advanced PD. Pharmacokinetic parameters vary from patient to patient and may depend on factors such as s.c. fat and depth of injection. Intranasal, sublingual, iontophoretic trans-

dermal, and rectal administration are also possible and have been explored in clinical studies. When delivered via s.c. injection, apomorphine has the most rapid onset of motor action of any anti-parkinson therapy (within 7.5 to 10 minutes), and its action lasts up to 90 minutes. The pharmacokinetics and metabolism of apomorphine after s.c. injection are complex, possibly contributing to variability in its usefulness as a rescue therapy for patients with advanced PD.

References

1. Poewe W, Wenning GK. Apomorphine: an underutilized therapy for Parkinson's disease. *Mov Disord* 2000;15:789–794.
2. Schwab RS, Amador LV, Lettvin JY. Apomorphine in Parkinson's disease. *Trans Am Neurol Assoc* 1951;76:252–255.
3. Cotzias GC, Papavasiliou PS, Fehling C, Kaufman B, Mena I. Similarities between neurological effects of L-dopa and apomorphine. *N Engl J Med* 1970;282:31–33.
4. Stibe CM, Kempster PA, Lees AJ, Stern GM. Subcutaneous apomorphine in Parkinsonian on-off fluctuations. *Lancet* 1988;1:403–406.
5. Hardie RRJ, Lees AJ, Stern GM. On-off fluctuations in Parkinson's disease: a clinical and neuropharmacological study. *Brain* 1984;107:487–506.
6. LeWitt PA. Extending the action of levodopa's effects. In: LeWitt PA, Oertel WH, eds. *Parkinson's disease: the treatment options*. London: Martin Dunitz Publishers, 1999;141–158.
7. Colzi A, Turner K, Lees AJ. Continuous subcutaneous waking day apomorphine in the long term treatment of levodopa induced interdose dyskinesias in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1998;64:573–576.
8. Manson AJ, Turner K, Lees AJ. Apomorphine monotherapy in the treatment of refractory motor complications of Parkinson's disease: long-term follow-up study of 64 patients. *Mov Disord* 2002;17:1235–1241.
9. Pollak P, Champay AS, Gaio JM, Hommel M, Benabid AL. Subcutaneous apomorphine in Parkinson's disease. *Rev Neurol* 1990;146:116–122.
10. Frankel JP, Lees AJ, Kempster PA, Stern GM. Subcutaneous apomorphine infusional in the treatment of Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1990;53:96–101.
11. Chaudhuri KR, Critchley P, Abbott RJ, Pye IF, Millac PA. Subcutaneous apomorphine for on-off oscillations in Parkinson's disease. *Lancet* 1998;2:1260.
12. Colosimo C, Merello M, Albanese A. Clinical usefulness of apomorphine in movement disorders. *Clin Neuropharmacol* 1994;17:243–259.
13. Dewey RB, Hutton JT, LeWitt PA, Factor SA. A randomized double-blind placebo-controlled trial of subcutaneously injected apomorphine for Parkinsonian "off" states. *Arch Neurol* 2001;58:1385–1392.
14. Neumeyer JL, Lal S, Baldessarini RJ. Historical highlights of the chemistry, pharmacology, and early clinical uses of apomorphine. In: Gessa GL, Corsini GU, eds. *Apomorphine and other dopaminomimetics*. Basic pharmacology. Vol. 1. New York: Raven Press, 1981:1–17.
15. Hutchinson WD, Levy R, Dostrovsky JO, Lozano AM, Lang AE. Effects of apomorphine on globus pallidus neurons in Parkinsonian patients. *Ann Neurol* 1997;42:767–775.
16. Goldman ME, Kebejian J. Apomorphine enantiomers: interactions with D1 and D2 dopamine receptors. *Mol Pharmacol* 1984;25:18–23.
17. Millan MJ, Maiorini L, Cussac D, Audinot V, Boutin JA, Newman-Tancredi A. Differential actions of antiparkinson agents at multiple classes of monoaminergic receptor. I. A multivariate analysis of the binding profiles of 14 drugs at 21 native and cloned human receptor subtypes. *J Pharmacol Exp Ther* 2002;303:791–804.
18. Newman-Tancredi A, Cussac D, et al. Differential actions of antiparkinson agents at multiple classes of monoaminergic receptor. II. Agonist and antagonist properties at subtypes of dopamine D₂-like receptor and alpha₁/alpha₂-adrenoceptor. *J Pharmacol Exp Ther* 2002;303:805–814.
19. Newman-Tancredi A, Cussac D, et al. Differential actions of antiparkinson agents at multiple classes of monoaminergic receptor. III. Agonist and antagonist properties at serotonin, 5-HT₁, and 5-HT₂ receptor subtypes. *J Pharmacol Exp Ther* 2002;303:815–822.
20. van Laar T, van der Geest R, Danhof M. Future delivery systems for apomorphine in patients with Parkinson's disease. *Adv Neurol* 1999;80:535–544.
21. Manson AJ, Hanagasi H, Turner K, et al. Intravenous apomorphine therapy in Parkinson's disease: clinical and pharmacokinetic observations. *Brain* 2001;124:331–340.
22. Priano L, Albani G, Calderoni S, et al. Controlled-release transdermal apomorphine treatment for motor fluctuations in Parkinson's disease. *Neurol Sci* 2002;23(suppl 2):S99–100.
23. van der Geest R, van Laar T, Gubbens-Stibbe JM, Bodde HE, Danhof M. Iontophoretic delivery of apomorphine. II: An *in vivo* study in patients with Parkinson's disease. *Pharmacol Res* 1997;14:1804–1810.

24. Dewey RB, Marangore DM, Ahlskog JE. 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.
25. Gancher ST, Woodward WR, Boucher B, Nutt JG. Peripheral pharmacokinetics of apomorphine in humans. *Ann Neurol* 1989;26:232-238.
26. Nicolle E, Pollak P, Serre-Debeauvais F, et al. Pharmacokinetics of apomorphine in parkinsonian patients. *Fund Clin Pharmacol* 1993;7:245-252.
27. Neef C, van Laar T. Pharmacokinetic-pharmacodynamic relationships of apomorphine in patients with Parkinson's disease. *Clin Pharmacokinet* 1999;37:257-271.
28. Gervason CL, Pollak PR, Limousin P, Perret JE. Reproducibility of motor effects induced by successive subcutaneous apomorphine injections in Parkinson's disease. *Clin Neuropharmacol* 1993;16:113-119.
29. van Laar T, Jansen EN, Essink AW, Neef C, Oosterloo S, Roos RA. A double-blind study of the efficacy of apomorphine and its assessment in "off"-periods in Parkinson's disease. *Clin Neurol Neurosurg* 1993;95:231-235.
30. Deffond D, Durif F, Tournilhax M. Apomorphine in treatment of Parkinson's disease: comparison between subcutaneous and sublingual routes. *J Neurol Neurosurg Psychiatry* 1993;56:101-103.
31. Harder S, Baas H, Demisch L, Simon E. Dose response and concentration response relationship of patients with Parkinson's disease and end-of-dose akinesia. *Int J Clin Pharmacol Ther* 1998;36:355-362.
32. Hofstee DJ, Neef C, van Laar T, Jansen EN. Pharmacokinetics of apomorphine in Parkinson's disease: plasma and cerebrospinal fluid levels in relation to motor responses. *Clin Neuropharmacol* 1994;17:45-52.
33. Przedborski S, Levivier M, Raftopoulos C, Naini AS, Hildebrand J. Peripheral and central pharmacokinetics of apomorphine and its effect on dopaminergic metabolism in humans. *Mov Disord* 1995;10:28-36.
34. Gancher ST, Nutt JG, Woodward WR. Absorption of apomorphine by several routes in parkinsonism. *Mov Disord* 1991;6:212-216.
35. Østergaard L, Wetdelin L, Odin P, et al. Pen injected apomorphine against off phenomena in late Parkinson's disease: a double-blind, placebo controlled study. *J Neurol Neurosurg Psychiatry* 1995;59:681-687.
36. Sam E, Jeanjean AP, Maloteaux JM, Verbeke N. Apomorphine pharmacokinetics after intranasal and subcutaneous application. *Eur J Drug Metab Pharmacokinet* 1995;1995;20:27-33.
37. van Laar T, Neef C, Danhof M, Roon KI, Roos RA. A new sublingual formulation of apomorphine in the treatment of patients with Parkinson's disease. *Mov Disord* 1996;11:633-638.
38. 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.