reviews

molecular pharmaceutics

Apomorphine in Dopaminergic Therapy

J. Anand Subramony*

ALZA Corporation, 1900 Charleston Road, Mountain View, California 94043

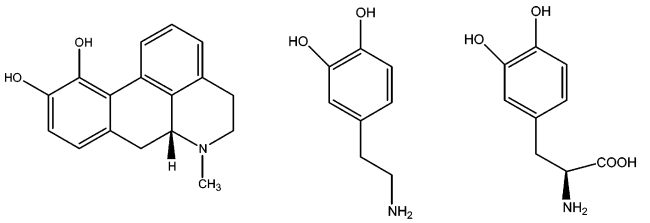
Received February 7, 2006

Abstract: Apomorphine is a potent molecule for the treatment of Parkinson's disease (PD). It can be obtained in both the *R* and *S* forms, and it is the former that is the therapeutically active form. Due to its structural similarity with 3,4-dihydroxyphenethylamine, dopamine, apomorphine can function as an agonist in the treatment of PD as it can stimulate both the D1 and D2 receptors of the striatum. The clinical efficacy of apomorphine is similar to that of 3,4-dihydroxyphenylalanine, levodopa (L-dopa), the cornerstone drug in dopaminergic therapy. (*R*)-Apomorphine is efficacious for one of the most challenging aspects in the management of PD, namely, managing the unpredictable "on−off" period as a rescue medication after oral administration of a therapeutic drug such as L-dopa. The effectiveness is due to its rapid control of the wearing-off period of the orally administered medicine. This short review will trace the progress of apomorphine use starting with its initial discovery and the first indications for which it was used, discovery of its "cure" for PD, and the studies that led to demonstrating its therapeutic efficacy. The key structural features of apomorphine responsible for its activity are illustrated along with major issues of chemical stability. From a drug delivery point of view, the current form of administration of apomorphine and some of the potential alternate methods of delivery are reviewed.

Keywords: Apomorphine; Parkinson's disease; dopamine; receptor; L-dopa; drug delivery

Historical Aspects of Apomorphine Development

Apomorphine (**I**, Figure 1), as the name implies, is a derivative of morphine and is formed by the acidic rearrangement of morphine.[1] First discovered in 1869 by Mathiesen and Wright, apomorphine was used initially as an emetic drug.[2] In 1884, evidence suggested that apomorphine could be useful for convulsive disorders for patients with abnormal physical motion.[3] In the next three decades, apomorphine gained attention as a drug that could stimulate the central nervous system (CNS). Most of these observations were isolated; Douglas wrote in the *New York Medical Journal* about the effect of apomorphine for the treatment of alcoholic intoxications and its favorable effects on delirium tremens,[4,5] while Dent in London observed similar results and reported the impact of apomorphine on the actions of the brain.[6] Research and clinical studies continued using apomorphine as a drug for the treatment of alcoholism as



R-Apomorphine (**I**) Dopamine (**II**) Levodopa (**III**)

Figure 1. Chemical structures of apomorphine, dopamine, and levodopa.

* Author to whom correspondence should be addressed. Mailing address: ALZA Corporation, 1900 Charleston Road, Mountain View, CA. Tel: 650-564-2418. Fax: 650-564-2484. E-mail: asubramo@alzus.jnj.com.

(1) Zurich, F. M. Apomorphine. The formation of Apomorphine on heating and preserving morphine solutions, *Z. Physiol. Chem.* **1913**, *84*, 363−378.
(2) Mathiesen, A.; Wright, C. R.; Apomorphine. *Proc. R. Soc. Med.* **1869**, *17*, 455.
(3) Weill, E. De l'apomorphine Dans Certains Troubles Nerveux. *Lyon Méd.* **1884**, *48*, 411−419.
(4) Douglas, C. J. Alcoholism. *N.Y. Med. J.* **1899**, *70*, 626−628.
(5) Douglas, C. J. Delirium Tremens. *N.Y. Med. J.* **1900**, *72*, 852.

10.1021/mp060012c CCC: $33.50
Published on Web 06/13/2006

well as a subemetic drug. In 1950, Feldman summarized results in his thesis at the University of Geneva from clinical studies of apomorphine in the treatment of alcoholics.[7]

However, a publication in 1951 changed the scope of apomorphine therapy and triggered the use of apomorphine for a totally new indication. Schwab and colleagues reported the effectiveness of apomorphine in Parkinson's disease (PD),[8] a serious neurological disorder of the CNS characterized by increased deterioration of neurons responsible for the normal functioning of the human motor system. It was recognized that the loss of dopaminergic nigostriatal neurons would lead to reduction in the availability of neurotransmitter dopamine in the striatum resulting in abnormalities in the human motor system. Schwab and co-workers reported the favorable effects of apomorphine from a study conducted on 20 patients with subcutaneous injections and 10 patients with an oral preparation. The effect of oral apomorphine was shown to be less dramatic and more sustained than the subcutaneous injection. Treated patients showed less rigidity and tremor, reported feeling less tense, and were less easily upset by the usual stresses they encountered.

In subsequent years several studies were conducted to determine the effect of apomorphine in the treatment of PD. In 1967, Ernst outlined the structural similarities between apomorphine and dopamine (**II**, Figure 1) since administration of the latter can address the need for extra dopamine for the control of the motor system (such as the conscious movement of muscles). Through studies in the rat, he demonstrated that both apomorphine and dopamine can produce the same results and proposed that the efficacy of apomorphine could result from a dopamine-like effect on the receptors.[9] In the same year, Anden and co-workers confirmed the hypothesis by reporting evidence of dopamine receptor stimulation by apomorphine in rats.[10] Results from human clinical studies on the efficacy of apomorphine on PD patients further supported the hypothesis that the therapeutic activity of apomorphine could be due to its structural similarity to dopamine.[11] The various findings confirmed that apomorphine is a potent D1 and D2 receptor agonist[12] and can induce regeneration of dopaminergic neurons.[13]

However, apomorphine administered orally in advanced PD patients was not successful due to the requirement of high doses as a result of metabolic constraints and the first-pass effect. High doses administered orally were found to cause side reactions such as nausea and elevation of blood urea and creatinine levels.[14] The introduction of L-dopa (**III**, Figure 1) therapy in 1970 further limited the advancement of apomorphine. Levodopa, the gold standard in PD therapy, is the metabolic precursor of dopamine. Since dopamine cannot cross the blood−brain barrier, one of the L-dopa treatments involves transfer of the precursor of dopamine across the barrier with the help of metabolic inhibitors such as amino acid transporters. Levodopa subsequently undergoes decarboxylation to form dopamine. There are downsides to L-dopa therapy, one of which is insufficient dopamine availability due to extensive decarboxylation in its first passage through the liver, which is rich in the enzyme decarboxylase. Other disadvantages include distribution of L-dopa in the body, peripheral decarboxylation before it is actively transported to the brain, side effects such as dyskinesias, wear-off, and rapid fluctuations.

In spite of the introduction of L-dopa therapy, researchers continued to investigate the potential of apomorphine. Particularly in 1968 and 1969, two groups reported results from a human clinical study where the use of metoclopramide in reducing the apomorphine-induced nausea and vomiting was established. In these studies, 30 mg of metoclopramide was administered orally approximately 40 min before apomorphine was injected.[15,16] In 1979, two important observations came as a breakthrough for the advancement of apomorphine therapy. Agid and co-workers discovered that domperidone, 4-(5-chloro-2-oxo-1-benzimidazolinyl)-1-[3-(2-oxobenzimidazolinyl)propyl]piperidine, a peripherally acting dopamine antagonist, could potentially prevent the side effects such as nausea associated with administration of an agonist to stimulate dopaminergic receptors.[17] In the same publication Corsini and co-workers reported that simultaneous coadministration of domperidone as a second dopam-

(6) Dent, J. Y. Apomorphine in the Treatment of Anxiety States, With Special Reference to Alcoholism. *Br. J. Inebriety* **1934**, *32* (2), 65−88.
(7) Feldmann, H. Contribution a la Therapeutique Biologique de l'Alcoolism Chronique. Le Traitement Par L'Apomorphine. Etude de 150 cas. Thesis, University of Geneva, 1950.
(8) Schwab, R. S.; Amador, L. V.; Lettvin, J. Y. Apomorphine in Parkinson's Disease. *Trans. Am. Neurol. Assoc.* **1951**, *76*, 251−253.
(9) Ernst, A. M. Mode of Action of Apomorphine and Dexamphetamine on Gnawing Compulsion in Rats. *Psychopharmacologia* **1967**, *10*, 316−323.
(10) Andén, N. E.; Rubenson, A.; Fuxe, K.; Hökfelt, T. Evidence for Dopamine Receptor Stimulation by Apomorphine. *J. Pharm. Pharmacol.* **1967**, *19*, 627−629.
(11) Castaigne, P.; Laplane, D.; Dordain, G. Clinical Experimentation With Apomorphine in Parkinson's Disease. *Res. Commun. Chem. Pathol. Pharmacol.* **1971**, *2* (2), 154−158.
(12) Seeman, P.; Grigoriadis, D. Dopamine Receptors in Brain and Periphery. *Neurochem. Int.* **1987**, *10* (1), 1−25.
(13) Hiroshi, W.; Simple method for evaluation of stimulatory effect of drugs on presynaptic dopamine receptors in mice, *J. Pharm. Methods* **1985**, *14* (1), 41−47.
(14) Cotzias, G. C.; Papavasiliou, P. S.; Tolosa, E. S.; Mendez, J. S.; Bell-Midura, M. Treatment of Parkinson's Disease with Aporphines: Possible Role of Growth Hormone. *N. Engl. J. Med.* **1976**, *294*, 567−572.
(15) Klien, R. L.; Militello, T. E.; Ballinger, C. M. Antiemetic Effect of Metoclopramide. Evaluation in Humans. *Anesth. Analg.* **1968**, *47*, 259−264.
(16) Gylding-Sabroe, J. P.; Hattel, T. Metoclopramide. A New Quick Acting Antiemetic. *Nord. Med.* **1969**, *81*, 141−142.
(17) Agid, Y.; Bonnet, A. M.; Pollak, P.; Signoret, J. L. Bromocriptine Associated With a Peripheral Dopamine Blocking Agent in Treatment of Parkinson's Disease. *Lancet* **1979**, *1*, 570−572.

ine receptor antagonist largely reduced the side effects of apomorphine.[18] Subsequent clinical studies reported by Stibe and co-workers demonstrated the benefits of apomorphine administered subcutaneously via bolus injections as a rescue drug during the "off" period in L-dopa therapy.[19] The study reported that using apomorphine as a rescue medication could reduce the total daily "off" time by 50−60% and possibly reduce the L-dopa dose by ∼20%. The studies that followed confirmed these findings, and the rapid onset of results provided by apomorphine within a few minutes of administration with a sustained steady state of drug level made it an attractive rescue drug.[20] In 1993, apomorphine was licensed in the United Kingdom for use in patients with PD for use with L-dopa therapy. Several clinical studies continued until 2000 using apomorphine in various double-blinded, placebo-controlled trials.[21−23] In 2004 apomorphine was approved in the United States as a rescue medication in PD, particularly to treat the "off" periods by subcutaneous injection. However, as Clarke[24] pointed out in a recent review, apomorphine injections are potentially useful only in advanced PD patients with several off periods and those patients who normally do not respond to oral therapy. Apomorphine may therefore not be the first in line agent for most patients. Other drawbacks of apomorphine infusions are its high cost[24] and the formation of subcutaneous nodules and hypotension.[25]

Key Structural Features of Apomorphine

The determination of structure−activity relationships (SAR), a benchmark exercise in the science of medicinal chemistry with relevance to contemporary combinatorial chemistry and high-throughput screening of potent molecules, has aided in the understanding of receptor−agonist interactions. Many such SAR correlations have been put forth by researchers for indications in the CNS.[26,27] Particularly for PD, the vast majority of these analyses have been based upon dopamine and molecules that have structural similarities with dopamine,[28−30] such as apomorphine.[31−33] Structure−activity relationships have been established for the ergot alkaloid derivatives and their fragments as well as lergotrile, pergolide, and bromocriptine. Ergot is naturally occurring dried sclerotium of the fungus *Claviceps purpurea*, which can be found in the ovary of the rye *Secale cereale*. The ergot alkaloids (2% of the composition of ergot) were found to have useful medicinal properties due to their high biological activity and a broad spectrum of pharmacological effects. The similarity of the ergoline ring structure in bromocriptine, lisuride, and pergolide to the endogenous monoamides is believed to be the cause of action of these compounds on dopaminergic receptors. Dopamine agonists in the non-ergoline family includes pramipexole, ropinirole, and piribedil.[34,35]

Since both dopamine and apomorphine belong to the class of β-phenylethylamines with a catechol moiety, the models developed for dopamine can also be applied to apomorphine in terms of understanding the receptor−agonist interactions. For instance, as in the case of dopamine, it is intuitive to think that when apomorphine interacts with adenosine triphosphate (ATP), a key component of some dopamine receptors, the complex could be stabilized by hydrogen bonding between catechol hydroxyls and the nitrogens of

(18) Corsini, G. U.; Gessa, G. L.; Del Zompo, M.; Mangoni, A. Therapeutic Efficacy of Apomorphine Combined With an Extracerebral Inhibitor of Dopamine Receptors in Parkinson's Disease. *Lancet* **1979**, *1*, 954−956.

(19) Stibe, C. M. H.; Kempster, P. A.; Lees, A. J.; Stern, G. M. Subcutaneous Apomorphine in Parkinsonian On-off Oscillations. *Lancet* **1988**, *1*, 403−406.

(20) Van Laar, T.; Janseen, E. N.; Essink, A. W.; Neef, C.; Oosterloo, S.; Roos, R. A. 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.

(21) Ostergaard, L.; Werdelin, L.; Odin, P. Pen Injected Apomorphine Against Off Phenomena in Late Parkinsons's Disease: a Double Blind, Placebo Controlled Study. *J. Neurol., Neurosurg. Psychiatry* **1995**, *58*, 681−687.

(22) Merello, M.; Pikielny, R.; Cammarota, A.; Leiguarda, R. Comparison of Subcutaneous Apomorphine Versus Dispersible Madopar Latency and Effect Duration in Parkinson's Disease Patients; a Double-Blind Single-Dose Study. *Clin. Neuropharmacol.* **1997**, *20*, 165−167.

(23) Hutton, J. T.; Dewey, R. B., Jr.; LeWitt, P. A.; Factor, S. A. A Randomized, Double Blind, Placebo-Controlled Trial of Subcutaneously-Injected Apomorphine for Parkinsonian "Off" States. *Mov. Disord.* **2000**, *15* (Suppl. 3), 130.

(24) Clarke, C.E.; Neuroprotection and pharmacotherapy for motor symptoms in Parkinson's disease, *Lancet Neurol.* **2004**, *3*, 466−474.

(25) 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.

(26) Jiang, H.; Wang, L.; Peng, T. Advances in the structure-activity relationship of anti-dementia drugs, *Zhongguo Xinyao Zazhi* **2005**, *14* (5), 535−539.

(27) Lloyd, E. J.; Andrews, P. R. A common structural model for central nervous system drugs and their receptors, **1986**, *J. Med. Chem. 29* (4), 453−462.

(28) Carlsson, A.; Engel, J.; Strombom. U.; Svensson, T. H.; Waldeck B. Suppression by Dopamine-Agonists of the Ethanol-Induced Stimulation of Locomotor Activity and Brain Dopamine Synthesis. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1974**, *283*, 117−128.

(29) Lees, A. J. Dopamine Agonists in Parkinson's Disease: a Look at Apomorphine. *Fundam. Clin. Pharmacol.* **1993**, *7*, 121−128,

(30) Cannon, J. G. Dopamine Analogue Stereoisomers. In *Handbook of Stereoisomers: Drugs in Psychopharmacology*; Smith, D. F., Ed.; CRC: Boca Raton, FL, 1983.

(31) Pettersson, I.; Liljefors, T. Structure-activity relationships for apomorphine congeners. Conformational energies vs. biological activities. *J. Comput.-Aided Mol. Des.* **1987**, *1* (2), 143−152.

(32) Gomez-Jeria, J. S.; Ojeda-Vergara, M. Electrostatic medium effects and formal quantum structure-activity relationships in apomorphines interacting with D1 and D2 dopamine receptors. *Int. J. Quantum Chem.* **1997**, *61* (6), 997−1002.

(33) Waefelaer, A. Structural analogs of apomorphine. *Ing. Chim. (Brussels)* **1981**, *63* (299), 12−24.

(34) Komarova, E. L.; Tolkachev, O. N. The Chemistry of Peptide Ergot Alkaloids. Part 1. Classification and Chemistry of Ergot Peptides. *Pharm. Chem. J.* **2001**, *35*, 504−513.

(35) Lange, K. W. Clinical Pharmacology of Dopamine Agonists in Parkinson's Disease. *Drugs Aging* **1998**, *123*, 381−389.

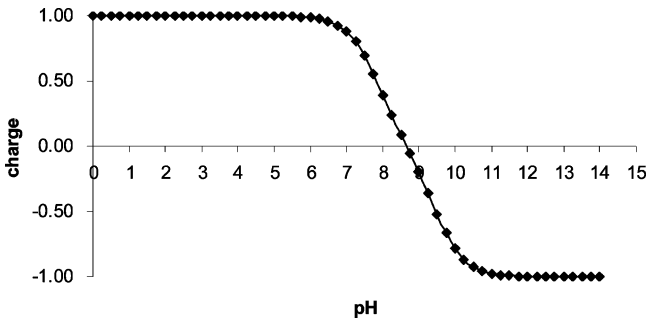


Figure 2. Apomorphine charge versus pH profile computed using the pK_a value of apomorphine.

the ring.[36] It is therefore important to preserve the catechol moiety of apomorphine in its completely protonated state. There could also be electrostatic interactions between the cationic form of apomorphine and the anionic phosphate groups of the ATP, if the delivered form is the cationic form of **I**. The simulated charge profile calculations based on the pK_a of apomorphine are shown in Figure 2, and it is clear that the molecule will indeed remain as a cation at the physiological pH of 7.4. Another important aspect of the presence of the two hydroxyl groups in the structure is their location. On the basis of molecular orbital theory, it has been predicted that the *m*-phenolic monoanion of dopamine free base is more stable than the *p*-anion.[37] Similarly, adding an electronegative substituent such as fluorine to the ring containing the catechol moiety could change the acidity of the phenolic groups, which might have a subtle if not large dependence on the strength of the agonist−receptor interaction.[38] However, modifying the structure with an electronegative substituent such as fluorine could potentially alter the octanol-to-water partition coefficient (log *p*) value, as well as the lipophilicity and aqueous solubility. These properties are particularly important from a drug delivery and formulation perspective. Finally, even though monohydroxy derivatives of apomorphines have been synthesized, evaluation of the therapeutic effects of these derivatives have found them to be less potent than the dihydroxy form as in apomorphine.[39,40]

Key Stability Issues of Apomorphine

One of the key stability issues of apomorphine is its susceptibility to oxidation. Oxidation of the hydroxyl groups

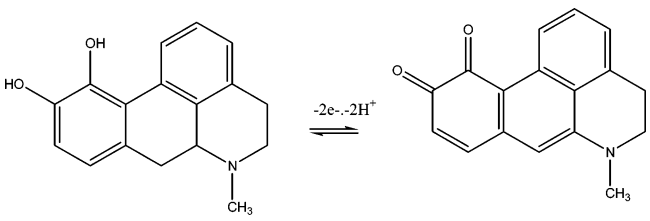


Figure 3. Schematic showing the oxidation of apomorphine to the quinone form.

of the catechol moiety to the quinone form (Figure 3) in aqueous solution is one of the factors retarding the stability of apomorphine. The kinetics of oxidation have been probed both electrochemically and via electron spin resonance.[41−43] Aqueous solutions of apomorphine turn color in less than 30 min, which indicates oxidation and formation of the quinone. In order to mitigate the kinetics of oxidation, several methods, including use of antioxidants, excipients that chelate oxidants in the formulation, and alteration of the formulation pH, have been described in the apomorphine literature.[44−46] Formulations of apomorphine in nonaqueous media using protic solvents and those enriched with antioxidants will have higher stability in providing extended shelf life than their aqueous counterparts.

Racemization or internal conversion from the *R* to the *S* form at physiological pH is another concern for apomorphine[47] (Figure 4). Conversion of one of the hydroxyl groups to the methoxy form with the help of catechol-*O*-methyl transferase (COMT) enzyme is postulated as a path for

(36) Granot, J. Nuclear Magnetic Resonance Studies of Catecholamines. Complex Formation With Adenosine 5′-triphosphate in Aqueous Solution. Stoichiometry and Molecular Conformations. *J. Am. Chem. Soc*. **1978**, *100*, 1539−1548.

(37) Katz, R.; Heller, S. R.; Jacobson, A. E. A Molecular Orbital Study of Norepinephrine and 3,4,-dihydroxy phenethylamine: a Re-evaluation of Structure-Activity Relationships in Norepinephrine. *Mol. Pharmacol.* **1973**, *9*, 486-494.

(38) Kirk, K. L. Photochemistry of Diazonium Salts. 4. Synthesis of Ring Fluorinated Tyramines and Dopamines. *J. Org. Chem.* **1976**, *41*, 2373−2376.

(39) Saari, W. S.; King, S. W.; Lotti, V. J.; Scriabine, A. Synthesis and Biological Activity of Some Aporphine Derivatives Related to Apomorphine. *J. Med. Chem*. **1974**, *17*, 1086−1090.

(40) Neumeyer, J. L.; Dafeldecker, W. P.; Costall, B.; Naylor, R. J. Aporphines. 21. Dopaminergic Activity of Apomorphine and Benzylisoquinoline Derivatives. Synthesis of 8-hydroxyaporphines and 1-(hydroxybenzyl)-2-*n*-propyl-1,2,3,4-tetrahydroisoquinolines. *J. Med. Chem*. **1977**, *20*, 190−196.

(41) Olea-Azar, C.; Alarcon, J.; Opazo, L.; Abarca, B.; Ballesteros, R.; Bielsa, P. Electron Spin Resonance and Electrochemical Studies of Oxidation Products Derivatives of Apomorphine in Aprotic Solvents. *Bol. Soc. Chil. Quim.* **2002**, *47* (4), 379−384.

(42) Garrido, J. M. P. J.; Delerue-Matos, C.; Borges, M. F. M.; Macedo, T. R. A.; Oliveira-Brett, A. M. Oxidative Behaviour of Apomorphine and its Metabolites. *Bioelectrochemistry* **2002**, *55* (1−2), 113−114.

(43) Burkman, A. M. Some Kinetic and Thermodynamic Characteristics of Apomorphine Degradation. *J. Pharm. Sci*. **1965**, *54* (2), 325−326.

(44) Sam, E.; Augustijns, P.; Verbeke, N. Stability of Apomorphine in Plasma and its Determination by High-Performance Liquid Chromatography With Electrochemical Detection. *J. Chromatogr., B: Biomed.Sci. Appl.* **1994**, *658* (2), 311−317.

(45) Priston, M. J.; Sewell, G. J. The Analysis of Apomorphine Formulations for Ambulatory Infusions. *J. Pharm. Sci.* **1995**, *1* (2), 91−94.

(46) Machovicova, F.; Mohelska, O.; Parrak, V. Stability of Apomorphine Studied by Paper Chromatography. *Cesko-Slov. Farm.* **1960**, *9*, 243−246.

(47) Van Der Geest, R.; Van Laar, T.; Kruger, P. P.; Gubbens-Stibbe, J. M.; Bodde, H. E.; Roos, R. A. C.; Danhof, M. Pharmacokinetics, Enantiomer Interconversions and Metabolism of R-apomorphine in Patients With Idiopathic Parkinson's Disease. *Clin. Neuropharmacol*. **1998**, *21*, 159−168.

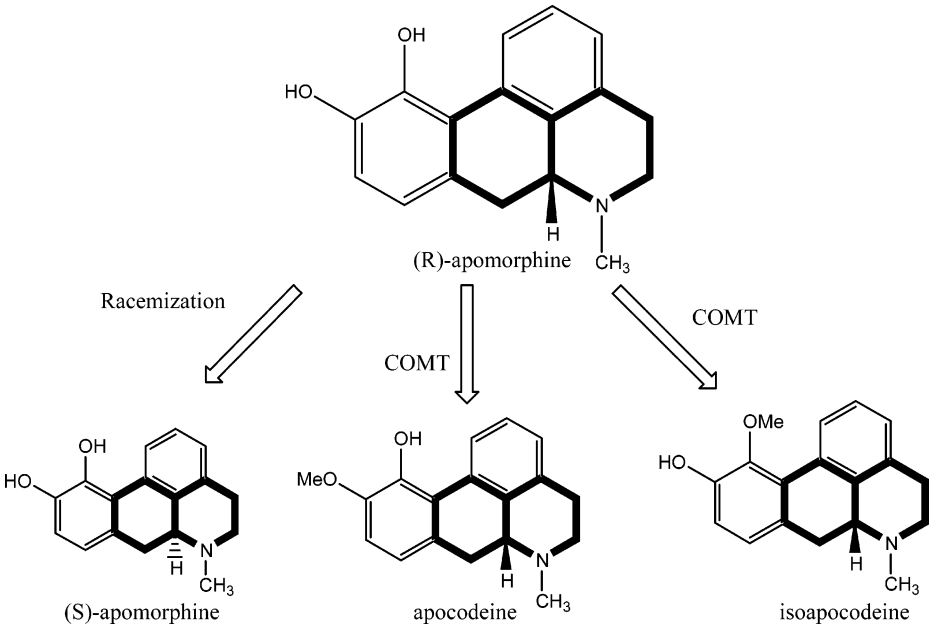


Figure 4. Potential metabolites of (*R*)-apomorphine. COMT can potentially convert apomorphine into apocodeine and isoapocodeine.[47]

formation of another potential metabolite for apomorphine. Even though assays for the various potential metabolites of apomorphine have been developed for physiological samples,[48] the paucity of extensive data sets makes it difficult to generalize the metabolic breakdown of apomorphine after administration.

Alternate Routes of Drug Delivery for Apomorphine

The efficacy of apomorphine from various clinical trials and the recent approval of apomorphine as a rescue medication for "wearing-off" periods after an oral dosage have opened up the possibility for several alternate routes of apomorphine delivery. Continuous subcutaneous infusion and intermittent subcutaneous injections are preferred to oral routes due to the first-pass effect and poor oral bioavailability.[49] Since the late 1980s, various alternate routes of delivery have been explored in addition to intravenous infusion. These methods include nasal,[50,51] sublingual,[52,53] rectal,[54,55] and transdermal routes including both passive diffusion[56] and iontophoresis.[57,58] Dewey and co-workers[59] carried out a double-blinded placebo-controlled clinical trial of an intranasal apomorphine spray and reported promising results with nasal irritation as a side effect. On the transdermal administration front, Lemachatti and Couarraze tested a passive transdermal therapeutic system for apomorphine using in

(48) van der Geest, R.; Kruger, P.; Gubbens-Stibbe, J. M.; van Laar, T.; Bodde, H. E.; 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: Biomedical Sci. Appl.* **1997**, *702* (1 + 2), 131−141.

(49) Frankel, J. P.; Lees, A. J.; Kempster, P. A.; Stern, G. M. Subcutaneous Apomorphine in the Treatment of Parkinson's Disease. *J. Neurol. Neurosurg. Psychiatry* **1990**, *53*, 96−101.

(50) Kleedorfer, B.; Turjanski, N.; Ryan, R.; Lees, A. J.; Milroy, C.; Stern, G. M. Intranasal Apomorphine in Parkinson's Disease. *Neurology* **1991**, *41*, 761−762.

(51) Kapoor, R.; Turjanski, N.; Frankel, J.; Kleedorfer, B.; Lees, A.; Stern, G.; Bovingdon, M.; Webster, R. Intranasal Apomorphine: a New Treatment in Parkinson's Disease. *J. Neurol. Neurosurg. Psychiatry* **1990**, *53*, 1015.

(52) Lees, A. J.; Montastruc, J. L.; Turjanski, N.; Rascol, O.; Kleedorfer, B.; Peyro Saint-Paul, H.; Stern, G. M.; Rascol, A. Sublingual Apomorphine in Parkinson's Disease. *J. Neurol. Neurosurg. Psychiatry* **1989**, *52*, 1440.

(53) Montastruc, J. L.; Rascol, O.; Senard, J. M.; Gaulano, V.; Bagheri, H.; Houin, G.; Lees, A.; Rascol, A. Sublingual Apomorphine in Parkinsons's Disease: a Clinical and Pharmacokinetic Study. *Clin. Neuropharmacol*. **1991**, *14*, 432−437.

(54) Hughes, A. J.; Bishop, S.; Lees, A. J.; Stern, G. M.; Webster, R.; Bovingdon, M. Rectal Apomorphine in Parkinson's Disease. *Lancet* **1991**, *337*, 118.

(55) van Laar, T.; Jansen, E. N.; Neef, C.; Danhof, M.; Roos, R. A. 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.

(56) Lemachatti, S.; Couarraze, G. Feasibility of Percutaneous Apomorphine Delivery by a Transdermal Therapeutic System for Parkinson's Disease Treatment. *Acta Technol. Legis Med.* **1996**, *7* (3), 231−238.

(57) Junginger, H. E. Iontophoretic Delivery of Apomorphine: From In-vitro Modelling to the Parkinson Patient. *Adv. Drug Delivery Rev.* **2002**, *54* (Suppl. 1), S57−S75.

(58) Li, G. L.; Grossklaus, A.; Danhof, M.; Bouwstra, J. A. Iontophoretic R-apomorphine Delivery in Combination With Surfactant Pretreatment: In Vitro Validation Studies. *Int. J. Pharm.* **2003**, *266*, 61−68.

(59) Dewey, R. B., Jr.; Maraganore, D. M.; Ahlskog, J. E.; Matsumoto, J. Y. 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.

vitro diffusion cell experiments and have reported percutaneous flux of 8 μg cm^{-2} h^{-1} for apomorphine.[56] The iontophoretic delivery of apomorphine has been extensively studied by Bouwstra and co-workers.[58]

Among the various drug delivery routes, transdermal delivery via iontophoresis has tremendous potential since it avoids the first-pass effect and has the ability to precisely control the dose as a function of applied current in any desired form (direct current [DC], alternating current [AC], or even pulsed to simulate a bolus dose).[60] Controllable transdermal drug delivery such as iontophoresis will undoubtedly appeal to health care practitioners and patients due to its capabilities coupled with the ongoing shift to personalized, on-demand delivery of drugs. There is extensive literature on the transdermal iontophoretic delivery of apomorphine from formulations stabilized with antioxidant excipients and buffers[61−63] including data from human clinical studies.[64] The key issue from a product concept is again to preserve the stability of the drug when it comes to the shelf life of an apomorphine iontophoretic patch and to be able to apply a high on-demand dose that is fast acting. Recent results regarding the stabilization of apomorphine via complex formation of catechol groups with borate and the formation of a diacetyl derivative of apomorphine leading to increased oxidative stability have been quite promising for a prodrug approach.[65] However, the prodrug approach opens up the additional need for converting to the diol form while maintaining the charge of the molecule before crossing the transdermal interface for systemic uptake and subsequent interaction with the receptors.

Conclusions

The development of apomorphine from an emetic drug to a rescue medication for PD has been quite fascinating. The century-old molecule's usage has been prolonged due to persistent studies by researchers and clinicians through a better understanding of its structural features, activity, and interactions with the physiological media. Further work needs to be in done in terms of preserving the chemical integrity of apomorphine both during use and during storage. Work also needs to be done to advance understanding of the transport of apomorphine across the skin from a clinical perspective for potential transdermal application, as a rescue medication either by itself or coadministered with another dopamine agonist.

MP060012C

(60) Scott, E. R.; Phipps, J. B.; Gyory, J. R.; Padmanabhan, R. V. Electrotransport Systems for Transdermal Delivery: A Practical Implementation of Iontophoresis. In *Handbook of Pharmaceutical Controlled Release Technology*; Wise, D. L., Ed.; Marcel Dekker: New York, 2000; pp 617−659.

(61) Li, G. L.; Danhof, M.; Bouwstra, J. A. Iontophoretic Delivery of Apomorphine In Vitro: Physicochemic Considerations. *Pharm. Res.* **2001**, *18* (11), 1509−1513.

(62) Li, G. L.; van der Geest, R.; Chanet, L.; van Zanten. E.; Danhof, M.; Bouwstra J. A. In Vitro Iontophoresis of R-apomorphine Across Human Stratum Corneum. Structure-transport Relationship of Penetration Enhancement. *J. Controlled Release* **2002**, *84*, 49−57.

(63) Li, G. L.; Danhof, M.; Frederik, P. M.; Bouwstra, J. A. Pretreatment With a Water-Based Surfactant Formulation Affects Transdermal Iontophoretic Delivery of R-apomorphine In Vitro. *Pharm. Res.* **2003**, *20*, 653−659.

(64) Li, G. L. Transdermal Iontophoretic Delivery of R-apomorphine for the Treatment of Patients With Parkinson's Disease. Ph.D. Thesis, Leiden University, Leiden, The Netherlands, 2003.

(65) Garrido, J. M. P. J.; Delerue-Matos, C.; Borges F.; Macedo, T. R. A.; Oliveira-Brett, A. M. New Insights Into the Oxidation Pathways of Apomorphine. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1713−1717.