Parkinsonism and Related Disorders 33 (2016) S13–S21

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Apomorphine - pharmacological properties and clinical trials in Parkinson's disease

Peter Jenner [a, *], Regina Katzenschlager [b, **]

[a] Neurodegenerative Diseases Research Group, Institute of Pharmaceutical Sciences, Faculty of Life Science and Medicine, King's College London, London, UK
[b] Department of Neurology and Karl Landsteiner Institute for Neuroimmunological and Neurodegenerative Disorders, Danube Hospital, Vienna, Austria

ARTICLE INFO

Article history:
Received 5 July 2016
Received in revised form
25 November 2016
Accepted 5 December 2016

Keywords:
Apomorphine
Pharmacology
Receptor profile
Pharmacokinetics
Clinical trial
Parkinson's disease

ABSTRACT

Apomorphine is often considered an archetypal dopamine agonist used in the treatment of Parkinson's disease (PD). However, it can be clearly differentiated from most other commonly used dopamine agonists on the basis of its pharmacology and on its unique clinical profile. Like levodopa and dopamine, apomorphine acts as a potent, direct and broad spectrum dopamine agonist activating all dopamine receptor subtypes. It also has affinity for serotonin receptors, and α-adrenergic receptors. Apomorphine is usually titrated to a dose that provides an equivalent antiparkinsonian response to that provided by levodopa, and its subcutaneous delivery allows a rapid onset of action, usually within 7–10 min. The mode of apomorphine delivery impacts on its clinical profile so as to provide two very different approaches to therapy in PD. When administered as an acute subcutaneous injection, it induces reliable and rapid relief from OFF periods underscoring its utility as a rescue medication. When given as a subcutaneous infusion, it significantly improves overall daily OFF time and there is also evidence to suggest that, in those patients who replace most or all of their oral drugs with apomorphine infusion, dyskinesia may also improve. In this paper, we review the rich pharmacology of apomorphine and review its efficacy in PD based on data from clinical trials.

1. Introduction

Apomorphine as a natural product has been used over many centuries as an emetic, sedative, anticonvulsant, antipsychotic, as well as for alcohol dependence and for sexual dysfunction [1]. It was first suggested as a treatment of Parkinson's disease (PD) by Weil in 1844, but its utility in the treatment of parkinsonian disorders was not reported until the work of Schwab in 1951. This was based on the ability of apomorphine to relieve rigidity in experimental animals [2] and it was not until 1967, that its strong structural similarity to dopamine was noted [1,3,4]. However, the widespread use of apomorphine in PD was impeded by its poor oral bioavailability and initial side-effect profile. The peripheral adverse effects of apomorphine, notably nausea, reflect its dopamine agonist activity and became easier to manage with the introduction of peripherally acting dopamine antagonists such as domperidone in Europe and trimethobenzamide in the USA [5].

Even so, the use of apomorphine to treat PD remained limited as levodopa had become established as the cornerstone of PD treatment, and other dopamine agonists that could be orally administered were introduced. The focus on using levodopa and dopamine agonists as monotherapy or in combination took attention away from apomorphine, and its clinical use was limited to a small group of neurologists who championed its use by acute subcutaneous injection and continuous infusion for many years, most notably Andrew Lees in London, UK [6–9]. They were proved to be right, and with the demonstration of the limitations of oral levodopa and dopamine agonist therapy in the later stages of PD, there is increasing recognition of the value of the use of apomorphine in the treatment of sudden OFF periods and 'wearing-off' where oral medication does not provide adequate clinical efficacy. Yet, even today, apomorphine is an underused drug in PD, mainly employed in specialist tertiary referral centers because its potent clinical effectiveness often is not fully appreciated by general neurologists

* Corresponding author. Neurodegenerative Diseases Research Group, Institute of Pharmaceutical Sciences, Faculty of Life Science and Medicine, Hodgkin Building, King's College London, London SE1 1UL, UK.
** Corresponding author. Department of Neurology and Karl Landsteiner Institute for Neuroimmunological and Neurodegenerative Disorders, Danube Hospital, 1220 Vienna, Austria.
E-mail addresses: peter.jenner@kcl.ac.uk (P. Jenner), regina.katzenschlager@wienkav.at (R. Katzenschlager).

http://dx.doi.org/10.1016/j.parkreldis.2016.12.003
1353-8020/

[10–12]. Questions are frequently raised about the comparative efficacy of apomorphine compared with oral levodopa or dopamine agonist therapy and other therapies for treating advanced disease (levodopa infusion and deep brain stimulation [DBS]). There is also apprehension about employing a therapy that requires the use of delivery devices.

However, apomorphine can be clearly differentiated from most other commonly used dopamine agonists on the basis of its pharmacology and its unique clinical profile, and the objective of this short review is to emphasize that differentiation. The safety of apomorphine has been extensively reviewed by Bhidayasiri and colleagues elsewhere in this supplement [13] and so, will not be covered here.

1.1. Receptor pharmacology of apomorphine

Apomorphine is an aporphine derivative of the dibenzoquinoline class, which has a molecular structure that in simple terms looks like a 'rigid' form of dopamine (Fig. 1). This structural similarity gives apomorphine its dopaminergic activity and it is why it acts as a potent direct and broad spectrum dopamine agonist drug activating all dopamine D1-like (D1, D5) and D2-like (D2, D3, D4) receptors [14]. Its high potency and affinity for dopamine receptors together with its reliability and rapid onset of action after subcutaneous administration has led to apomorphine becoming a key 'tool' compound in countless laboratory investigations of experimental models of PD. In normal rodents, it induces stereotyped behavior in rats and climbing behavior in mice. It reverses motor deficits in reserpine or haloperidol treated rodents, 6-OHDA lesioned rats, and MPTP treated primates [15], all reflecting its central dopamine agonist actions.

The commonly held view is that apomorphine is the archetypal dopamine agonist, but this is not correct when looking at its wealth of actions on dopamine receptors and other receptor sites relevant to PD. In fact, apomorphine is a molecule with a diverse range of pharmacological effects (Table 1). Even when considering its interactions with dopamine receptors, it differs from oral dopamine agonists in common use. For example, whereas the actions of pramipexole and ropinirole are limited to D2-like receptors (D2 and D3), apomorphine interacts with both the D1 and D2 receptor classes and with all major subtypes (D1, D2, D3, D4, D5) [14–17], which may have important functional consequences as outlined below.

The restricted interaction of oral dopamine agonists with dopamine receptor subtypes is often cited as a key reason why compounds like ropinirole and pramipexole do not appear to have equivalent antiparkinsonian efficacy to levodopa as assessed in monotherapy studies [18]. Through its conversion to dopamine, levodopa acts at all types of dopamine receptor (as does the endogenous neurotransmitter) in the normal brain. In contrast, oral dopamine agonists have a restricted interaction with dopamine receptors, with less activation of D1 receptors, which has been cited as a reason why they produce less dyskinesia than levodopa. The D1 receptor (notably its trafficking and signaling pathways associated with the direct striatal output pathway) has been blamed for initiating dyskinesia [19,20], but in reality this has never been proven. In preclinical studies, the administration of D1 agonists does not lead to a greater degree of dyskinesia induction or expression than seen with D2 agonist drugs. Rather, there looks to be an advantage in stimulating D1 receptors as this is known to reverse motor deficits in animal models of PD and in humans [21,22]. D1 receptor activity also may be of benefit in treating a non-motor symptom of PD: There is an association between the D1 receptor activity and improvement in bladder hyperreflexia, which has been demonstrated in both experimental models of PD and in clinical studies [23,24]. Apomorphine, which also has D1 receptor activity, has been shown to improve bladder function in a biphasic manner in rodent studies [25], and this has been reflected in clinical investigations [26,27].

Dopamine receptors are located in many parts of the brain other than the basal ganglia. Areas include cortical and limbic regions and the actions of dopamine agonists at these sites are associated with some adverse effects of dopamine replacement therapy in PD including impulse control disorders (ICDs) and visual hallucinations. So, a broad dopamine-like action of apomorphine might be seen as a disadvantage. For example, it has been suggested that ICDs may be due to activity at D3 receptors in limbic regions [28]. Indeed, the relatively high proportions of patients with ICDs on pramipexole, ropinirole and rotigotine has been shown to be linearly correlated with their D3 receptor selectivity relative to D2 receptors [28]. Apomorphine has a lower D3:D2 ratio than pramipexole and ropinirole [17] and this may be of clinical relevance although it is currently unknown whether the incidence of ICDs is actually lower when administering apomorphine, compared with other dopamine agonists.

Replacement of dopamine through levodopa may not be the only reason why levodopa is so highly effective in PD. Some of the dopamine produced from levodopa is, in turn, converted to noradrenaline (which is also deficient in PD). In addition, dopamine derived from levodopa accumulates in serotonergic neurons and can displace 5-HT. In this respect, apomorphine also has a rich pharmacology in that it has affinity for serotonin receptors (5HT1A, 5HT2A, 5HT2B, and 5HT2C), and α-adrenergic receptors (α1B, α1D, α2A, α2B, and α2C) [14]. This is not the case for the most commonly used oral agonists, ropinirole and pramipexole, which have a generally more restricted pharmacological profile.

Almost all drugs show selectivity for one particular receptor that mediates their major pharmacological and clinical activity. However, very few are specific in their receptor interactions with the majority showing off target activities that are a potential cause of undesirable side effects. In the past, when an off target pharmacologic action occurred at therapeutic doses, a drug with multiple pharmacological actions was not considered multimodal for its rich pharmacology but rather a "dirty" drug. This was certainly the case for the ergot derivatives (bromocriptine, pergolide and cabergoline) which were all held to be highly effective drugs for the treatment of PD, but which largely went out of use due to the rare but serious occurrence of pulmonary fibrosis and cardiac fibrotic valvulopathies, which were attributed to their potent effects at 5-HT2B receptors [29,30]. It was a major reason why the non-ergots, such as ropinirole and pramipexole, were developed and why their activities were purposefully designed to be limited to dopamine receptors and only some dopamine receptor subtypes.

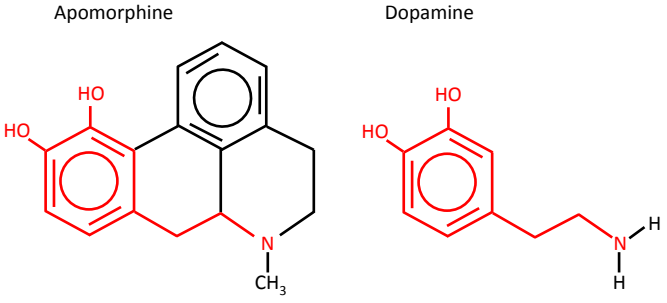

Fig. 1. Molecular structure of (a) apomorphine and (b) dopamine. Red lines denote the common dopaminergic moiety.