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A Scientific Methodology for Expansion of Anti-Parkinson Drug Product Range

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Abstract

Parkinson's disease (PD) is a chronic and progressive brain disease associated primarily with dopamine neurons degeneration of substantia nigra. More than 10 millions of people worldwide are affected by this disease manifested by combination of hypokinesia and rigidity, shaking, and postural instability. The high prevalence of disease has determined the aim of the study: to develop a methodology for expansion of anti-Parkinson drug product range. The information analysis methods were used for unbiased evaluation of novel anti-Parkinson drugs creation prospects.

A systemic analysis of active pharmaceutical ingredients (AFIs) used in anti-Parkinson drug products allowed for discovery of most widely used, levodopa being the top one. A comparative assessment of dosage forms used in Parkinson's disease treatment showed that they are represented primarily by intestinal gels, tablets, dispersible tablets, capsules, and modified release capsules.

The authors conclude, that the novel anti-Parkinson drug product should contain levodopa in form of an endonasal spray which provides optimal bioavailability due to necessary excipients (triglycerides, sodium monohydrogen phosphate, volatile and fatty oils, herbal extracts, stabilizers, and flavouring agents).

Keywords: Parkinson's disease, active pharmaceutical ingredients, novel drug discovery, dosage form

INTRODUCTION

Parkinson's disease (PD) is a chronic progressive brain disease associated primarily with dopamine neurons degeneration of substantia nigra and manifested by combination of the following symptoms: hypokinesia, rigidity, shaking, and postural instability. PD is one of the most prevalent neurological disease in elderly patients; the symptoms usually begin to develop at the age of 60, and the progression is slow and lengthy. [1, 2, 3, 4] The outcome is relatively unfavorable: the self-care of untreated patients is usually becomes challenging in 8 years after the onset of PD, and in 10 years the patients become bedridden. [1] The patients with adequate treatment are becoming dependent on their caregivers in 15 years at the average. [1] The motion activity is more affected if the onset of the disease was rather early, whereas mental disorders are dominating if the PD begins to develop at the age 70 or older. [5] Currently, PD is diagnosed even in younger patients. An increase in incidence is associated with several factors, including environmental pollution with neurotoxical xenobiotics, and also with an increase of life expectancy in economically developed countries since PD is found mostly in older patients. [6, 7] About 15% of patients with Parkinson have family history of this disease, however, genes responsible for it has not been identified yet. Some other factors responsible for Parkinson-like manifestations include viral infections, tumors, mechanical trauma of substantia nigra neurons, environmental factors (pesticides, herbicides, salts of heavy metals), chronic cerebrovascular insufficiency, and some drug products causing extrapyramidal side effects: phenothiazine neuroleptics, butyrophenone or thioxanthene derivatives, calcium channel blockers and others . [6, 8]

Taking aforementioned into account, **the aim** of the study was to develop scientific methodology for expansion of anti-Parkinson drug product range.

MATERIALS AND METHODS

Development of an unbiased evaluation of novel anti-Parkinson drugs creation prospects was performed using information analysis methods. It involved systemic analysis of active pharmaceutical ingredients (AFIs) used in drug products for PD treatment, followed by comparative assessment of dosage forms in which these drug products are available.

RESULTS

Currently, PD is considered incurable and all existing treatment methods are aimed at alleviation of symptoms. The main drug products used for reducing of movement disorders severity are [9, 10, 11, 12, 13]:

- dopamine precursors (levodopa, a levorotatory dioxyphenylalanine (L-DOPA) and levodopa with peripheral DOPA decarboxylase inhibitor);
- D2 dopamine receptors agonists (bromocriptine – an ergoline derivative);
- MAO-B inhibitors (selegiline, a substituted phenethylamine);
- other dopaminergic agents (entacapone, a selective catechol-O-methyl transferase inhibitor);

- glutamate antagonists (amantadine);
- anticholinergic agents (trihexyphenidyl, biperiden, and diphenyltropine)/

Levodopa, being one of the most effective anti-Parkinson drug products [14, 15], is a levorotatory dioxyphenylalanine isomer which is turned into dopamine by DOPA decarboxylase replenishing its deficiency. Levodopa guarantees positive effect in more than 95% of PD patients [6]; treatment with this drug product is an example of substitution therapy. [1, 16, 17] It was shown, that levodopa is effective against three main symptoms of PD: hypokinesia, tremor, and rigidity. [1, 17, 18] Levodopa products are prescribed to the majority of PD patients due to its high efficacy at all stages of Parkinson's.

Levodopa is an aminoacid, a direct dopamine precursor, which, unlike dopamine, can cross the blood-brain barrier and compensate for dopamine brain deficiency, that causes many clinical manifestations of PD. The drug is absorbed in the proximal part of the small intestine and is captured by the remaining dopaminergic nigrostriatal neurons. After decarboxylation is is turned into dopamine which is released into synaptic cleft supporting adequate function of striate body and other basal ganglia. [1, 17, 19] Dopamine-production efficiency and bioavailability of levodopa is much higher than of other dopamine precursors, phenylalanine and tyrosine. The fact, that therapeutic doses of levodopa do not interfere with endogenic dopamine synthesis is yet another advantage of this drug. [1] Its therapeutic effect remains almost the same throughout treatment time. [6]

For effective and safe treatment of Parkinson's with levodopa the decarboxilation process should occur after the drug has reached central nervous system (CNS) and not in peripheral organs, i.e. intestine, liver, kidneys. Peripherally-formed dopamine not only lowers levodopa's therapeutic effect, but also causes adverse reactions, primarily in heart and vascular system. It can cause arrhythmia, ischemic heart pain, peripheral vascular spasm, and hypotension. Therefore, levodopa is usually combined with peripheral DOPA decarboxylase inhibitors, such as carbidopa or benserazide. Only about 1% of absorber levodopa can reach brain without peripheral decarboxylation inhibition. [16]

During early stages of levodopa treatment the most common adverse reactions include nausea (about 80% of patients), vomiting, and heat flashing over. The rate of these reactions can be reduced by taking levodopa strictly after meals and using combination drug products (levodopa plus peripheral DOPA decarboxylase inhibitors): for example, the rate of nausea is reduced to 15% or less. Usage of short (less than 10 days) courses of small doses of domperidone or metoclopramide to adapt the patients to levodopa is also possible. Stomach-irritating and ulerogenic effects of levodopa are rather rare. The next group of adverse reactions is connected with CNS: headache, vertigo, confusion, psychosis, and hallucinations. They are typical in elderly patients. Psychotic symptoms caused by stimulation of dopaminergic processes in CNS can be neutralized by atypical neuroleptic clozapine, a central dopamine receptors blocker, which binds to D4 receptors more actively, than to D2 receptors. Prolonged treatment with levodopa can cause different dyskinesias, such as mild choreiform movements (especially of the face muscles) or severe dystonic movements. Rare adverse reactions include vision disorders, hemolytic anemia, leukopenia, and even agranulocytosis. Alopecia and allergic reactions are possible, but they are also rather rare. In order to facilitate transfer from levodopa to combined drug products and prevent intensification of adverse effects it is necessary to stop taking levodopa for al least 12 hours and take combined drugs in small doses. Besides combinations of levodopa and peripheral DOPA decarboxylase inhibitors the inhibitors of catechol-o-methyl transferase can also be used to alleviate adverse reactions. Entacapone prevents L-DOPA and dopamine destruction, and destruction of other catecholamines as well, so it is recommended to combine levodopa with this drug. It is also rational to combine levodopa and midantane, since it makes possible to lower levodopa dosage. However, MAO inhibitors and levodopa are incompatible; this combination leads to high dopamine concentrations in the brain and high blood pressure levels. [16, 20, 21, 22, 23, 24, 25]

The following dosage forms of levodopa are currently in use: intestinal gel, tablets, dispersed tablets, capsules and capsules with modified release. Intestinal gel is injected into intestines (duodenum, small intestine, ileum, colon) by means of a special device, so minimally invasive surgery is required to install the pump. Oral dosage forms have several adverse reactions which were described above. [9, 10]

DISCUSSION

It is well recognized that levodopa products currently are the most effective medications for PD symptomatic treatment – a "gold standard" for this neurodegenerative disease. [26] Despite its efficacy the optimal duration of therapy is still highly debated. [15, 27]

One of the possible ways of neutralizing the aforementioned drawbacks of levodopa drug products, alleviating possible adverse effects, enhancing efficacy along with the metabolic optimization is the use of optimal dosage form, which will help to lower the dose necessary to achieve the desired effect by means of controlled release and optimized bioavailability.

It was shown, that liposomes can be used to protect L-DOPA from enzymatic destruction [28, 29] and prospectivity of utilizing nanosomal DOPA to treat Parkinson's. [30] Among disadvantages of this approach is the high price of the phospholipids, and their low stability during storage.

The use of biocompatible, biodegradable polymers, for example, co-polymers of glycolic and lactic acids, is an alternative to liposomal preparations. [31] A way [32] of production of L-DOPA based preparation is known; polyvinyl alcohol is used in the preparation for emulsion stabilization. The particles are formed using double emulsion method.

Inclusion of DOPA and dopamine in polyamide microspheres was assessed in some studies, [33] However,

in vitro release kinetics studies have shown lack of prospects for this approach.

It was demonstrated, that noninvasive drug delivery from the nasal cavity to the brain makes it possible to use lower concentrations of AFIs due to reflex neuro- and vasoactive action on the stuctures and receptors of the nasal mucosa. This way of delivery modifies permeability of the blood-brain barrier membrane structures, predominantly in the hypothalamic area, allowing different substances to reach the brain.

It should be taken into account, that endonasal drug products should contain substances that protect nasal mucosa, and customer performance, e.g., triglycerides, sodium monohydrogen phosphate, volatile and fatty oils, herbal extracts, and flavouring agents. Because enonosal drugs are nonstable products they should include stabilizers, e.g., benzoic acid or its salts, ethylenediaminetetraacetic acid or its salts, and others.

CONCLUSION

The results of the study suggest that current PD treatment with levodopa should also be viable in the future. In order to minimize adverse reactions rate it is reasonable to develop novel dosage forms of this drug, the most promising is an endonasal dosage form. The disadvantages of this way of AFI delivery can be mitigated by careful selection of excipients. Also, new treatment modalities are of great interest [34].

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