#02/2023
ISSN 2299-1247

JHPOR | Journal of Health Policy & Outcomes Research

How does the method of formulation a drug affect its efficacy and safety, based on the comparison of modified and conventional release amantadine in the treatment of levodopa induced dyskinesia in patients with Parkinson's disease?

DOI:10.7365/JHPOR.2023.2.5

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Keywords:

levodopa - induced dyskinesias, Parkinson's disease, amantadine ER, amantadine IR

How to cite this article?
JaworskaM., How does the method of formulation a drug affect its efficacy and safety, based on the comparison of modified and conventional release amantadine in the treatment of levodopa induced dyskinesia in patients with Parkinson's disease?, J Health Policy Outcomes Res [Internet]. 2023[cited YYYY Mon DD];. Available from: http://jhpor.com/article/2293-how-does-the-method-of-formulation-a-drug-affect-its-efficacy-and-safety-based-on-the-comparison-of-modified-and-conventional-release-amantadine-in-the-treatment-of-levodopa-induced-dyskinesia-in

contributed: 2022-10-28
final review: 2023-06-14
published: 2023-10-08

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Abstract

Background

The choice of the appropriate method of drug production is determined mainly by the characteristics of the medicinal substances and excipients, the type of disease in which the drug is to be used and the expectations of patients. The appropriate method of drug production may be key importance for achieving clinically significant treatment effects. For this reason, an attempt has been made to evaluate modified and conventional release forms of amantadine for the treatment of levodopa-induced dyskinesias in patients with Parkinosn's disease.

Methods

The effect of two different forms of amantadine on the treatment of levodopa - induced dyskinesias in patients with Parkinson's disease was assessed through a systematic review of clinical trials following the PICOS regimen. The clinical efficacy of the treatment of levodopa-induced dyskinesias in patients with Parkinson's disease was assessed by a measure of the appropriate scale and the effect on the ON and OFF times.

Results

Although no studies were found directly comparing the use of amantadine ER with amantadine IR in this disease, in the studies of amantadine ER, the UDysRS score showed a significantly greater improvement in the treatment of dyskinesia in the study group compared to placebo. The amantadine IR studies did not show any significant effect on the treatment effects.

Conclusions

The choice of the method of producing a drug has a significant impact on the effects of treatment.

Introduction

The biopharmaceutical division of oral drug forms includes conventional release and modified release forms. According to the basic definition, conventional release drug forms (IR) are characterized by a short disintegration time and an unmodified release rate. The auxiliary substances used in the production method do not significantly change the dissolution rate of the active substance, its release and absorption. The modified release dosage forms determine the rate, profile or site of release of the active ingredient. These features are different from the conventional form administered by the same route. These differences can be achieved with a special formulation or production method. Among the modified release drugs we can distinguish the forms of extended release, delayed release, pulsatile release and controlled release. Extended release forms of drugs (ER) have many advantages, the most important of which is that the concentration of the active ingredient remains constant over a longer period of time.[1] According to the guidelines of the European Medicines Agency, the development and use of prolonged and delayed-release drugs should be based on a well-documented clinical need.[2] Parkinson's disease is one of the most common neurodegenerative diseases, mainly among people over 50 years old. After 4-6 years of treatment with levodopa, nearly 40% of patients develop levodopa-induced dyskinesias.[3] Dyskinesias are movement disorders that can affect the face, limbs and, or trunk muscles and can not be controlled by the patient. Levodopa induced dyskinesia (LID) is one of the most common motor complications in the pharmacological therapy of advanced Parkinson's disease.[4] Due to the lack of effective therapy in treating levodopa induced dyskinesias in patients with Parkinson's disease, it was decided to analyze whether the new form of modified release amantadine is more effective compared to conventional release amantadine. The publication includes the results of the master's thesis written by Jaworska Marzena.[5]

Methodology and scheme of carrying out the analysis

The clinical analysis was performed on the basis of the results of clinical trials found in the systematic review. After determining the criteria for inclusion of clinical trials in the analysis, a search strategy was created in which the most important medical information databases of PubMed and Embase were searched. Research was selected on the basis of titles and abstracts and then full texts. After the decision to include or exclude studies from the review, the data was synthesized and the statistical and clinical significance of the results was assessed. The final stage of the review was the elaboration of the results. The systematic review of the research is based on the AOTMiT guidelines.

Criteria for the inclusion

It was assumed that the analysis will include studies that meet the PICOS criteria for population, interventions, comparators, methodology, endpoints and do not meet the exclusion criteria. The adopted criteria for the inclusion of studies in the analysis are presented in Table 1.

Table 1. Scope of the clinical analysis - PICOS scheme

Area	Definition
Population	Parkinson's disease patients with levodopa - induced dyskinesia
Assessed intervention	Modified release amantadine
Comparators	Conventional release amantadine
End points	Unified Parkinson's Disease Scale Scores, the results of the unified dyskinesia scale, reduction of OFF state, extension of ON state
Types of studies included	RCT

Criteria for excluding studies from the analysis

It was assumed that studies that do not meet the PICOS assumptions will not be included in the analysis. Observational and cohort studies, review articles and expert opinions were rejected, as well as works not available in full text and published in languages other than Polish or English.

Search strategy

To search for relevant clinical trials an electronic medical information database Medline and Embase, was searched using population and intervention keywords. The search strategy is schown in Table 2.

Table 2. Search strategy

No	Keywords	The number of records
4	1 and 2 and 3	154
3	Levodopa induced dyskinesia	2 858
2	Amantadine	7 572
1	Parkinson's disease	121 512

Analyzing the results by means of an indirect comparison
If no clinical trials are found directly comparing the assessed medical technology with alternative medical technology an indirect comparison may be considered. One of the tools, that allows for an indirect comparison of the two drug technologies is the method proposed by Bucher from 1997. The basic assumption of this method is research with a common comparator and the studies included in the analysis should be consistent in terms of methodology, interventions used, population and assessed endpoints. Before deciding to analyze the results of tests using the Bucher method, the homogeneity of these tests should be assessed in terms of methodological and clinical characteristics. The clinical effectiveness of one intervention over another can be assessed on the basis of statistical parameters: OR, RR, RD, MD, HR.[6]

Clinical trial search results

As a result of searching the Medline and Embase databases 154 references were obtained. No studies were found directly comparing modified release amantadine to conventional release amantadine in the treatment of levodopa induced dyskinesias in patients with Parkinson's disease. Therefore studies in which the intervention studied were amantadine with a modified release or amantadine with conventional release and the control option no treatment or placebo, were qualified for the analysis, which gives an opportunity to make an indirect comparison. After analyzing the full texts, 8 clinical trials met the requirements of which 5 were related to amantadine IR and 3 to amantadine ER. The selected studies were randomized with phase III and II, double-blinds. The trial selection process is shown in the PRISMA diagram (Figure 1).

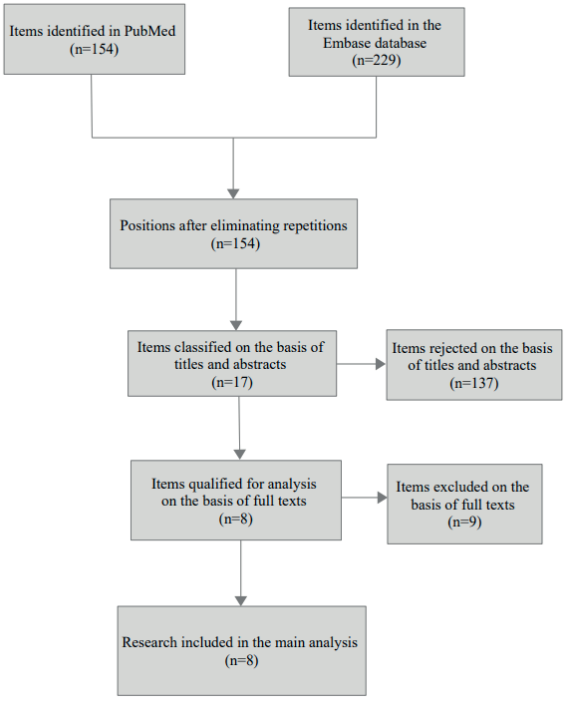

Figure 1. Prisma diagram

Reasons for excluding publication on the basis of full texts

After verifying the full texts 9 studies were excluded from the analysis. Most studies were rejected due to inconsistent methodology. The second factor determining the exclusion was the difference in the scope of the study group. Two studies were characterized by an inadequate population. One study was dropped due to incompatible intervention regimen.

Included research

The review includes 8 double-blind, randomized trials comparing interventions with no active treatment. In clinical trials, the effect of the study intervention on the incidence of levodopa induced dyskinesias was assessed using appropriate scales and the score on the scales was the primary endpoint. Secondary endpoints was ON and OFF duration. A summary of studies included in the analysis is presented in Table 3 and Table 4.

Table 3. Included studies - summary part I

No	Study on Amantadine IR	End points	Study population	Sample size	The way of administering the drug	Duration of the study
1	Verhagen Metman L. et al. 1998.[7]	The result on the UPDRS scale part IV	Parkinson's disease patients with LD-induced dyskinesia (USA)	18	p.o. 300-400 mg	6 weeks (2 periods 3 weeks)
2	Luginger E., et al. 2000 [8]	The result on the UPDRS scale, part IV	Patients with advanced Parkinson's disease, with motor complications in the form of dyskinesias. Patients with dementia and renal, hepatic or heart failure were excluded from the study (Austria)	11	p.o. 300 mg	5 weeks (2-week periods separated by a 1-week washout period)
3	Snow BJ., et al. 2000 [9]	The result on the UPDRS scale, part III and part IV	Parkinson's disease patients with LD induced dyskinesias (New Zealand). Patients recruited from the Department of Movement Disorders, Auckland Hospital	24	p.o. 100 mg for the 1 week, 200 mg for the next 2 weeks	6 weeks (2 periods of 3 weeks)
4	Thomas A. et al. 2004 [10]	Score UPDRS scale part IV, scale DRS and IGA	Patients with advanced Parkinson's disease with complications in the form of motor fluctuations and LD-induced dyskinesias (Italy)	40	p.o. 300 mg	34 weeks
5	Da Silva-Junior FP. et al. 2005 [11]	Score UPDRS part IV, II and III, scale CDRS	Parkinson's disease patients with LD-induced dyskinesia (Brazil) Patients recruited from the movement disorders clinic	18	p.o. 100 mg for 1 week, 200 mg for the next 2 weeks	3 weeks

DRS - Dyskinesias Rating Scale
IGA - Investigator Global Assessment
UPDRS - Unified Parkinson's disease rating scale

Table 4. Included studies - summary part II

No	Study on Amantadine ER	End points	Study population	Sample size	The way of administering the drug	Duration of the study
1	Pahwa R. et al. EASED Study 2015 [12]	Score UDysRS, FSS, MDS-UPDRS	Parkinson's disease patients with LD-induced dyskinesia (USA)	83	p.o. 260 mg, 340 mg, 420 mg	8 weeks
2	Pahwa R. et al. EASE LID Study 2017 [13]	Score UDysRS	Parkinson's disease patients with LD-induced dyskinesia (USA)	121	p.o. 274 mg	25 weeks
3	Oertel W. et al. EASE LID 3 2017 [14]	Score UDysRS	Parkinson's disease patients with LD-induced dyskinesia (USA)	75	p.o. 274 mg	13 weeks

FSS - Fatigue Severity Scale
MDS - Movement Disorder Society
UDysRS - Unified Dyskinesia Rating Scale

Assessment of the quality of the included studies, the Jadad scale and Cochrane tool

The quality of the included studies was assessed using the Jadad scale, which is a 5-point scale. In study by Verhagen Metman L. et al. descriptions of randomization and the appropriate randomization method were not provided, while the Snow BJ. et al. the desription of the blinding, and the correct method of blinding were not provided. The study Da Silva-Junior FP. et al. was scored at 3 points because this study did not describe randomization and the appropriate method of randomization, did not describe blinding and the correct method of blinding. The remaining trials received a score of 5. The Cochrane tool was used to assess the risk of bias. Among the studies found in the review, the study by Verhagen Metman L. et al. is characterized by a high risk of bias in terms of not reporting complete results.

Statistical analysis of the results

The results of the comparison of amantadine ER versus amantadine IR for continuous endpoints; scale values for assessing the severity of dyskinesia and the duration of ON and OFF state are presented, as changes expressed as mean value (Mean) with standard deviation (SD). In all cases, the results are presented with 95% confidence intervals. When concluding it was intended to accept the result from the indirect comparison using the Bucher method. The analytical tool MS Excel 365 was used to process the results.

Clinical analysis results

Before starting the indirect comparison the homogeneity of the studies was assessed. The size of the population and the observation period may be a potential source of research heterogeneity. The studies on amantadine in the modified release form had a much larger number of study participants and a longer follow-up period. Due to the differences in the observation period, some studies were too heterogeneous, therefore studies with a similar observation period were qualified for further analysis. The study by Thomas A. et al. was qualified for amantadine IR with the observation period of 39 weeks. EASED study with the observation period of 8 weeks, EASE LID with observation period of 24 weeks and EASE LID 3 with observation period of 12 weeks were qualified for amantadine ER. A further assessment of compliance in terms of the input population, intervention and comparator and endpoints, was performed for the above 4 studies. In study by Thomas A. et al. no data on side effects of amantadine IR were collected. Therefore the homogeneity of the studies with respect to the safety profile can not be assessed and no comparison can be made.

Results

Comparison of amantadine ER and amantadine IR versus placebo

Although the endpoints in the included studies were consistent as the severity of dyskinesias was assessed in each trial, different measurement scales were used for this purpose. Hence inhomogeneous results were obtained, which cannot be assessed by indirect comparison using the Bucher method. How to measure the length of the ON state when the patient felt good and the length of the OFF state when the patient felt bad and worsening Parkinsonism symptoms in the EASE LID 3 study and Thomas A. et al. was similar, but nevertheless the results in the control groups were significantly different. For these reasons, it is also not possible to perform an indirect comparison using the Bucher method for this endpoint. Due to the fact that making an indirect comparison using the Bucher method is not justified the evaluation of the effectiveness of amantadine ER against amantadine IR was performed by comparing each form of amantadine, against placebo by calculating the MD with a 95% confidence interval. The EASED STUDY was not included in the evaluation of the endpoint results for amantadine ER as it was a phase II study.

In the study by Thomas A. et al. to assess dyskinesia, the DRS scale was used, which measures the severity of dyskinesia for each part of the body (face, neck, trunk, left and right, upper and lower limbs) on the basis of a 5-point scale giving a maximum score of 28 points. The MDS-UPDRS was developed to assess various aspects of Parkinson's disease including non-motor and motor experiences of daily living and motor complications. This scale consists of 4 parts, of which part III covers motor symptoms and part IV covers movement complications. In study by Thomas A. et al. where the assessed intervention was Amantadine IR the average difference between the study group and the control group was 1 point on the DRS scale 95% [-0,44 ; 2,44]. According to the UPDRS part III, the difference between the study group and the control group was 3,3 95% CI[-4,37 ; 10,97] and UPDRS part IV mean difference 0,7 95% CI[-1,84 ; 3,24]. For the length of the ON state [h], the value of MD = 0,2 95% CI[-1,85 ; 2,25] and for OFF [h] MD value = - 0,4 95% CI[-2,72 ; 1,92]. The obtained results do not show statistical significance. In the EASE LID where the effectiveness of amantadine ER was checked, the change in the total score of the UDysRS scale in the treated group compared to placebo was MD = -7,9 95%[-12,5 ; -3,3]. In terms of change in the results of the MDS-UPDRS scale, the value of MD=-1,9 95% CI[-2,9 ; -0,9]. The study showed a significant increase in ON time [h] compared to placebo at the level of MD = 2,8 95% CI [1,6 ; 4,0] and shortening the OFF time [h] at the level of MD=-0,9 95% CI[-1,6 ; -0,2]. In the EASE LID 3 study, also on amantadine ER, a change in the total score of the UDysRS scale was obtained for the study intervention by the value of MD=-14,4 95%CI [-20,4 ; -8,3], while the change in the value of the MDS-UPDRS scale was MD=-3,0 95%CI [-4,5 ; -1,6] compared to placebo. With respect to the lenght of the ON state, an increase of MD=1,9 was obtained 95% CI [0,37 ; 3,43] in favor of amantadine ER, also OFF decreased by MD=-1,1 95% CI [-1,93 ; -0,27]. It should be emphasized that in the EASE LID 3 study, the full measurement of the UDysRS scale showed a significant improvement in the treatment of dyskinesias in the amantadine ER group compared to placebo at the score level -14,4 points. For comparison in the work of Makkos A. et al. it was shown that any improvement greater than 3,9 points on the whole UDysRS scale or any deterioration greater than 3,5 points represents a minimal but clinically significant change [15]. Meanwhile in study by Thomas A. et al. the DRS and UPDRS scores were slightly lower in the amantadine IR group compared to placebo. Based on the EASE LID 3 study it was also shown that amantadine

ER prolongs ON time by 1,9 hours compared to placebo (a change of approx 24%), while the OFF time is reduced by 1,1 hours compared to placebo (55% change). For amantadine IR study by Thomas A. et al. it has been found not to extend the ON state and not to shorten the OFF state since the results are statistically insignificant. In clinical trials with amantadine ER the MD and 95% CI values indicate statistical significance and benefit of the study intervention over placebo (Table 5).

Table 5. Results for the comparison of amantadine ER and amantadine IR versus placebo

Study/End point	UPDRS IV	Worsening of dyskinesia	UPDRS III	State ON [h]	State OFF [h]
Thomas A. et al. 2004 Amantaidne IR	MD=0,7 [-1,84 ; 3,24]	MD=1,0 [-0,44 ; 2,44] Scale DRS	MD=3,3 [-4,37 ; 10,97]	MD=0,2 [-1,85 ; 2,25]	MD=0,4 [-2,72 ; 1,92]
EASE LID 2017 Amantadine ER	MD=-1,9 [-2,9 ; -0,9] Scale MDS-UPDRS	MD=-7,9 [-12,5 ; -3,3] Scale UDysRS	-	MD=2,8 [1,6 ; 4,0]	MD=-0,9 [-1,6 ; -0,2]
EASE LID 3 2017 Amantadine ER	MD=-3,0 [-4,5 ; -1,6] Scale MDS-UPDRS	MD=-14,4 [-20,4 ; -8,3] Scale UDysRS	-	MD=1,9 [0,37 ; 3,43]	MD=-1,1 [-1,93 ; -0,27]

Discussion

Amantadine extended release may be used to treat levodopa - induced dyskinesias. The potential benefits of amantadine ER over amantadine IR result from the pharmacokinetics of these dosage forms. According to data from Summary of Product Characteristics amantadine is well absorbed after oral administration. Due to the lipophilic nature of the molecule it easily crossesthe blood-brain barier. It is excreted almost completely unchanged by the kidneys. The peak plasma concentration of the drug is achieved after 2-4 hours.[16] For comparison the median Tmax for amantadine ER in plasma after oral administration was approximately 12 hours (range 6-20 hours). Parkinson's symptoms are particularly troublesome in the morning. For these reasons administering amantadine ER once a day at bedtime is of greater benefit to the patient and reduces the risk of drug toxicity.[17;18] Amantadine ER has an advantage in the dosing distribution as it can be taken once a day at night. In contrast amantadine IR requires administration two or three times a day. Reducing the frequency of drug dosing through the use of a long-acting drug, has a positive effect on compliance with the recommendations and improves the effectiveness of therapy.[19] The clinical analysis was performed with the data collected from systematic review of clinical trials comparing amantadine ER to amantadine IR. No studies have been found directly comparing these two forms of amantadine. An attempt was made to evaluate the results of the found studies by means of an indirect comparison using the Bucher method. The studies qualified for the analysis differed in terms of the baseline population and the follow-up period. The amantadine IR studies were characterized by a small number of participants and a short follow up period. Clinical trials for amantadine ER were more numerous and had a longer follow-up period. The most similar in terms of observation period was the study of Thomas A. et al., and for amantadine ER - the EASE LID 3 study. However, differences in how results were reported between studies were a major limitation of the Bucher method. Dyskinesias were assessed using a variety of tools that were available at the time of the study. The obtained results may be affected by the low quality of the found clinical trials on amantadine IR. For this reason the indirect comparison using the Bucher method was not performed. A few small studies suggest that amantadine IR may have an anti-dykinetic effect, however the drug has not been extensively studied in well - controlled clinical trials and the durability of its effects has been questioned. A Cochrane review from 2003 year concluded that there is not enough evidence to say whether amantadine is an effective treatment for LID in patients with Parkinson's disease.[20] The work of Behzad Elahi investigated effect of NMDA receptor antagonists in the treatment of LID. The review included several clinical trials with a small study population. Therefore, evidence of the anti - dykinetic effect of amantadine may not be sufficient.[21] The results would need to be replicated on a larger study population. However the efficacy and safety of amantadine ER has been proven in better quality clinical trials.

Conclusions

In the light of current medical knowledge amantadine ER has proven effectiveness while the effectiveness of amantadine IR should be considered unconfirmed. Hence despite the lack of an indirect comparison it can be concluded that amantadine ER is superior to amantadine IR. Thus the appropriate method of producing a drug is critical to achieving good results, as exemplified by the use of amantadine ER in the treatment of levodopa-induced dyskinesias in patients with Parkison's disease.

Conflict of interest and funding statements

The author reports no conflict of interest.
The prepared work was not financed from any sources.

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