In vitro equivalence evaluation of betahistine generic medicinal products as a tool potentially determining the efficacy of pharmacotherapy

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Objective. To compare release parameters of various betahistine drugs in vitro using a comparative dissolution kinetics test. Material and methods. Objects of research are solid dosage forms (tablets) containing betahistine in a dose of 24 mg permitted for medical use in the Russian Federation. A method of comparative dissolution kinetics test was carried out as follows. The study was performed on a paddle stirrer at a speed of 50 rpm in three different pH dissolution media (pH 1.2, 4.5, 6.8), simulating the main sections of the digestive tract in which the active ingredient was decomposed, released and absorbed. This was performed in a quality controlled environment using a citrate buffer solution with pH 6.8. The time points for sampling the medium were 10 min, 15 min, 20 min and 30 min. Results. The results of betahistine release were significant (RSD<10%) for all time points, except the first time point (RSD<20%). Regardless of pH, there was a complete release (>80% over 15 minutes, <10%) of betahistine from betaserc, 24 mg, tablets (manufactured by Mylan Laboratories SAS). The dissolution profiles of betahistine in other investigational drugs did not show complete drug release (parameter <85% in 15 minutes, <10%) in different pH media. Therefore, dissolution profiles of the studied drugs were not comparable to the reference profile. Conclusion. Starting from 10 minutes, the reference drug of betahistine (betaserc, 24 mg) has a consistently higher release at different pH levels (representing the various stages of gastric digestion), vs. other studied generic analogues showing significantly lower levels of betahistine release. None of the studied drugs were found to be equivalent in vitro.

Keywords: reference drug of betahistine, generic analogues of betahistine, in vitro equivalence of generics.

Introduction

Histamine receptor modulators represent a group of medicinal products which are historically among the first pharmacological agents used in the treatment of vertigo [1, 2]. Clinical trials conducted to date and their meta-analyses have shown that betahistine is an effective treatment with established safety profile for Meniere’s disease [3], benign paroxysmal positional vertigo, vestibular neuronitis and other types of peripheral vertigo [4]. Betahistine is a partial histamine H1 receptor agonist with more selective H3 receptor antagonistic properties. As a result of its H1 receptor agonist action betahistine increases cochlear and vestibular blood flow, and the blockade of H3 receptors leads to suppression of neural impulse activation in ampullary cells of the inner ear and vestibular nuclei in the brainstem [5]. As the H3 histamine receptor mediates auto-inhibition of brain histamine release and autoregulation of histamine synthesis, its blockade leads to increased synthesis and release of histamine in neurons of the tuberomamillary nucleus.

To date, the pharmaceutical market of the RF offers, apart from the reference product Betaserc (‘Mylan Laboratories SAS’), about a dozen of generic betahistine drug products. From the standpoint of healthcare cost optimization, both with regard to State budget and patient affordability, generic drugs are economically profitable instruments as, according to statistical data, their cost is 20—90% lower compared to that of their reference counterpart [6]. From the State Law perspective, the requirements for generic drugs differ across countries. However, the overriding principle underlying generic drug safety and efficacy is the concept of bioequivalence. According to the FDA requirements, in order to receive FDA approval for a new generic drug, its bioequivalence value must lie in the range 80—125% of that of the reference drug [6]. Differences in bioequivalence may entail clinical consequences, e.g., a number of studies demonstrated that switching patients from reference drug to generic drug resulted in aggravation of the disease course, in particular, of some neurological diseases [7—9].

The information available to date makes the assessment of the clinical efficacy equivalence of betahistines present on the pharmaceutical market, a relevant topic for discussion. Clinical effect of betahistine is dose-dependent as demonstrated in animal models when the drugs were used for the improvement of cochlear and vestibular blood flow [10—13], and accelerated the recovering of body position in space and body balance [14]. Therefore, high plasma drug concentration is one of the major factors which determine clinical efficacy of betahistines.

Tablets are an established solid pharmaceutical form of betahistines. One of the main criteria for their quality evaluation is the dissolution kinetics which measures the in vitro rate and extent of release of active ingredient, i.e., the in vitro bioavailability. Use of this method for drug analysis, along with the evaluation of pharmaceutical equivalence, may serve as an instrument for preliminary evaluation of bioequivalence of generic medicinal product [15].

1Процесс для Approving Generic Drugs. Ссылка активна на 20.07.18. http://www.fda.gov/Training/ForHealthProfessionals/ucm090215.htm

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Our study aimed to comparatively evaluate the parameters of dissolution of reference betahistine Betasec («Mylan Laboratories SAS») versus those of its generic analogues.

**Materials and methods**

As the study objects, we have chosen medicinal products in solid pharmaceutical dosage form (tablets) containing betahistine at a dose of 24 mg approved for human use in the Russian Federation and available for purchase in Moscow pharmacies, namely, Betahistine Canon, 24 mg, tablets, batch 1171216 (ZAO «Raduga Production»), Betahistine, 24 mg, tablets, batch 160117 (OOO «Ozon»), Betahistine-SZ, 24 mg, tablets, batch 70517 (ZAO «Severnaya Zvezda»), Tagista, 24 mg, tablets, batch 0271216 (OOO «Hemofarm») and Betaserc, 24 mg, tablets, batch 645367 («Mylan Laboratories SAS»).

Comparative dissolution kinetics test was performed using paddle mixer at a rotating paddle speed of 50 rpm and three dissolution media simulating those present in three main parts of the gastrointestinal tract in which tablet disintegration and release, and absorption of active ingredient takes place, using media with pH values of 1.2, 4.5 and 6.8, respectively. Also, testing was performed in a quality control medium, i.e., citrate buffer solution, pH 6.8.

One tablet of the test drug was placed in each vessel for tablet dissolution containing 900 mL of dissolution medium prewarmed to 37±0.5 °C. After certain periods of time 5 mL aliquots were withdrawn, and the volume in the vessel was immediately replenished with an equivalent volume of dissolution medium. The withdrawn samples were passed through membrane filters, and the first 2 mL of filtrate was discarded. Filtered samples were cooled down to approximately 20 °C and transferred to the spectrophotometer cells for quantitative measurement of betahistine that was released from a tablet into the dissolution medium.

Sample collection time points were 10 min, 15 min, 20 min and 30 min from the start of the test, and such sampling schedule enabled the complete description of the dissolution profile of tested medicinal products, including complete drug release and leveling off the dissolution curve.


**Calculation of similarity factor.** The similarity factor \( f_2 \) was calculated using the equation:

\[
f_2 = 50 \times \log \left( \frac{100}{1 + \frac{\sum_{t=1}^{n} (Q_n(t) - Q_T(t))^2}{n}} \right),
\]

where \( n \) is the number of time points; \( R \) is the mean dissolution value for active ingredient of the reference product at time \( t \), %; \( T \) is the mean dissolution value for active ingredient of the test product at time \( t \), %.

The kinetics of dissolution of medicinal products is considered to be similar if the value of the similarity factor \( f_2 \) is in the 50—100 range.

**Calculation of difference factor.** The difference factor \( f_1 \) was used to confirm the similarity of dissolution profiles, and it was calculated using the equation:

\[
f_1 = \left( \frac{\sum_{t=1}^{n} R_T - T}{\sum_{t=1}^{n} R_T} \right) \times 100\%,
\]

where \( n \) is the number of time points; \( R \) is the mean dissolution value for active ingredient of the reference product at time \( t \), %; \( T \) is the mean dissolution value for active ingredient of the test product at time \( t \), %.

The difference factor \( f_1 \) measures the percent of error between two curves over all time points. The \( f_1 \) value is zero when the test and reference profiles are identical. The \( f_1 \) value increases as the difference between two dissolution profiles becomes greater. The kinetics of dissolution of medicinal products is considered to be similar if the value of the difference factor \( f_1 \) is in the 0—15 range.

**Results**

The averaged values for betahistine released into solution from medicinal products (%) are presented in the table. The averaged dissolution profiles for medicinal products are given in fig. 1—4. The results of betahistine release were considered reliable provided that, according to the requirements and guidelines of the above regulatory documents, the value of the relative standard deviation (RSD, %) did not exceed 10% for all time points except for the first time point where the RSD value did not exceed 20%. Also, according to regulatory documents, when more than 85% of active ingredient is released within 15 minutes the dissolution kinetics of compared medicinal products is considered as similar without mathematical evaluation.
As can be seen from the results obtained, complete release of betahistine from Betaserc, 24 mg, tablets («Mylan Laboratories SAS») occurred in all three different pH dissolution media, and corresponded to more than 85% within 15 minutes. The dissolution profiles for generic drugs in all dissolution media were significantly below 85% over a 15-minute period that attested to incomplete release of active ingredient.

Based on the results of the comparative dissolution kinetics test, Betahistine Canon, 24 mg, tablets («ZAO Raduga Production») and Betaserc, 24 mg, tablets, drugs were considered as nonequivalent in vitro in 0.1 M hydrochloric acid solution, pH 1.2 (f, 45); nonequivalent in vitro in acetate buffer solution, pH 4.5 (f, 38); nonequivalent in vitro in phosphate buffer solution, pH 6.8 (f, 41) and nonequivalent in vitro in citrate buffer solution, pH 6.8 (f, 38).

Based on the results of comparative dissolution kinetics test, Betahistine, 24 mg, tablets (OOO «Ozon») and Betaserc, 24 mg, tablets, drugs were considered as nonequivalent in vitro in 0.1 M hydrochloric acid solution, pH 1.2 (f, 31); nonequivalent in vitro in acetate buffer solution, pH 4.5 (f, 21); nonequivalent in vitro in phosphate buffer solution, pH 6.8 (f, 28) and nonequivalent in vitro in citrate buffer solution, pH 6.8 (f, 17).

Based on the results of the comparative dissolution kinetics test, Betahistine-SZ, 24 mg, tablets (ZAO «Severnaya Zvezda») and Betaserc, 24 mg, tablets, drugs were considered as nonequivalent in vitro in 0.1 M hydrochloric acid solution, pH 1.2 (f, 56); nonequivalent in vitro in acetate buffer solution, pH 4.5 (f, 57); nonequivalent in vitro in phosphate buffer solution, pH 6.8 (f, 54) and nonequivalent in vitro in citrate buffer solution, pH 6.8 (f, 57).

Based on the results of comparative dissolution kinetics test, Tagista, 24 mg, tablets (OOO «Hemofarm») and Betaserc, 24 mg, tablets, drugs were considered as nonequivalent in vitro in 0.1 M hydrochloric acid solution, pH 1.2 (f, 40); nonequivalent in vitro in acetate buffer solution, pH 4.5 (f, 48); nonequivalent in vitro in phosphate buffer solution, pH 6.8 (f, 34) and nonequivalent in vitro in citrate buffer solution, pH 6.8 (f, 38).

**Discussion**

The results of this study confirm a faster release rate of reference product Betaserc, 24 mg, tablets over the generic versions of betahistine, namely, Betahistine Canon, 24 mg, tablets (ZAO «Raduga Production»), Betahistine, 24 mg, tablets (OOO «Ozon»), Betahistine-SZ, 24 mg, tablets (ZAO «Severnaya Zvezda») and Tagista, 24 mg, tablets (OOO «Hemofarm») when they were evaluated for active ingredient release in all dissolution media regardless of pH. It was the reference product that consistently demonstrated complete release of active ingredient starting from 10 min of dissolution whereas for the majority of generics the 85% limit appeared to be overcome only at 30 min (except for Betahistine-SZ, 24 mg, tablets: release is 80.31% in phosphate buffer, pH 6.8, 30 min). These results suggest that administration of similar doses of betahistine from different manufacturers may result in variation in drug bioavailability and, hence, in plasma drug concentrations. At the same time, according to

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Indicating average values (%) of betahistine release into solution from different study drugs, using the dissolution kinetics test.

<table>
<thead>
<tr>
<th>Time, min.</th>
<th>Betahistine Canon, 24 mg, tablets</th>
<th>Betahistine, 24 mg, tablets</th>
<th>Betahistine-SZ, 24 mg, tablets</th>
<th>Tagista, 24 mg, tablets</th>
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ЖУРНАЛ НЕВРОЛОГИИ И ПСИХИАТРИИ, 11, 2018
several studies, clinical effect of betahistine is dose-dependent and requires a sufficient concentration of the drug in the plasma. Therefore, a higher bioavailability of the reference drug due to the composition of its dosage form may suggest a better clinical response. C. Adrion et al., 2016, showed the recommended daily dose of betahistine of 48 mg/kg is probably ineffective in patients with Meniere’s disease [18] whereas higher doses can significantly reduce the frequency of vertigo episodes [19]. B. Tighilet et al, 2018 studied pharmacokinetics and pharmacodynamics of different doses of betahistine in cats and demonstrated that low-dose betahistine (0.2 mg/kg) does not influence the postural restoration while causing an acute symptomatic effect manifesting in rapid (within 4—6 days) improvement of body balance. High-dose betahistine (2 mg/kg) caused both acute effect and significant acceleration of the postural restoration, as well as significantly increased histaminergic activity in histamine neurons in the tuberomamillary nucleus [20]. Some other studies in animal models demonstrated a similar dose-dependent effect of betahistine causing an increased blood flow in cochlear capillaries [10]. According to these authors, successful pharmacotherapy with betahistine rests on achieving maximum plasma concentrations which suggests optimal effectiveness of a drug with the highest possible bioavailability. Faster release rate of betahistine from a reference drug demonstrated in the dissolution kinetics test suggests that the composition of dosage form of Betaserc®, 24 mg, tablets («Mylan Laboratories SAS») is an optimal pharmacotherapeutic agent among those used in the treatment of vertigo.

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REFERENCES


