Global Journal of Medical Research: B
Pharma, Drug Discovery, Toxicology & Medicine
Volume 22 Issue 2 Version 1.0 Year 2022
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Quantitative Determination of Ethyl Methyl Hydroxypyridina Succinate in the Preparation Seroxidol and its Bioequivalence

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Research on the need for new drugs for those neurological disorders in Uzbekistan has been done and successfully produced an injectable solution of Seroxidol.

This drug is an inhibitor of free radical processes and a membrane protector with antihypoxic, stress-protective, nootropic, anticonvulsant and anxiolytic effects. Seroxidol increases the resistance to the effects of various damaging factors (shock, hypoxia and ischaemia, cerebral circulation disorders, alcohol intoxication and antipsychotic drugs with neuroleptics) and improves the functional state of the ischaemic myocardium. It effectively restores myocardial contractility in cases of reversible cardiac dysfunction. Seroxidol contains ethyl methyl hydroxypyridine succinate and sodium metabisulfite.

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GJMR-B Classification: *DDC Code: 616.105 LCC Code: RC691*

Strictly as per the compliance and regulations of:

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Keywords: seroxidol, factor, antioxidant, toxicity, diuresis, blockade, intensity.

I. Introduction

Modern world requires people to adapt to the increased stress on the psyche associated with economic and political instability, social problems, and man-made and environmental factors, which together lead to the development of urban stress, accompanied by fatigue, irritability, tension and even unmotivated hatred and aggression [1].

When the body is under the influence of extreme environmental factors, both physiological shifts and psychological changes of varying degrees of severity can occur, with a pattern of manifestations commonly including a kind of "blockade" of cognitive processes, in which the volume of perception narrows, synthesis processes in thinking are disrupted, and purposeful behaviour becomes disorganized [2].

Accordingly, the discovery, development and use of drugs that increase stress resistance, resistance to pathogenic factors and work capacity and that activate mental activity, the ability to concentrate and learn, with minimal side effects, is an urgent task in pharmacology[8].

The domestic drug Seroxidol, injected as a 50 mg/ml solution, has pronounced antioxidant, antihypoxic and membranotropic effects.

Purpose of the study: This study pursued the development of a method for the quantitative determination of ethyl methyl hydroxypyridine succinate by UV spectrophotometry of the drug Seroxidol in a 50 mg/ml solution for injection and its bioequivalence.

II. Materials and Methods

Class A volumetric glassware was used in the work: conical flasks of 50 ml and 100 ml, volumetric pipettes, an AS-220/X ser # B635963283 analytical balance (Ohaus, Germany), a SHIMADZU UV-1900UV spectrophotometer, and cuvettes with a thickness of 10 mm.

The object of the study was injection solutions corresponding to the TPA Seroxidol, a 50 mg/ml solution for injection. Determination was carried out by UV spectrophotometry.

The acute toxicity of the preparations was studied in 60 white mice of both sexes, weighing 19-21 g. From the compared preparations Seroxidol produced by LLC "MEDIOFARM", Uzbekistan and "Mexidol®" produced by LLC "Ellara", Russia, a 2.5% solution was prepared and administered to the mice once intravenously at doses of 150 mg/kg, 175 mg/kg, 200 mg/kg, 225 mg/kg and 250 mg/kg (0.12-0.2 ml) [3].

The animals were kept under continuous observation during the first hour, then under hourly observation throughout the first day of the experiment and once a day for the next 13 days of the experiment.

As indicators of the functional state of animals, the general condition of the mice and their behaviour, the intensity and nature of the motor activity, the presence of seizures, coordination of movements, reaction to external stimuli and tone of skeletal muscles, appetite, body weight, and number and consistency of faecal masses were monitored[7].

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During the experiment, the clinical state of the animals was monitored: the presence/absence of signs of poisoning, the time of their appearance, and death.

All experimental animals were kept under standard conditions on a common diet with free access to water and food [3].

After completion of the experiment, the average lethal doses (LD50) were determined [5].

III. Results and Discussion

Two millilitres of the medicine were placed in a volumetric flask with a capacity of 100 ml, and the volume of the solution was brought up to the mark with 0.01 mol/l hydrochloric acid and stirred.

Next, 1.0 ml of the resulting solution was placed in a 100 ml volumetric flask, and the volume of the solution was brought to the mark with 0.01 mol/L hydrochloric acid and mixed (test solution).

The optical density of the resulting solution was measured on a spectrophotometer at the absorption maximum at a wavelength of 297 nm in a cuvette with a layer thickness of 10 mm, using 0.01 mol/L hydrochloric acid as a reference solution.

$$X = \frac{D_1 x a_0 x\ 1\ x\ 100\ x\ 100\ x\ P\ x\ (100 - W)}{D_0 x\ 2\ x\ 1\ x\ 100\ x\ 1\ x\ 100\ x\ 100\ x\ 100} = \frac{D_1 x a_0 x\ P\ x\ (100 - W)}{D_0 x\ 20000},$$

where:

D_1- optical density of the test solution;

D_0- optical density of the working standard solution of ethyl methyl hydroxypyridine succinate;

A_0- weighed portion of WS of ethyl methyl hydroxypyridine succinate, g;

P- content of the main ingredient ethyl methyl hydroxypyridine succinate in the WS of ethyl methyl hydroxypyridine succinate, %;

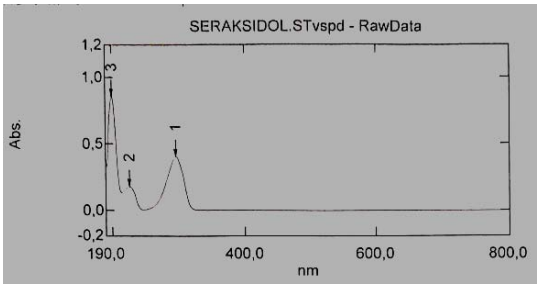
W- moisture content in the WS of ethyl methyl hydroxypyridine succinate, in %.

The content of C12H47NO5 (ethyl methyl hydroxypyridine succinate) in 1 ml of the preparation should be from 0.045 to 0.055 g.

Preparation of WS of ethyl methyl hydroxypyridine succinate: Approximately 0.1 g (accurately weighed) of ethyl methyl hydroxypyridine succinate was placed in a volumetric flask with a capacity of 100 ml, and 50.0 ml of 0.01 mol/l hydrochloric acid solution was added.

After the complete dissolution of the sample, the volume of the solution was brought to the mark with the same solvent and mixed. Then, 1.0 ml of the resulting solution was placed in a 100 ml volumetric flask, the volume of the solution was brought to the mark with the same solvent, and the solution was mixed. One millilitre of WS contained approximately 0.00001 g of ethyl methyl hydroxypyridine succinate.

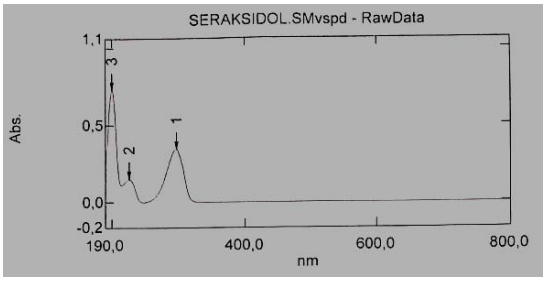
The solution must be freshly prepared. The data obtained are presented in Figures 1, 2 and 3.



[Peak Pick Table]
Threshold: 0,001000
Number of Points: 4

No.	P/V	Wavelength nm.	Abs.	Description
1	↑	296,0	0,403	
2	↑	226,0	0,179	
3	↑	200,0	0,855	
4	↓	247,0	0,006	
5	↓	214,0	0,133	

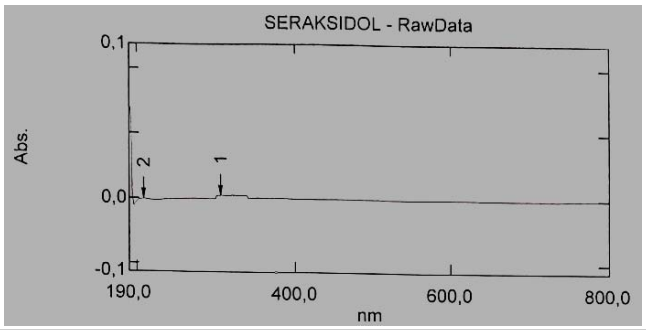
Fig. 1: Typical spectrum of a standard sample of the tested succinate



[Peak Pick Table]
Threshold: 0,001000
Number of Points: 4

No.	P/V	Wavelength nm.	Abs.	Description
1	↑	297,0	0,345	
2	↑	226,0	0,148	
3	↑	200,0	0,731	
4	↓	350,0	-0,003	
5	↓	247,0	-0,001	
6	↓	214,0	0,109	

Fig. 2: Spectrum of the product ethyl methyl hydroxypyridine, Seroxidol



[Peak Pick Table]
Threshold: 0,001000
Number of Points: 4

No.	P/V	Wavelength nm.	Abs.	Description
1	↑	306,0	0,003	
2	↑	209,0	-0,000	
3	↓	225,0	-0,001	
4	↓	196,0	-0,006	

Fig. 3: Spectrum of the "placebo" solution

Table 1: The results of the quantitative determination of the medicine Seroxidol

X_i, %	$\overline{X}$,%	f	S^2	S	$\Delta\overline{X}$	$\overline{\varepsilon}$,%
X_1=0.049 X_2=0.047 X_3=0.051 X_4=0.050 X_5=0.050	0.049	4	0.0000023	0.00152	0.0042	3.812

Experiments have shown that after a single intravenous administration of the Seroxidol preparation, produced by MEDIOFARM LLC, Uzbekistan, and Mexidol®, produced by Ellara LLC, Russia, at a dose of 150 mg/kg, no visible changes were observed in the behaviour and functional state of the animals.

All mice were active and responded to external stimuli, and food and water consumption was normal. No pathological changes in the hair and skin, diuresis, no diuresis, and no changes in the consistency and amount of faeces were observed. No signs of intoxication were observed. In this group, until the end of the experiment, no deaths were observed among the animals.

When the drugs were administered at a dose of 175 mg/kg, the mice developed clonic-tonic seizures, 1 mouse died in the generic group, and 2 mice died in the comparison group. [4]

When the drugs were administered at a dose of 200 mg/kg, a decrease in motor activity, rapid breathing, impaired coordination of movements, a weakening of the reaction to external stimuli, and a decrease in food and water consumption were observed in experimental animals. Three mice died in the comparison group.

At a dose of 225 mg/kg, the animals ceased to respond to external stimuli, and no food or water consumption was observed. During the experiment, 5 individuals in each group died [4].

The administration of a dose of 250 mg/kg of either Seroxidol produced by LLC "MEDIOFARM", Uzbekistan, or "Mexidol®" produced by LLC "Ellara", Russia, caused the immediate death of some animals after the administration of the medicine. By the end of the experiment, the condition of the surviving animals returned to normal as the signs of intoxication decreased. The LD50 of the drug Seroxidol produced by LLC "MEDIOFARM", Uzbekistan, was 200.0 (188.7 ÷ 211.1) mg/kg. The LD50 of the drug "Mexidol®" produced by LLC "Ellara", Russia, was 193.9 (178.5 ÷ 209.6) mg/kg. The acute toxicities of the compared drugs are shown in Table 2.

Table 2: Determination of the acute toxicity (LD50) of Seroxidol preparations produced by MEDIOFARM LLC, Uzbekistan, and Mexidol® manufactured by Ellara LLC, Russia

№ animals	Seroxidol produced by LLC "MEDIOFARM", Uzbekistan					"Mexidol®" produced by LLC "Ellara", Russia				
	weight, g	dose		method of administration	lethality	weight, g	dose		way introduction	lethality
		mg/kg	ml				mg /kg	ml		
1 2 3 4 5 6	21 20 21 20 20 21	150	0.13 0.12 0.13 0.12 0.12 0.13	i/v	No No No No No No	21 20 19 21 21 19	150	0.13 0.12 0.11 0.13 0.13 0.11	i/v	No No No No No No
1 2 3 4 5 6	20 19 19 19 20 21	175	0.14 0.13 0.13 0.13 0.14 0.15	i/v	No death No No No No	20 20 21 19 20 19	175	0.14 0.14 0.15 0.13 0.14 0.13	i/v	No death No death No No
1 2 3 4 5 6	21 20 19 19 20 20	200	0.17 0.16 0.15 0.15 0.16 0.16	i/v	death death No death No No	21 20 21 19 21 21	200	0.17 0.16 0.17 0.15 0.17 0.17	i/v	death No death No No death
1 2 3 4 5 6	19 19 20 20 21 21	225	0.17 0.17 0.18 0.18 0.19 0.19	i/v	death No death death death death	20 21 20 21 19 21	225	0.18 0.19 0.18 0.19 0.17 0.19	i/v	death death death No death death
1 2 3 4 5 6	20 1921 20 2019	250	0.20 0.19 0.21 0.20 0.20 0.19	i/Av	death death death death death death	21 2120 19 2121	250	0.21 0.21 0.20 0.19 0.21 0.21	i/v	death death death death death death
LD_{50}		200.0 (188.7÷211.1) mg/kg				193.9 (178.5÷209.6) mg/kg				

IV. Conclusion

This method was carried out in accordance with the requirements of the TPA. One millilitre of the drug Seroxidol contained 0.049 mg of ethyl methyl hydroxypyridine succinate.

Thus, the data obtained show that the preparations Seroxidol (50 mg/ml solution for injection) produced by "MEDIOFARM" LLC (Uzbekistan) and "Mexidol®" (50 mg/ml solution for injection)produced by "Ellara" LLC, (Russia) at 5 ml each are biologically equivalent in terms of acute toxicity.

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