COMPARATIVE EVALUATION OF ACUTE TOXICITY AND PHARMACOLOGICAL ACTIVITY OF THE "ZUMAGRAST" PREPARATION IN COMPARISON WITH THE REFERENCE DRUG "ZARSIO®"

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Abstract

Background: The development of locally manufactured biopharmaceuticals in the Republic of Uzbekistan requires comprehensive preclinical evaluation of their safety, pharmacological activity, and therapeutic equivalence to internationally recognized reference products. Granulocyte colony-stimulating factor (G-CSF) preparations play a pivotal role in the prevention and treatment of neutropenia associated with cytotoxic chemotherapy, radiation exposure, and various immunopathological conditions.

Objective: This study aimed to conduct a comparative assessment of the acute toxicity and specific pharmacological activity of the locally produced recombinant G-CSF preparation "Zumagrast" and the reference drug "Zarsio®" (Sandoz GmbH, Austria).

Methods: Acute toxicity was evaluated in white laboratory mice following intravenous administration of both preparations at doses of 3, 9, and 15 mg/kg, with a 14-day observation period. Pharmacological activity was assessed in rabbits using an experimental leukocytosis model, based on quantitative changes in peripheral leukocyte counts.

Results: Both preparations were well tolerated at all tested doses. No mortality or severe toxic manifestations were observed, even at the maximum dose. The median lethal dose (LD_{50}) for both drugs exceeded 15 mg/kg, indicating low acute toxicity. In the

experimental leukocytosis model, administration of “Zumagrast” and “Zarsio®” resulted in a statistically significant restoration of leukocyte levels toward physiological values, demonstrating comparable biological activity.

Conclusion: The results confirm that “Zumagrast” exhibits a safety profile and pharmacological efficacy comparable to the reference drug “Zarsio®”. The demonstrated biological equivalence supports the potential clinical use of “Zumagrast” as a safe and effective domestic alternative to imported G-CSF preparations.

Introduction: In contemporary clinical practice, the correction of leukopenic and neutropenic conditions induced by cytostatic chemotherapy, ionizing radiation, and immune-mediated disorders remains a critical therapeutic challenge. Recombinant granulocyte colony-stimulating factor (G-CSF) preparations constitute one of the cornerstone therapies for both prevention and treatment of neutropenia.

Against the backdrop of rapid development of the pharmaceutical industry in Uzbekistan, preclinical investigations aimed at substantiating the safety, efficacy, and biological equivalence of domestically produced drugs relative to established foreign analogues are of particular importance. Such studies form the scientific basis for import substitution and ensure compliance with international regulatory and publication standards.

The present study was designed to comparatively evaluate the acute toxicity and specific pharmacological activity of the locally manufactured G-CSF preparation “Zumagrast” and the reference drug “Zarsio®” produced by Sandoz GmbH.

Materials and Methods

Study Drugs

The following preparations were investigated: - **Zumagrast**, solution for injection, 30 million IU / 0.5 mL (Uzbekistan); - **Zarsio®**, solution for intravenous and subcutaneous administration, 30 million IU / 0.5 mL (Sandoz GmbH, Kundl, Austria).

All experimental procedures were conducted in accordance with international bioethical standards and methodological guidelines for preclinical studies of medicinal products.

Acute Toxicity Study

Acute toxicity was assessed in 36 white laboratory mice weighing 19–21 g. Animals were acclimatized under standard vivarium conditions for 14 days prior to experimentation. The study consisted of two series corresponding to the administration of “Zumagrast” and “Zarsio®”, respectively.

Animals were divided into groups of six and received a single intravenous injection of the test drugs at the following doses: - 3 mg/kg (0.1 mL), - 9 mg/kg (0.3 mL), - 15 mg/kg (0.5 mL).

Clinical observations were performed hourly on the first day, every three hours on the second day, and daily thereafter for 14 days. The following parameters were monitored: general condition, behavior, locomotor activity, skin and fur condition, respiratory and cardiovascular function, food intake, body weight, and mortality.

Pharmacological Activity Study

Pharmacological activity was evaluated in 16 rabbits weighing 2000–2400 g, divided into four groups: 1. Intact group; 2. Control group (leukocytosis + NaCl); 3. Leukocytosis + Zumagrast; 4. Leukocytosis + Zarsio®.

Experimental leukocytosis was induced by intraperitoneal injection of 5 mL of boiled milk diluted 1:1 with physiological saline. Peripheral blood leukocyte counts were determined using a Goryaev counting chamber.

Results: Acute Toxicity

No pathological or significant physiological changes were observed in animals receiving 3 or 9 mg/kg of either preparation. At the dose of 15 mg/kg, a transient state of mild lethargy lasting approximately 30–40 minutes was noted, which resolved spontaneously within one hour. No deaths were recorded in any group.

The LD_{50} value for both “Zumagrast” and “Zarsio®” exceeded 15 mg/kg, confirming their low acute toxicity and high safety margin.

Pharmacological Activity

In the control group, leukocyte counts decreased by 46.4% compared with intact animals. Administration of "Zumagrast" resulted in restoration of leukocyte levels to 4.6 ± 0.5 ×10³/μL ($p < 0.05$), corresponding to 76% of normal values. In the "Zarsio®" group, leukocyte counts reached 5.0 ± 1.0 ×10³/μL ($p < 0.05$), equivalent to 92% of normal levels.

These findings indicate a pronounced and statistically significant biological activity of both preparations, with comparable efficacy in restoring leukopoiesis.

Discussion: The obtained data demonstrate that the safety profile of "Zumagrast" is comparable to that of the reference drug "Zarsio®". The absence of lethal outcomes and severe toxic effects even at the highest tested dose indicates a favorable toxicological profile. Furthermore, the pharmacological activity study confirmed the ability of "Zumagrast" to effectively normalize leukocyte counts under experimental leukocytosis conditions. The comparable efficacy of "Zumagrast" and "Zarsio®" supports the classification of the domestic preparation as a biologically equivalent analogue of the imported reference drug, with potential for broad clinical application.

Conclusion: "Zumagrast" and "Zarsio®" are biologically equivalent with respect to acute toxicity parameters, both exhibiting an LD_{50} greater than 15 mg/kg. Under conditions of experimental leukocytosis, both drugs demonstrate pronounced pharmacological activity in restoring leukocyte levels. "Zumagrast" may therefore be considered a safe, effective, and therapeutically equivalent domestic alternative suitable for clinical use.

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