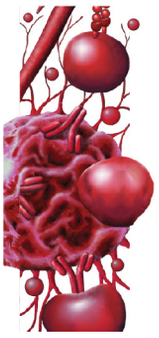
Research Article

Immunotherapy



The safety profile of Polyoxidonium in daily practice: results from postauthorization safety study in Slovakia

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Aim: This study assessed the safety of Polyoxidonium® 6 mg lyophilisate for solution for injection in routine practice with a special focus on signs or symptoms of potential adverse renal effects. **Materials & methods:** A local, multicenter, prospective, open-label, noninterventional, uncontrolled postauthorization safety study was conducted in 15 healthcare centers in Slovakia. Adult patients who received commercially available Polyoxidonium 6 mg lyophilisate for solution for injection as a part of their routine care were observed for one cycle of treatment, consisting of five or ten injections. For safety assessment, adverse events were monitored with a special focus on signs or symptoms of potential adverse renal effects. At the end of the study, investigators and subjects rated the overall tolerance of Polyoxidonium treatment as well as improvement. Data collection was based on the review of medical records and routine examination of subjects. **Results:** In total, 502 subjects were enrolled and 498 (99.2%) subjects completed the study. 19 (3.8%) subjects experienced a total of 34 adverse events. Only one (0.1%) subject experienced eight adverse drug reactions (ADRs): restlessness, fatigue, feeling hot (n = 2), pyrexia (n = 3) and asthenia. There were no renal ADRs or serious ADRs. At the end of the study, both investigators and subjects very positively rated global tolerability and global improvement. **Conclusion:** Polyoxidonium was well tolerated in the heterogenous population of patients, mostly with chronic recurrent bacterial or viral infections. No renal ADRs were reported in this postauthorization safety study, which was designed with a special focus on identifying potential adverse renal effects.

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The conventional management of infectious diseases includes vaccination and treatment with antibacterial or antiviral agents. Due to safety issues of these treatment modalities as well as emerging resistance, scientific efforts have been directed into developing novel treatment modalities that nonspecifically manipulate the host's immune system [1,2]. The mode of action of immunomodulators includes augmentation of the anti-infectious immunity by the cells of the immune system (i.e., lymphocytes, macrophages and natural killer cells), also induction or restoration of immune effector functions [2]. Currently available immunomodulators include synthetic agent inosine pranobex [3], pidotimod [4], immunoglobulins [6], bacterial lysates and extracts [7], thymus extract preparations [2], extracts of *Echinacea purpurea* [8], etc. The potential of immunomodulators in the treatment of allergic diseases has also been explored [9,10].

A unique synthetic immunomodulator azoximer bromide was developed by the Institute of Immunology of the Ministry of Health of the Russian Federation. Azoximer bromide is a copolymer of N-oxidized 1,4-ethylenepiperazine and (N-carboxyethyl)-1,4-ethylenepiperazine bromide. In addition to immunomodulatory effects, azoximer bromide exhibits antioxidant and antiinflammatory properties [11–13]. The efficacy and safety of azoximer bromide has been assessed in patients with various diseases accompanied by secondary immunodeficiency, including acute and recurrent infections and allergic conditions.

Future Medicine

Azoximer bromide was first launched under the brand name Polyoxidonium® in Russian Federation in 1996 and subsequently, it was authorized across CIS countries (Armenia, Belarus, Kazakhstan, Kyrgyzstan, Moldova and Uzbekistan), Georgia, Ukraine, Kuba and Slovakia. Various pharmaceutical formulations of Polyoxidonium are currently available, including lyophilisate for solution for injection, tablets, vaginal and rectal suppositories. In Slovakia, Polyoxidonium 6 mg lyophilisate for solution for injection has been authorized since 2002 for the treatment of diseases accompanied by secondary immunodeficiency in adults, including acute and recurrent infections, allergies, septic conditions, postsurgical complications and treatment-induced immune deficiency [14].

Polyoxidonium lyophilisate for solution for injection is well tolerated. No safety concerns were identified during clinical development and through routine postauthorization pharmacovigilance activities. A number of published clinical studies reported no adverse reactions in Polyoxidonium-treated patients suffering from various conditions, including bronchial asthma [15–18], chronic recurrent herpes simplex infections [19], pneumonia [20], pyelonephritis [21], recurrent urogenital chlamydial infections [22,23] and atopic dermatitis [15]. However, data from acute and subacute toxicity studies in rodents and chronic toxicity studies in dogs showed nephrotoxic effects, which occurred at azoximer bromide doses well above the maximum recommended human dose (MRDH). Nephrotoxic effect was observed in dogs after 40 daily injections or 3-month treatment at doses of 1 mg/kg (ten-times the MRDH) and in rats after 15 daily injections at doses as high as 25 mg/kg (100-times the MRDH) (data on file). Azoximer bromide is excreted predominantly by the kidneys, which further implies a potential risk of renal injury.

To investigate if the safety information from animal studies might be of concern in humans, the Marketing Authorization Holder Medigroup s.r.o. (Bratislava, Slovak Republic) and the Manufacturer NPO Petrovaxpharm (Moscow, Russian Federation) voluntary undertook a noninterventional postauthorization safety study (PASS). This PASS aimed to collect data on the safety of Polyoxidonium in patients, for whom the medicine was prescribed in routine practice in accordance with the terms of the marketing authorization. The special focus of this PASS was on signs or symptoms of potential adverse renal effects.

Methods

This PASS was a local, multicenter, prospective, open-label, noninterventional, uncontrolled study, conducted by immunologists and allergologists in 15 centers in Slovakia. The study was approved by the Slovakia State Institute for Drug Control and Ethics Committee of Bratislava Self-Governing Region. All patients had to give their written informed consent. The protocol and final report of this PASS was entered into the European Union electronic Register of Post-Authorisation Studies (EU PAS Register number ENCEPP/SDPP/12387).

The patients were eligible for inclusion if they were at least 18 years old and were prescribed Polyoxidonium in accordance to the current Summary of Product Characteristics (SmPC) (i.e., for the treatment of any of the following diseases or conditions accompanied by secondary immunodeficiency: chronic recurrent bacterial infection; chronic recurrent viral infection; acute bacterial infection; acute viral infection; allergic disease with complicated infection). The patients could not participate if they had any contraindication to Polyoxidonium (i.e., known hypersensitivity to azoximer bromide or any of the excipients of Polyoxidonium; pregnancy or breast feeding; a woman of childbearing potential not using an effective contraception method); if they were prescribed more than ten injections of Polyoxidonium per a single treatment course; had any clinically significant underlying medical illness, condition or disorder that could interfere with the conduct of the study; or participated in another investigational study at the same time or within the past 4 weeks.

All patients received commercially available Polyoxidonium 6 mg lyophilisate for solution for injection as a part of their routine care. Each patient was observed for one cycle of treatment, consisting of five or ten injections depending on the disease (a disease that was the reason of Polyoxidonium prescription is further referred as a disease of interest). Thus, study duration and number of visits for individual patient coincided with routine visits to receive Polyoxidonium injections at the healthcare center. At 7 (±1) days after the last injection (this period corresponds to five half-lives of azoximer bromide), a telephone follow-up was conducted. In addition, if any visit (scheduled or unscheduled) occurred within 7 days after the last injection of Polyoxidonium as a part of routine practice, information on adverse events (AEs) was recorded.

Primary treatment of a disease, Polyoxidonium administration, diagnostic procedures and assessments as well as visits schedule were left at the discretion of investigators, according to local guidelines and routine clinical practices.

Data collection was based on the review of medical records and routine examination of patients. At the end of study, investigators and patients were asked to assess treatment tolerability as well as improvement.

Table 1. Demographic and clinical characteristics at baseline.

Characteristics	n (%)
Gender, n (%)	
– Men	142 (28.3)
– Women	360 (71.7)
Age (years), mean ± SD	44.9 ± 15.2
Indications for Polyoxidonium® prescription, n (%)	
– Chronic recurrent bacterial infection	194 (38.6)
– Chronic recurrent viral infection	209 (41.6)
– Acute bacterial infection	18 (3.6)
– Acute viral infection	23 (4.6)
– Allergic disease accompanied by secondary immonudeficiency	58 (11.6)
Patients who previously received Polyoxidonium, n (%)	86 (17.1)
Polyoxidonium exposure	
Number of injections prescribed, n (%)	
– 5	159 (31.7)
– 10	342 (68.1)
Treatment duration (days), mean ± SD	21.8 ± 8.3
Number of doses taken, mean ± SD	8.5 ± 2.4
Total dose (mg), mean ± SD	50.6 ± 14.4

The main events of interest in this study were adverse renal effects. In the case of suspected adverse renal effect, investigators were encouraged to apply clinical judgement, to perform diagnostic workup and collect as much data as possible to confirm or reject the diagnosis of renal impairment. An independent assessor was assigned to review the data collected on a suspected adverse renal effect and to make a final adjudicated conclusion about its qualification as the event of interest. Other safety outcome measures included AEs, adverse drug reactions (ADRs), global assessment of tolerability by patients and investigators. Adverse event was defined as any untoward medical occurrence in a patient administered Polyoxidonium and which did not necessarily had to have a causal relationship with this treatment [24]. Any AE that was assessed by the investigator as related to the treatment with Polyoxidonium was considered an ADR. Clinical benefit assessment included global assessment of improvement by patients (0–4 scale: 0 = much worse; 1 = somewhat worse; 2 = same; 3 = somewhat improved; 4 = greatly improved) and investigators (0 to 5 scale: 0 = worse; 1 = no appreciable improvement; 2 = slight improvement; 3 = moderate improvement; 4 = marked improvement; 5 = complete resolution).

The descriptive statistics were applied for data analysis. Analyses were performed using IBM SPSS Statistics V22.

Results

Baseline patient demographics & clinical characteristics

A total of 502 patients were recruited between June 2016 and December 2016. A total of 498 (99.2%) patients completed the study. Four patients (0.8%) did not complete the study: two patients were withdrawn due to AEs, one was lost to follow-up and one withdrew consent. Table 1 shows the baseline demographic and clinical characteristics of study population. The patients were mostly female, the mean age was 44.9 years. Most of the patients were prescribed Polyoxidonium because of chronic recurrent viral or bacterial infections (Table 1). Respiratory tract infections were the most common reason for Polyoxidonium prescriptions.

Exposure to Polyoxidonium

During the study period, the mean duration of treatment with Polyoxidonium was 21.8 ± 8.3 days (Table 1). Dosing regimens were various, ranging from once daily to once weekly injections. A total of 86 (17.1%) patients had previously received at least one cycle of Polyoxidonium treatment (range: one to ten treatment cycles; mean, 2.9 ± 2.2 cycles).

Nearly half of patients (42.6%) took concomitant medications, but only 69 (13.7%) patients took medications for the primary treatment of disease of interest.

Tolerability

Polyoxidonium was very well tolerated. Over the course of the study, 19 (3.8%) patients reported a total of 34 AEs. Only one (0.1%) patient experienced eight ADRs (Table 2), none of those ADRs was serious. Elevated body

Table 2. Number, rate of occurrence and severity of adverse drug reactions.

Adverse drug reaction	n (%)	Severity
Psychiatric disorders		
Restlessness	1 (0.2%)	Mild
General disorders and administration site conditions		
Fatigue	1 (0.2%)	Moderate
Feeling hot	2 (0.4%)	Mild
Pyrexia	3 (0.6%)	Mild
Asthenia	1 (0.2%)	Mild

Table 3. Assessment of Polyoxidonium tolerability at the end of study by investigators and patients.

Tolerability	Investigators' assessment n (%)	Subjects' assessment n (%)
Very good	400 (79.7)	378 (75.3)
Good	97 (19.3)	106 (21.1)
Moderate	2 (0.4)	1 (0.2)
Poor	1 (0.2)	1 (0.2)
Missing data	2 (0.4)	16 (3.2)

temperature and restlessness are listed in the current SmPC of Polyoxidonium as very rare undesirable effects.

There were no renal ADRs. At enrollment, one patient had elevated serum creatinine. This patient received the full treatment course with Polyoxidonium and repeated laboratory tests showed no significant changes in serum creatinine values.

At the end of study, both investigators and patients very positively rated global tolerability of Polyoxidonium. The tolerability of Polyoxidonium was ranked as 'good' or 'very good' by 99.0% of investigators and 96.4% of patients (Table 3).

Clinical benefit

As judged by investigators, complete disease resolution occurred in 26.1% of patients, marked improvement was observed in 56.0% of patients. The patients also assessed their own improvement very positively – over 90% of patients reported improvement. Analysis of global improvement assessments by therapeutic indications showed that there were numerically less subjects with physician assessment score 'complete resolution' among subjects with acute infections or allergic diseases accompanied by secondary immonudeficiency to compare to those with chronic infections (Table 4).

A quarter of patients (24.9%) had ongoing symptoms of disease of interest at the time Polyoxidonium was prescribed. A large variety of symptoms were reported, the most common being cough (5.4%), oropharyngeal pain (2.2%) and fatigue (2.6%). Out of 343 symptoms reported, 155 (45.2%) symptoms resolved, 186 (54.2%) – improved and only 2 (0.6%) symptoms worsened during the study period.

Discussion

This study assessed the safety of Polyoxidonium 6 mg lyophilisate for solution for injection in a real-life world, with a special focus on potential adverse renal effects. Overall, Polyoxidonium was well tolerated in the heterogeneous population of patients who received the treatment in accordance with the terms of the marketing authorization, with over 95% of both investigators and patients rating treatment tolerability as 'good' or 'very good'. None of patients experiences any renal ADR, suggesting that renal effects seen in animal studies seem to be absent in patients taking therapeutic doses of Polyoxidonium. Only one (0.1%) patient experienced eight ADRs (restlessness, feeling hot (n = 2), pyrexia (n = 3), fatigue and asthenia), most of which were mild.

The data obtained in this study add further evidence on the favorable safety profile of Polyoxidonium. In clinical studies, Polyoxidonium lyophilisate for solution for injection was well tolerated, with only few reports on painful injections or pain at injection site. Skin redness, induration, slight elevation of the temperature, restlessness and tremor within the first hour after administration are undesirable effects listed in the current product information.

Table 4. Assessment of global improvement at the end of study by investigators and patients, n (%).

	All subjects	Chronic recurrent bacterial infection	Chronic recurrent viral infection	Acute bacterial infection	Acute viral infection	Allergic disease accompanied by secondary immonudeficiency
Investigators' assessment						
Complete resolution	131 (26.1)	52 (27.1)	68 (32.5)	2 (11.1)	1 (4.3)	8 (13.8)
Marked improvement	281 (56.0)	91 (47.4)	119 (56.9)	13 (72.2)	20 (87.0)	38 (65.5)
Moderate improvement	73 (14.5)	44 (22.9)	16 (7.7)	3 (16.7)	1 (4.3)	9 (15.5)
Slight improvement	11 (2.2)	4 (2.1)	3 (1.4)	0	1 (4.3)	3 (5.2)
No appreciable improvement	4 (0.8)	1 (0.5)	3 (1.4)	0	0	0
Subjects' assessment						
Greatly improved	180 (35.9)	71 (37.4)	83 (40.5)	7 (38.9)	6 (27.3)	13 (22.8)
Somewhat improved	304 (60.6)	115 (60.5)	118 (57.6)	11 (61.1)	16 (72.7)	44 (77.2)
Same	5 (1.0)	4 (2.1)	1 (0.5)	0	0	0
Somewhat worse	2 (0.4)	0	2 (1.0)	0	0	0
Much worse	1 (0.2)	0	1 (0.5)	0	0	0

In this study, few unlisted ADRs were reported (fatigue, asthenia and feeling hot). Of note, all these ARDs occurred in a single patient, therefore further monitoring is necessary to make a final causality assessment for these events.

Since in study patients Polyoxidonium was prescribed because of various diseases, it was not possible to assess its effectiveness using objective end points. Based on subjective assessments, global improvement was highly rated. According to the opinion of investigators, complete resolution of disease or marked improvement was observed in 82% of patients. The patients assessed their own improvement also very positively – over 90% of the patients reported improvement. Out of 343 various symptoms reported at enrollment, almost all resolved or improved (99%) during the course of the study.

Some study limitations should be noted when interpreting study results. Efforts were made to ensure that study patients represented the source population (i.e., target patients of Polyoxidonium therapy) in Slovakia. Most of enrolled patients (80%) received Polyoxidonium prescription because of chronic recurrent bacterial or viral infections. The rest of the patients had acute bacterial or viral infections or allergic disease complicated by recurrent bacterial, fungal or viral infection. No data are available on Polyoxidonium prescriptions according to therapeutic indications in Slovakia, thus, it is unknown if the studied population represented target patient population. Of note, Polyoxidonium is also approved for the treatment of septic conditions, postsurgical complications and treatment-induced immune deficiency [14]. Due to potentially severe condition and polytherapy, those patients were not considered as eligible for this study.

Due to relatively small number of study patients with acute bacterial or viral infections or allergic diseases accompanied by complicated infections, it is unknown whether study results can be generalized to patients who are taking Polyoxidonium because of therapeutic indications other than chronic recurrent infections. Furthermore, the patients were observed for one cycle of treatment with Polyoxidonium and only 17% of them had previously received Polyoxidonium, thus the results obtained in this study cannot be generalized to long-term or repetitive treatment.

There were no patients with a diagnosis of renal insufficiency in the study population, thus no conclusions can be drawn regarding the safety of Polyoxidonium in patients with impaired renal function. Of note, renal function did not further deteriorate in the only subject with elevated serum creatinine at enrollment.

Conclusion

This PASS confirmed the excellent safety profile of Polyoxidonium 6 mg lyophilisate for solution for injection. When used in accordance with the terms of the marketing authorization, Polyoxidonium was well tolerated in the heterogeneous population of patients, mostly with chronic recurrent bacterial or viral infections. No renal ADRs were reported in this PASS, which was designed with a special focus on identifying potential adverse renal effects. Thus, the risk of nephrotoxicity observed in animal studies has not been confirmed in patients receiving short-term treatment with Polyoxidonium.

Summary points

- A postauthorization safety study assessed the safety of Polyoxidonium® 6 mg lyophilisate for solution for injection with a special focus on signs or symptoms of potential adverse renal effects.
- In total, 502 subjects receiving Polyoxidonium as a part of their routine care were observed for one cycle of treatment, consisting of five or ten injections.
- Polyoxidonium was well tolerated, with over 95% of both investigators and patients rating treatment tolerability as 'good' or 'very good'.
- Only one (0.1%) subject experienced eight adverse drug reactions (ADRs): restlessness, fatigue, feeling hot (n = 2), pyrexia (n = 3) and asthenia.
- There were no renal ADRs or serious ADRs.
- According to the opinion of investigators, complete resolution of disease or marked improvement was observed in 82% of the patients during the course of treatment with Polyoxidonium.

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