Healthcare Workers' Perceptions of Prophylactic Use of Azoximer Bromide and Incidence of Acute Respiratory Infections and COVID-19 Infection at Red Zone Infectious Hospitals in the Russian Federation

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Abstract

Aim: The aim of the study was to assess the prophylactic efficacy of Polyoxidonium (INN: Azoximer bromide) in healthcare workers working with patients with COVID-19.

Materials and Methods: Two confidential surveys were conducted in this study to compare the experience of self-medicated healthcare workers who used Azoximer bromide (AZB) prophylactically to those who did not. The first part of the survey consisted of 577 medical workers in one group who were self-prescribed polyoxidonium (12 mg, tablets under the tongue) once a day for 30 days. Participants who worked at the designated hospitals were provided Polyoxidonium by NPO Petrovax as an aid to protect against COVID-19. The second group consisted of 336 medical workers from the same hospital who did not receive preventive medications. For both groups, the number of acute respiratory infection (ARI) and COVID-19 diseases was assessed over the period of taking the drug and 1 month follow-up period. The first questionnaire was a paper survey that was conducted from 1 September 2020 to 15 September 2020, which was followed three months after by an electronic survey taken from 1st November 2020 and 30 November 2020. In the second part of the survey, the number of cases of ARI and COVID-19 was assessed during the period of taking the drug and 3 months after prophylactic treatment had ended. Statistical analyses were conducted which was used to compare the responses from participants who had received prophylactic treatment with AZB to those who had not received treatment.

Results: Of the 913 survey responses, 577 participants had received AZB (AZB group, 12 mg tablets, sublingual once per day (QD) for 30 days compared with 336 participants who had not received any treatment (control group). Polymerase chain reaction tests were conducted if healthcare workers showed signs symptoms of ARI. According to the data presented in the paper survey, in the period of 1 of July till 1 of September 2020 0.7% of the participants fell ill with ARI, and 0.3% participants were diagnosed with COVID-19 in the AZB group. In the control group, 12.2% of participants were diagnosed with ARI and 5.1% of participants had COVID-19. These differences in group were statistically significant ($p<0.0001$). In the second survey, 247 of 350 participants used AZB as prophylactic treatment compared with 103 participants who did not receive any treatment; the AZB and control groups showed similar characteristics.

Two-hundred and thirteen (86.9%) participants responded that they believed AZB had provided some preventative benefit and 216 (88.2%) participants expressed that they would continue to use AZB as a form of preventative treatment.

Conclusion: Preventative treatment with AZB results in fewer cases of ARI and COVID-19 in healthcare professionals both during the treatment and three months after the treatment

Introduction

Since its emergence, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19, has become a global health threat [1]. As of September 3, 2020, more than 231 million cases

of COVID-19 have been documented worldwide, with nearly 4.7 million deaths [2]. Since its emergence COVID-19 has created a substantial strain on the healthcare system, with frontline healthcare workers in patient-facing roles at increased risk of infection [3], and yet they are simultaneously essential for sustaining an adequate emergency response. Because this work requires close personal exposure to patients with SARS-CoV-2, front-line health-care workers are at high risk of infection, contributing to further spread [4]. Every effort was taken to reduce nosocomial transmission based on experience with other respiratory viruses, consistent use of personal protective equipment (PPE) and appropriate patient handling procedures. Nevertheless, as the pandemic progressed it was clear that healthcare workers were paying the price for their dedication to duty [5, 6].

During the early days of the pandemic there was no effective oral chemoprophylaxis or vaccination against COVID-19. On 23 September 2021, the Centres for Disease Control and Prevention (CDC) reported over 558, 747 cases of COVID-19 among healthcare personnel in the United States [7]. It was conceived that an effective pre-exposure prophylaxis medication that could be used by healthcare workers with repeated SARS-CoV-2 exposure, even if only partially effective, would be a powerful public health tool to reduce transmission of SARS-CoV-2 and protect frontline workers from COVID-19 [8].

While intensive efforts were being directed towards treatment discovery and vaccine development, repurposing existing medications represents a more rapid and economical approach to fulfil the urgent need for effective prophylaxis. Azoximer bromide (AZB; Polyoxidonium®: NPO Petrovax Pharm, LLC Russia) is a high-molecular weight synthetic immune modulator that increases resistance to local and general infection and is indicated for the treatment of viral infections [9]. In clinical use in the Russian Federation, Commonwealth of Independent States (both licensed in 1996) and Slovakia (licensed in 2006) [10], AZB has shown a generally well-tolerated safety profile in multiple infectious diseases of viral and bacterial aetiology [11].

The surge in cases of infections and hospital admissions in the local Kemerovo State area during the first wave of the pandemic, and the perceived risk of infection experienced by healthcare workers, saw many initiating prophylactic administration of AZB. The present study sought to record their experience in the form of a survey.

Materials And Methods

Study design

The work conducted took the form of two confidential surveys to compare the experience of self-medicated healthcare workers who used AZB prophylactically and those who did not. The study included sample responses from healthcare workers at ‘redzone hospitals’ (COVID-19 hospitals) who self-prescribed themselves AZB and who had not taken AZB in July 2020. The healthcare workers were given an option to participate in the questionnaire. The healthcare workers had direct contact with, provided

care to and performed medical examinations/manipulations on patients with COVID19, the study also included anyone cleaning the rooms occupied by patients with coronavirus infection.

Participants started to take AZB from 01 July 2020 and the first survey (Paper Survey) was conducted from 1 September 2020 to 15 September 2020. Volunteers were excluded from taking part in the survey if they had previously been diagnosed with COVID-19, tested positive for COVID-19 or various other considerations relating to their immune status and tolerance of AZB. The questions included in the survey are provided in Appendix 1. In the first survey, the number of ARI and COVID-19 cases was recorded. A second survey was conducted to extract results from both the period of taking the drug and within 3 months after the end of taking the drug which was expected to reflect differing results.

The second survey (Electronic Survey) was conducted electronically three months after the first survey (November 1 and November 30 2020) which included the same population. Questions requested information on demography, the type of institution where they were employed, the use, dose duration and dosage of AZB, if ARI developed during drug administration and 1 month later, whether they felt that AZB had served a preventative effect, if the participant would continue to take preventative treatment and how they would take AZB, if they had suffered from ARI in the last 4 months, if COVID was confirmed after a PCR test, if antibodies immunoglobulin G (IgG) to SAR-CoV-2 were detected after the disease and if they were vaccinated against influenza in 2020.

Statistical analysis

All statistical analyses were performed using STATA v.14 (StataCorp, USA). The analysis was based on the use of descriptive statistics. The mean value (Mean), standard deviation (SD), 95% confidence interval for the mean value (95% CI), minimum value (Min), maximum value (Max), median (Me), as well as the first and third quartiles (Q1 and Q3) were determined for quantitative variables; for qualitative variables, the absolute number in each category and the percentage (%) are presented.

Responses from participants who had received prophylactic treatment with AZB was compared with those who had not received treatment. Unpaired t-tests were used when comparing the groups by numeric variables, and the hypothesis was tested for the normality of distribution; chi-square test (or Fisher’s exact test, where applicable) was used when comparing the groups by qualitative variables. The level of statistical significance was taken as $p < 0.05$.

Results

Paper survey

Nine hundred and thirteen people provided survey responses. Of these, 577 participants had received AZB (AZB group, 12 mg tablets, sublingual once per day [QD] for 30 days) versus 336 participants who had not received any prophylactic treatment (control group).

Overall, the AZB and control groups showed similar characteristics in age and gender ($p > 0.05$). The median age was 43 years (range: 2459) in both the AZB and control groups. Threehundred and ten (53.8%) participants in the AZB group and 168 (50.1%) participants in the control group were female. Three-hundred and twelve (54.1%) participants in the AZB group and 121 (36.0%) participants in the control group had a chronic disease ($p < 0.0001$). Among chronic diseases in both groups, most often these were infectious and inflammatory diseases of the respiratory system. The proportion of participants vaccinated against the influenza virus in 2019 included 423 (73.4%) participants in the AZB group and 238 (70.8%) participants in the control group; this difference was not statistically significant which was not a significant difference. Similarly, the proportion of participants vaccinated against *pneumococcal* infection five years prior to study included only 39 (6.8%) participants in the AZB group and 10 (3.0%) participants in the control group.

From 1 March 2020 to 15 July 2020, 78 (13.5%) AZB group participants experienced ARI compared with 29 (8.6%) participants in the control group. However, the mean (SD) number of ARI cases that they recorded in 2019 was 1.34 (0.47; range: 12) in the AZB group and 1.24 (0.43; range: 12) in the control group. The reported incidence of ARI in groups vaccinated and not vaccinated against influenza in 2019 included 30 (12.0%) participants in the vaccinated participants group and 77 (11.7%) unvaccinated participants group; this difference was not statistically significant. Notably, 78 (18.1%) participants with a chronic disease had an ARI in 2019 compared with 29 (6.0%) participants who did not have chronic diseases ($p < 0.0001$).

Polymerase chain reaction tests were conducted if healthcare workers showed signs or symptoms of ARI. In the paper survey, in the period of 1 July to 1 September 2020, 0.7% of participants in the AZB group fell ill with ARI, and 0.3% of participants were diagnosed with COVID-19. In the control group, 12.2% of participants were diagnosed with ARI and 5.1% of participants had COVID-19. These differences in groups were statistically significant ($p < 0.0001$). Seventeen medical workers from the control group suffered from pneumonia; according to the PCR test, 15 (88.2%) cases were to be caused by COVID19. In the AZB group, two people were diagnosed with a mild case of COVID-19 (with the symptoms of mild ARVI) cases of pneumonia were not reported.

Electronic survey

The second survey was completed by 350 healthcare professionals of whom 247 had taken AZB (AZB group) and 103 had not (control group). Overall, the AZB and control groups showed similar characteristics. Mean [range] age was 41.96 [2458] years in the AZB group and 41.25 [2455] years in the control group. One-hundred and nineteen (48.2%) participants in the AZB group and 50 (48.5%) participants in the control group were female. Similarly, 128 (51.8%) participants and 53 (51.5%) participants in the AZB group and control group were male, respectively. Participants vaccinated against influenza in 2020 included 169 (68.4%) participants in the AZB group and 75 (72.8%) participants in the control group.

The number of ARI cases reported in 4 months of 2020 (from 1 of July to 30 of October) was 32 (13.1%) participants in the AZB group and 59 (57.3%) participants in the control group. This included 17 (14.4%) female participants and 15 (11.8%) male participants in the main group and 34 (68.0%) female participants and 25 (47.2%) male participants in the control group.

According to the electronic survey, 2.4% of participants were diagnosed with COVID-19 in the AZB group. In the control group, 26.2% of participants were diagnosed with COVID-19, $p = 0.01206$.

Similarly, the number of ARI cases recorded in 4 months among those vaccinated against influenza and *pneumococcus* was 9 (5.3% of the number of vaccinated, n = 169) participants in the AZB group and 38 (50.7% of the number of vaccinated, n = 75) participants in the control group ($p < 0.00001$). In comparison, the number of ARI cases recorded in 4 months among those not vaccinated included 23 (30.3% of the number of unvaccinated, n = 76) in the AZB group and 21 (75.0% of the number of unvaccinated, n = 28) in the control group ($p < 0.0000420$).

Two-hundred and thirteen (86.9%) participants responded that they believed AZB had provided some preventative benefit and 216 (88.2%) participants expressed that they would continue to use AZB as a form of preventative treatment.

Discussion

The two questionnaires conducted in self-medicated healthcare workers demonstrate fewer cases of ARI and COVID-19 in healthcare professionals, both during and three months after AZB prophylactic treatment. These findings were supported by other studies where the use of AZB in medical workers led to an increase in the local immune defence of the nasopharyngeal mucosa which was associated with a decrease in the incidence of SARS and COVID-19 [12]. Similar studies conducted in the Chuvashia Republic reported that 51/52 healthcare professionals who took AZB prophylactically remained symptom free and tested negative for COVID19 during the 5-month dosing period [13].

In this study all participants worked in hospitals that were considered to be in the ‘red zone’ i.e. COVID-19 hospitals. The healthcare professionals in the study who used AZB self-administered the study drug as prophylactic treatment. Participants in the AZB group had a higher rate of chronic diseases compared with the control group and sought additional protection against contracting COVID-19.

The survey outcome showed that the majority of healthcare participants (86.9%) in the questionnaire considered preventative treatment with AZB effective, with the majority of respondents (88.2%) expressing the intention to continue with AZB prophylactic treatment. Additionally, the use of AZB had an impact on the number of ARIs reported in study participants with chronic diseases which were comparable to those of participants without chronic diseases. This suggests that AZB may reduce the additional risk of ARI infection associated with chronic diseases. In support of these statements, additional assessments were conducted where the number of cases of ARI and COVID-19 in healthcare workers with chronic diseases was analysed. The number of ARI and COVID-19 cases recorded in the AZB

group in subgroups with and without chronic diseases was almost the same. Whereas in the control group, the number of ARI cases in the subgroup of participants with chronic diseases was five times higher compared with the subgroup without chronic diseases. Thus, this provides the reasonable argument that Polyoxidonium may further reduce the risks of infection for people with chronic diseases.

A favourable point from this study is that standardised PPE equipment was used by all healthcare workers which could contribute to the validity of the results. The questionnaire was simple to conduct and was not time-consuming yet showed a significant difference in results between treated and non-treated participants. Participants disclosed their information in the questionnaire anonymously which ruled out any subjective interference during the study.

There are a number of limitations to this study which require consideration. The subjective nature of questionnaire based studies reduces their accuracy and the quantification of results. In this study the results were based on the opinions of participating healthcare professionals. Furthermore, medical history and use of concomitant medications was not recorded, which could have an impact interpretation of the results. The role of each healthcare worker was not documented which provides difficulty in distinguishing the proximity of the healthcare worker with the patient e.g. Care workers are in closer contact with some patients. Lastly, the questionnaire was only conducted in one country, Russia, and only in COVID-19 specified hospitals, which are not representative of general medical hospitals.

Based on the positive results obtained, future studies are expected to be conducted on the therapeutic benefit of AZB in the prevention of ARIs and COVID-19 in children and volunteers who have confirmed contact with a COVID-19 patient but have no symptoms of the disease before taking their first dose of the drug.

Declarations

Ethics approval and consent to participate:

All experiments and methods described in this study were performed in accordance with relevant guidelines and regulations. The Federal State Budgetary Educational Institution of Higher Education “Kemerovo State Medical University” of the Ministry of Health of the Russian Federation Ethics Committee approved the experiments.

Written informed consent was obtained from all participants.

Consent for publication:

All participants provided their consent for publication with their informed consent.

Availability of data and materials:

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests:

There were no competing interests.

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Author contribution:

Vera P. Vavilova: Principal Investigator. Design of the study, patient enrollment, results analysis, corresponding author.

Alexander M, Sofia A. Tsarkova, Svetlana V. Kudasheva, Ruslan A. Belous, and Mikhail S. Gordeev: Sub-editors. All provided some data and had equal involvement in review of the manuscript.

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