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THE EFFECTS OF TIME-RELEASED GARLIC POWDER TABLETS ON ACUTE RESPIRATORY DISEASES IN CHILDREN

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In spite of commonly spread positive opinion about the antibacterial and antiviral properties of garlic, very few and fragmented data exist on the benefits of garlic and garlic-based preparations in the prevention of acute respiratory diseases (ARD). This study was performed to elucidate the effect of time-released garlic powder tablets (Allicor) in prevention of ARD in children. At the first stage, in open-labeled 5-months study it has been shown that ARD morbidity was reduced by 2.4-fold in 172 Allicor-treated (600 mg daily) schoolchildren aged 7-16 as compared to 468 controls. At the second stage, the effects of Allicor (300 mg daily) on ARD morbidity were investigated in the double-blinded placebo-controlled randomized 5-months comparative study in 42 children aged 10-12 in comparison with 41 placebo-treated children and 73 benzimidazole-treated children. Allicor treatment reduced ARD morbidity by 2.4-fold as compared to placebo, and by 1.7-fold as compared to benzimidazole. Health index in Allicor-treated group was 1.5-fold higher as compared either to placebo- or benzimidazole-treated children. The results of this study have demonstrated that garlic powder tablets Allicor are effective in non-specific prevention of acute respiratory infections in children and possess no side effects. Additionally, the commonly used ARD prevention with benzimidazole turned to be entirely ineffective in placebo-controlled study, so the development of new useful and safe efficient drugs like garlic-based preparations is of ultimate importance.

Keywords: Acute respiratory diseases, grippe, children, garlic, placebo-controlled study.
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Introduction

The enhancement of human organism's ability to resist against acute respiratory viral infections is one of the most actual problems in children's care (Williams et al., 2002). More than 200 different types of viruses are able to induce acute respiratory diseases (ARD), and polyetiologic nature of ARD does not allow obtaining maximum effect from specific immunologic prevention. So, the use of different agents possessing the effects on non-specific natural immunity is well justified. For this purpose, the drugs capable of stimulating the immune response are usually used in clinical practice. However, such medications are usually relatively selective in mechanisms of action and, therefore, demand individual immunologic control (Kieny, Girard, 2005) and cannot be widely used in pediatrics. The use of dietary supplements of natural origin, mainly derived from botanicals and/or food components seems to be much more promising, since such preparations possess no side effects and may not be necessarily prescribed by a physician. Many of them may induce the enhancement of natural immunologic non-specific resistance to all types of viruses responsible for ARD morbidity, and garlic-based preparations deserve the most thorough attention. Bactericidal properties of garlic are known for centuries, and the mixture of garlic and honey is used in traditional medicine of many cultures under different inflammatory conditions from the ancient times. The first works on the anti-inflammatory effects of garlic date back to the end of XIX – beginning of XX centuries (Rossiyskiy, 1933). However, in spite of commonly spread positive opinion about the antibacterial and antiviral properties of garlic, very few and fragmented

data exist on the benefits of garlic and garlic-based preparations in the prevention of acute respiratory viral diseases. So, the given study was performed to investigate the effect of time-released garlic powder tablets Allicor in prevention of acute respiratory diseases (ARD) in children, in comparison with benzimidazole (Dibazole).

Patients and methods

For the estimation of effects of non-specific immunostimulation on the ARD rate in children, time-released tablets Allicor (INAT-Farma, Moscow, Russia) containing 150 or 300 mg of dehydrated garlic powder were used. This study was kept in accordance with the Helsinki Declaration of 1975 as revised in 1983, as well as with the principles of Good Clinical Practice, and was approved by the local ethical committee. The parents of participants gave their informed consent prior to their inclusion in the study.

The study was performed in two consecutive years in two stages. At the first stage, the safety, tolerability and effectiveness of Allicor (one 300-mg tablet twice a day, 600 mg daily) was investigated in open-labeled 5-months study (from November to March) in 172 schoolchildren aged 7-16 in comparison with 468 controls (the total number of participants accounted for 640 children). The presence of acute or chronic gastrointestinal disease, asthmatic bronchitis or bronchial asthma was the exclusion criteria. The treated group consisted of 80 children of elementary school age (7-9 years old) and 92 preteens and teenagers (10-16 years old). The control group consisted of 329 children of elementary school age and 311 preteens and teenagers. The events of ARD (including grippe) were registered in both groups during the whole study as well as one month before (lead-in period) and one month after the treatment (lead-out period). The episodes with subfebrile temperature or fewer accompanied with nasal cold and/or headache, and/or conjunctivitis that prevented children from attending the school for one and more days were classified as the ARD event. No differential diagnosis between grippe, parainfluenza and other types of ARD was performed. The case of ARD during the study did not demand the discontinuation of Allicor treatment, neither was the exclusion criterion.

At the second stage, the effects of Allicor (one 150-mg tablet twice a day, 300 mg daily) on ARD morbidity were investigated in the double-blinded placebo-controlled randomized 5-months comparative study in 42 children aged 10-12 in comparison with 41 placebo-treated children and 73 benzimidazole-treated children (active control). Placebo and Allicor looked identically. The total number of participants accounted for 156 children. The exclusion criteria were the same as described above. The rate of ARD was registered in all groups during the whole study as well as one month before and one month after the treatment period. The event of ARD was classified as described above. No differential diagnosis between grippe, parainfluenza and other types of ARD was performed, as well. The case of ARD, like at the previous stage of the study, did not demand the discontinuation of Allicor treatment, neither was the exclusion criterion. Additionally, at this stage of the study, "health index" (%) was calculated, that was defined as the rate of the number of children who had never experienced ARD event during the treatment period to the total number of children in the group.

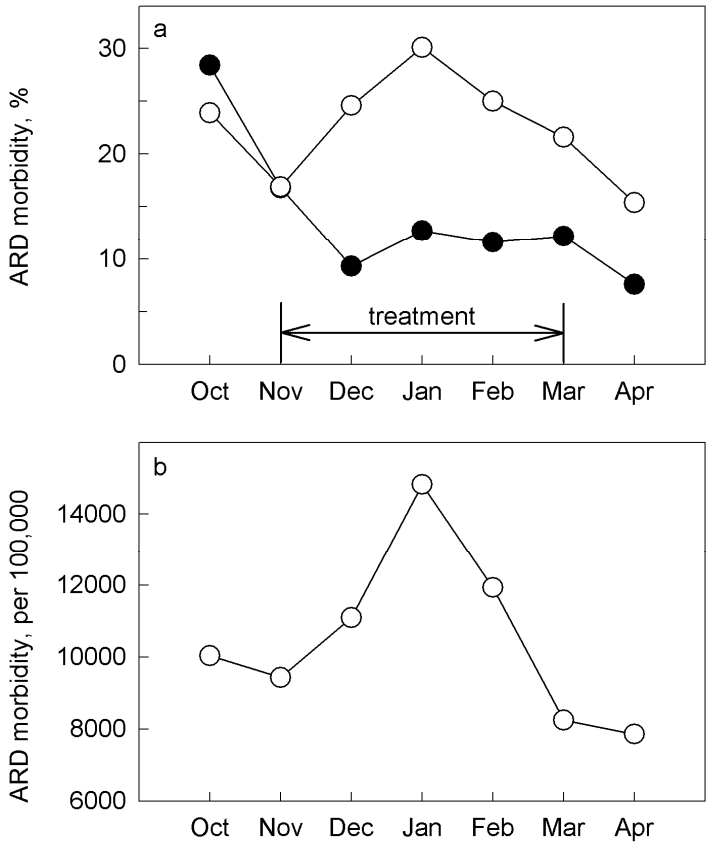
The significance of differences between groups was evaluated using SPSS 10.1.7 statistical program package (SPSS Inc., USA) and defined at the 0.05 level of confidence.

Results

The safety and tolerability of Allicor in children was assessed in both stages of the study. The treatment with Allicor at daily dosages of 300 or 600 mg did not induce any kind of gastrointestinal side effects. However, at open-labeled stage of the study, in one participant who had atopic diathesis in the anamnesis, the moderate allergic rash developed at the third day of Allicor treatment that lead to immediate discontinuation of

treatment and exclusion from the study. In all other participants, tolerability to Allicor was superbly good.

FIGURE 1. THE DYNAMICS OF ARD RATE IN OPEN-LABELED STAGE OF THE STUDY
a - The data on ARD morbidity in Allicor-treated children (solid circles) and control group (open circles); b - The population-based data on ARD morbidity in children provided by Central City Sanitary and Epidemiological Department

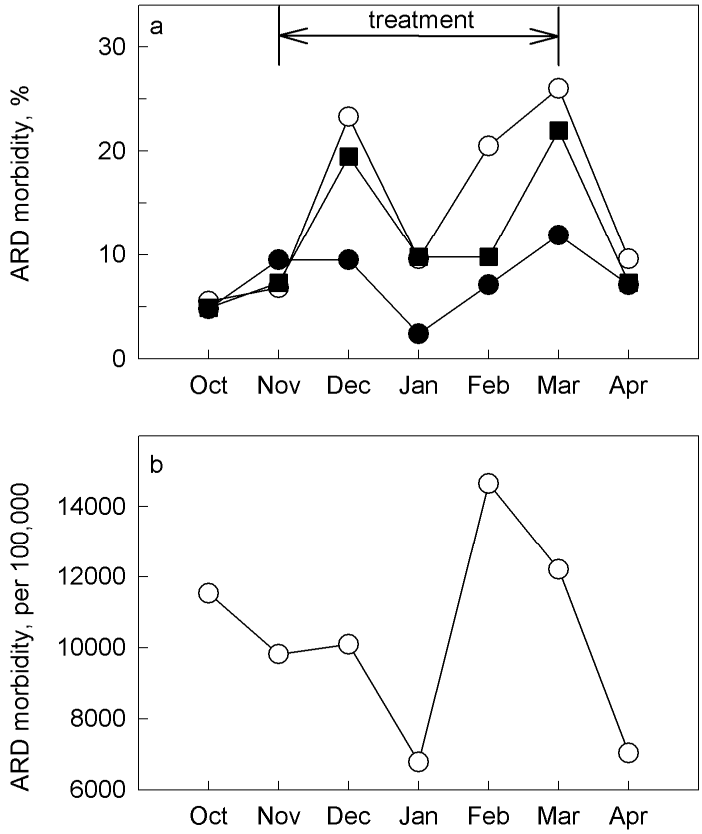


The results of the open-labeled stage of the study have demonstrated that Allicor treatment results in a significant reduction in ARD morbidity in children (Figure 1a). During the lead-in period and the first month of active treatment with Allicor, the incidence of ARD did not differ significantly in Allicor-treated and control group. At the same time, the incidence of ARD decreased significantly ($p<0.05$) in Allicor-treated children just in the first month of treatment as compared to a lead-in period (the data from control group have also demonstrated some decrease in ARD rate, but the difference from lead-in period did not reach statistical significance). Beginning from the second month of active treatment and up to the end of the treatment period, the ARD morbidity in Allicor-treated children was significantly ($p<0.05$) lowered by 1.8- to 2.6-fold as compared to control group. The most prominent effects were observed from December to February, when the epidemiologic seasonal increase in ARD rate occurred. By the end of active treatment period, ARD morbidity in control group in March

decreased below epidemiologic value, but in any case was significantly higher than in Allicor-treated children ($p<0.05$). At last, during the lead-out period in April when active treatment with Allicor was discontinued, the children who had received Allicor for the whole cold season experienced significantly less cases of ARD as compared to control group ($p<0.05$). The data on total ARD morbidity in Moscow children covering the same period of time (from October to April) were kindly provided by Central City Sanitary and Epidemiological Department (Figure 1b). According to these data, the highest ARD morbidity in children's population in Moscow was observed from December to February, and the form of the curve strictly corresponds to that derived from control group, but not in Allicor-treated children. However, direct comparisons in ARD morbidity between study groups and population-derived data would not be statistically correct due to insufficient sample size and inadequacy in distribution by age as compared to population.

FIGURE 2. THE DYNAMICS OF ARD RATE IN PLACEBO-CONTROLLED STAGE OF THE STUDY

a – The data on ARD morbidity in Allicor-treated children (solid circles), placebo group (open circles) and active control (benzimidazole-treated group) (solid squares); b – The population-based data on ARD morbidity in children provided by Central City Sanitary and Epidemiological Department



The results of double-masked placebo-controlled stage of the study have confirmed previous findings that Allicor treatment results in a significant reduction in ARD morbidity in children (Figure 2a). During the lead-in period and the first month of active treatment with Allicor, the incidence of ARD did not differ significantly in Allicor-treated, placebo- and active-controlled group. Beginning from the second month of active treatment and up to the end of the treatment period, the ARD morbidity in Allicor-treated children was significantly ($p<0.05$) lowered by 2.2- to 4.0-fold as compared to control group. The most prominent effects were observed in December, February and March, when two seasonal increases in ARD rate occurred. During the lead-out period in April when ARD morbidity in all groups decreased below epidemiologic value and active treatment with Allicor was discontinued, the children from Allicor-treated group did not differ significantly in ARD rate as compared either to placebo or to active-controlled group. The data on total ARD morbidity in Moscow children of corresponding age covering the same period of time (from October to April) were kindly provided by Central City Sanitary and Epidemiological Department (Figure 2b). As it can be seen, in placebo group, but not in Allicor-treated children, the shape of the morbidity curve corresponds well to that derived from population. However, direct comparisons in ARD morbidity between study groups and population-derived data are inequitable again due to insufficient sample size.

It should be noted that in this particular year the rate of ARD was very low in January, and the results obtained from placebo group coincide with the population-derived data. However, even in January children treated with Allicor experienced significantly less ARD events as compared to placebo group ($p<0.05$).

At this stage of the study, active-controlled group of children who received benzimidazole for ARD prevention was used for obtaining comparative data. As it could be seen from Figure 2a, benzimidazole treatment was significantly less effective as compared to Allicor. Statistically significant difference in ARD rate between benzimidazole-treated children and placebo recipients was observed only in February, while in other months of the study these groups did not differ significantly. On the other hand, the ARD morbidity in Allicor-treated children was significantly lower as compared to benzimidazole-treated group in December, January and March ($p<0.05$).

At last, the "health index" in Allicor-treated children during active treatment period was more than 1.5-fold higher as compared to placebo- or active-controlled children: it accounted for 67% in Allicor-treated group, 46% in benzimidazole-treated group, and 40% in placebo group.

Discussion

The results of the given two-stage study have demonstrated that garlic-based time-released tablets Allicor allow to reduce ARD rate in children by 2.4-fold, on an average, during seasonal epidemiologic increases in ARD morbidity. Practically, it can be stated that Allicor treatment eliminates the seasonal epidemic ARD outbreaks entirely. It is also important that low doses of garlic preparation used at the second stage of the study (300 mg daily) provided the same beneficial effect as the dose of 600 mg daily, used at the first open-labeled stage of the study.

Another important matter rises from the results of this study that concerns the perspectives of use of non-specific immunomodulator, benzimidazole (Dibazole), for ARD prevention. Primarily, the assumptions on benzimidazole potential effectiveness were based on the results of animal studies, which demonstrated the increase in interferon production and lower rate of complications in experimental influenza in mice (Szram, Denys, 1972; Sorokin et al., 1976). The results of placebo-controlled clinical study performed in adult volunteers have shown the beneficiary effects of benzimidazole and ascorbic acid combination in ARD prevention (Shaposhnikov et al., 1976), however, it should be noted that ascorbic acid may produce its own effect independent of benzimidazole. Additionally, it has been shown that benzimidazole treatment can prevent the rise in ARD rate only when initiated in the very beginning of epidemic outbreak

(Ershov et al., 1991). The results of our placebo-controlled study have clearly demonstrated low effectiveness of ARD prevention with benzimidazole, especially in comparison with garlic powder tablets Allicor.

This study seems to be the one of the first clinical trials to investigate the effects of garlic-based preparation on ARD morbidity. Unfortunately, the analysis of previously published works revealed only few publications someway concerning this matter. There are rather old studies that have demonstrated the beneficiary effects of raw garlic as well as garlic extract in the treatment of patients with different inflammatory diseases of the respiratory organs (Margolina, 1948; Vorob'eva, 1957; Bulatov et al., 1965) and in prevention of virus infections, including influenza (Nagai, 1973). It seems that garlic-based preparations are undeservedly left aside for exclusive use within the boundaries of traditional medicine, although *a priori* positive opinion of physicians on the usefulness of garlic in ARD prevention exists that is based on the common knowledge of antiviral and antibacterial properties of garlic phytoncides. So, it is rather surprising why the potentially effective with the respect to prevention of viral infections, safe and widely used "over the counter" herbal preparation remained out of focus for years. However, the recent trends in clinical epidemiology revive the interest to garlic utilization as a natural antiviral and antimicrobial remedy (Adetumbi and Lau, 1983; Abdullah, 2000). Antibacterial and antiviral effects of raw garlic, fresh garlic juice and garlic extracts have been extensively studied in vitro. It has been demonstrated that phytoncides from garlic produce bactericidal effects on different gram-positive and gram-negative bacteria that induce destructive inflammatory diseases of respiratory system (Margolina, 1948; Bulatov et al., 1965; Dankert et al., 1979; Tsai et al., 1985).

have demonstrated that garlic can produce antiviral effects in vitro on influenza B, herpes simplex and coxsackie viruses. Esanu and Prahoveany (1983) have shown that garlic extract was effective in experimental influenza in mice. The mechanisms underlying antimicrobial effects of garlic are not well elucidated yet. However, it is known that sulfur-containing amino acids from garlic may play the decisive role, among them are alliin, allicin and ajoene. These amino acids are the components of garlic essential oils that are considered to be the main source of phytoncides. Additionally, it has been shown that ajoene treatment abolished the effect of various activators on intracellular respiratory burst in a dose-dependent manner (Sud'ina et al., 1991). Garlic extract was also identified as a potent inhibitor of leukocyte migration through endothelial cell monolayers, thus potentially playing an important role in inflammation (Hobauer et al., 2000).

By far, a lot of garlic-based products are present on the market now. They can be generally classified into four groups, i.e., garlic essential oil, garlic oil macerate, garlic powder and garlic extract. As compared to other garlic preparations, dehydrated garlic powder is thought to retain the same ingredients as raw garlic, both water-soluble and organic-soluble, although the proportions and amounts of various constituents may differ significantly (Iberl et al., 1990; Amagase et al., 2001). Allicor contains dehydrated garlic powder and possesses time-released mode of action, as its biological effect lasts for 12-16 hours after single dose administration (Orekhov et al., 1995). So, the effects of different garlic-based preparations on ARD morbidity may vary. The prolonged biological action of Allicor allows reducing daily dosage without affecting its efficacy and offers suitable and non-consuming regimen of administration. So, Allicor may have considerable benefits in medicinal use.

The results of this study have demonstrated that garlic-based time-released tablets Allicor may be recommended for non-specific prevention of ARD in children in flu-cold seasons due to its high efficacy, safety and tolerability. However, this study has some limitations. First, the sample size of placebo-controlled phase of the study was small enough to provide high statistical power. Second, the effectiveness of Allicor in ARD prevention in children was assessed in particular flu-cold seasons characterized by usually observed increase in ARD morbidity; therefore, the results can be extrapolated to the situation when the morbidity exceeds the epidemic threshold only with caution. Finally, the effectiveness of Allicor against specific viral ARDs was not assessed in this study. Nevertheless, the preventive efficacy of Allicor and a significant reduction of ARD morbidity were further confirmed in adults in a wide heath support program (Sobenin et al., 2011).

In conclusion, the results of this study have demonstrated that garlic-based time-released tablets Allicor are effective in non-specific prevention of ARD in children; however, the

further development of safe and efficient drugs like garlic-based preparations is of ultimate importance.

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References

Abdullah, T., 2000. "A strategic call to utilize Echinacea-garlic in flu-cold seasons," J. Natl. Med. Assoc., Vol.92, pp.48-51

Adetumbi, M., Lau, B., 1983. "Allium sativum (garlic) - a natural antibiotic," Med Hypotheses, Vol.12, pp.227-37

Amagase, H., Petesch, B., Matsuura, H., Kasuga, S., Itakura, Y., 2001. "Intake of garlic and its bioactive components," J. Nutr., Vol.131, pp.955S-62S

Bulatov, P., Zlydnikov, D., Fedoseev, G., Khan, F., 1965. "The use of garlic phytoncides in the treatment of patients with different inflammatory diseases of the respiratory organs," Sov. Med. (Mosk.), Vol.28, pp. 86-90

Dankert, J., Tromp, T., de Vries, H., 1979. "Antimicrobial activity of crude juices of Allium ascalonicum, Allium cepa and Allium sativum," Zentralbl. Bakteriol. Orig. A., Vol.245, pp.229-39

Ershov, F., Grigorian, S., Semenenko, T., Malinovskaia, V., Tarasenko, O., Agafonov, V., 1991. "The efficacy of exogenous and endogenous interferonization in preventing influenza," Zh. Mikrobiol. Epidemiol. Immunobiol., Vol.3, pp.42-45

Esanu, V., Prahoveanu, E., 1983. "The effect of garlic extract, applied as such or in association with NaF, on experimental influenza in mice," Virologie, Vol.34, pp.11-17

Hobauer, R., Frass, M., Gmeiner, B., Kaye, A., Frost, E., 2000. "Garlic extract (allium sativum) reduces migration of neutrophils through endothelial cell monolayers," Middle East J. Anesthesiol., Vol.15, pp. 649-58

Iberl, B., Winkler, G., Miller, B., Knobloch, K., 1990. "Quantitative determination of allicin and alliin from garlic by HPLC," Planta Med. Vol.56, pp.320-26

Kieny, M., Girard, M., 2005. "Human vaccine research and development: an overview", Vaccine, Vol.23, pp.5705-707

Margolina, M., 1948. "The experience in the treatment of empyetic processes in lungs with phytoncides from garlic," Vrach. Delo (Mosk.), Vol.1, p.727

Nagai, K., 1973. "Preventive effect of garlic extract against influenza," Kansenshogaku Zasshi, Vol.47, pp. 321-25

Orekhov, A., Tertov, V., Sobenin, I., Pivovarova, E., 1995. "Direct anti-atherosclerosis-related efects of garlic," Ann. Med., Vol.27, pp.63-65

Rossiyskiy, D., 1933. "Garlic (Allium sativum) and its clinical use," Klin. Med. (Mosk.), Vol.1, pp. 315-17

Shaposhnikov, I., Yakovleva, R., Cherezova, L., 1976. "The methods of non-specific prevention of grippe and other acute respiratory diseases with dibazole and ascorbic acid," Vopr. Virusol. (Mosk.), Vol.2, pp.429-31

Sobenin, I., Surnin, S., Karagodin, V., Pryanishnikov, V., Orekhov, A., 2011. "The experience of the use of time-released prebiotic allicor," Health in Russian Federation (Mosk.), No.3, pp.28-31

Sorokin, A., Lushnikov, A., Kol'tsov, V., 1976. "The effects of benzimidazole derivatives in viral infections," Vopr. Virusol. (Mosk.), Vol.2, pp.206-11

Sud'ina, G., Tatarintsev, A., Koshkin, A., Zaitsev, S., Fedorov, N., Varfolomeev, S., 1991. "The role of adhesive interactions and extracellular matrix fibronectin from human polymorphonuclear leukocytes in the respiratory burst," Biochim. Biophys. Acta , Vol.1091, pp.257-60

Szram, S., Denys, A., 1972. "Effects of benzimidazole on the development of organ lesions in experimental influenza virus infection in mice," Med. Dosw. Mikrobiol., Vol.24, pp.55-57

Tsai, Y., Cole, L., Davis, L., Lockwood, S., Simmons, V., Wild, G., 1985. "Antiviral properties of garlic: in vitro effects on influenza B, herpes simplex and coxsackie viruses," Planta Med., Vol.1, pp.460-61

Vorob'eva, A., 1957. The reflex therapy, Medicine, Leningrad

Williams, B., Gouws, E., Boschi-Pinto, C., Bryce, J., Dye, C., 2002. "Estimates of world-wide distribution of child deaths from acute respiratory infections," Lancet Infect. Dis., Vol.2, pp.25-32