Antiviral activity of amiodarone in SARS-CoV-2 disease.

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Short title: Amiodarone and SARS-CoV-2.

Summary

Amiodarone seems to exhibit some antiviral activity in the disease caused by SARS-CoV-2. Here we have examined the SARS-CoV-2 disease course in the entire population of the Czech Republic and compared it with the course of the disease in patients treated with amiodarone in two major Prague's hospitals. In the whole population of the Czech Republic SARS-CoV-2 infected 1665070 persons (15.6 %) out of 10694000 (100 %) between 1 April 2020 and 30 June 2021. In the same time period only 35 patients (3.4 %) treated with amiodarone were infected with SARS-CoV-2 virus out of 1032 patients (100 %) who received

amiodarone. It appears that amiodarone can prevent SARS-CoV-2 virus infection by multiple mechanisms. In in-vitro experiments it exhibits SARS-CoV-2 virus replication inhibitions. Due to its anti-inflammatory and antioxidant properties, it may have beneficial effect on the complications caused by SARS-CoV-2 as well. Additionally, inorganic iodine released from amiodarone can be converted to hypoiodite (IO^-), which has antiviral and antibacterial activity, and thus can affect the life cycle of the virus.

Keywords: amiodarone, iodine, SARS-CoV-2, COVID-19, antiviral activity

No of words: 3797

Ethical approval: The study was conducted in accordance with the Declaration of Helsinki, and the Multicentric Ethics Committee The University Hospital Kralovske Vinohrady (protocol EK-R/06/0/2022).

Declaration of interest: Authors state no conflict of interest.

Introduction

Amiodarone has been identified as a drug for treatment of acute respiratory syndrome caused by coronavirus SARS-CoV-2 [1, 2]. It is a class III antiarrhythmic drug (potassium channel blocker) broadly used for the treatment of arrhytmias [3-5]. Amiodarone also has class I (sodium channel blockade), class II (noncompetitive α- and β–blocking) and class IV (calcium channel activity) related actions [6].

Due to the benzene ring, amiodarone is highly lipophilic, leading to strong tissue affinity and large volume of distribution [4]. When the dose of amiodarone is reduced or discontinued, the accumulated amiodarone is transferred back to the serum, which can lead to a long elimination half-life of amiodarone of about 100 days [5, 7]. Adipose tissue, liver, skeletal muscle, lung, pancreas, thyroid, kidney, heart, skin, adrenal glands, testes, eyes and lymph nodes are among the tissues with the highest amiodarone content [4, 8]. Amiodarone undergoes dealkylation in tissues to form N-desethylamiodarone (DEA), which also has antiarrhythmic activity. DEA accumulates in tissues with approximately the same half-life as amiodarone, but shows higher toxicity [7]. In general, the mean half-life of amiodarone or DEA is 40 or 57 days, respectively [4]. The structural formula of amiodarone and its biologically active metabolite DEA is shown in **Fig. 1**.

Amiodarone has several side effects, contraindications and drug interactions. It can cause lung toxicity and fibrosis, adversely affect the thyroid gland, cause hepatotoxicity, increase creatinine, prolong the QT interval and it can also lead to bradyarrhythmias [9, 10].

The antiviral and antibacterial activity of amiodarone may result from: 1) a significantly increased content of iodine in the circulation, with its own antiviral properties; 2) the internal antiviral action of amiodarone, which inhibits the spread of SARS-CoV-2 by blocking ion channels and interfering with the endocytic pathway. Its known anti-inflammatory and antioxidant effects are also significant [9].

Antiviral activity of iodine released from amiodarone

Iodine in the form of a water-soluble iodide ion (I^-) is a rate-limiting substrate for the synthesis of thyroid hormones [11]. Amiodarone contains two iodine atoms in the inner benzene ring. A patient taking a standard 200 mg daily dose of amiodarone [4] receives 75 mg of organic iodine each day [12]. During the

administration of amiodarone, there is an increased excretion of free iodine, which leads to a daily release of approximately 6 mg of free circulating iodine in the form of iodide [7]. This is 40 times higher than the recommended daily iodine intake of 150 μg/day [4, 13-15].

Iodine is considered one of the oldest antioxidants and enables elimination of reactive oxygen species (ROS). Tissue-specific peroxidases (salivary peroxidase, gastric peroxidase and lactoperoxidase in the intestinal mucus) allow the oxidation of iodide to hypoiodite (IO^-), which has antiviral, fungicidal and bactericidal activity [16]. Furthermore, iodide oxidation has been shown to have a strong antiviral effect against lung adenoviruses [16].

Intrinsic antiviral effect of amiodarone

Coronaviruses are RNA viruses whose surface is characterized by spikes formed by spike (S) protein trimers [17]. Entry of SARS-CoV-2 into cells is due to the binding of the viral spike protein subunit S1 to angiotensin converting enzyme 2 (ACE2) receptor. At the interface of the S1 and S2 subunits, fragmentation occurs leading to a membrane fusion reaction [17, 18]. Fusion of the virus with the cell membrane is facilitated by serine transmembrane protease type II (TMPRSS2), which cleaves viral spike glycoproteins. Spike proteins thus mediate the binding of the virus to the ACE2 receptor, but they are also involved in the subsequent membrane fusion [19]. Coronaviruses can also be internalized by clathrin- and non-clathrin-mediated endocytosis [20], where protein S is cleaved by cathepsin L [21, 22]. This is followed by the release of the viral genome into the cytoplasm and subsequent replication of the virus [19].

Amiodarone accumulates in endosomes and lysosomes. It reduces their acidity and can thus affect the transport of membrane components [23]. This will affect the cleavage of the envelope proteins of the virus, but also pinocytosis and transport of the proteins to lysosomes [24]. Ion channel-targeting pharmacological agents can modulate virus life cycle [19]. Amiodarone is a non-selective inhibitor of Ca^{2+}, Na^+ and K^+ voltage-gated ion channels. The binding and inhibition of Ca^{2+} channels takes place mainly during the quiescent state, in which it suppresses the Ca^{2+} dependent potentials of these channels [25, 26]. However, Ca^{2+} ions are necessary for the penetration of the fusion viral peptide into the lipid bilayer and for

subsequent endocytosis. Their interaction with the fusion peptide can induce spatial changes in the protein S, which alter the structure of the fusion peptide and the interaction with the cell membrane [27]. The spike and envelope proteins of the virus, along with membrane proteins, enter the endoplasmic reticulum (ER) and the resulting nucleocapsid protein binds to the (+) strand of the ribonucleic acid, forming a nucleoprotein complex. Thus, complete virus particles can form in the host ER and the Golgi apparatus. However, Ca^{2+} has an important effect on the processes taking place in the ER, in the Gogi apparatus and in lysosomes [28]. Amiodarone blocks Ca^{2+} channels and may affect endosomal transport in cells infected with SARS-CoV-2 [25]. Ca^{2+} levels decline rapidly under the action of efflux pumps in newly formed endocytic vesicles, whereas extracellular Ca^{2+} may be high [29].

SARS-CoV-2 is the cause of inflammation leading to myocarditis, cardiac arrhythmias and inflammatory vascular disease [30]. Inflammation-triggered activation of dendritic cells and monocyte/macrophage lineage cells leads to the secretion of proinflammatory cytokines such as interleukin IL-6, tumor necrosis factor α (TNF-α) and monocyte chemoattractant protein 1 (MCP-1) [31]. Due to the reduced activity of angiotensin-(1-7), inflammatory, vasoconstrictive, oxidative and fibrotic disorders increase [31]. Amiodarone anti-inflammatory effects are mediated by reducing circulating concentration of C-reactive protein, MCP 1 and inflammatory cytokines (IL-1b, IL-6, TNF-α) [32, 33]. Amiodarone can protect lung tissue from sepsis by inhibiting cytokine production and reducing oxidative stress. Antioxidant properties consist of minimal decrease in glutathione, glutathione reductase or superoxide dismutase [9] and a protective effect against O_2 radical-mediated heart damage [34]. The potential positive effects of amiodarone in SARS-CoV-2 may be mediated by inhibition of cytokine and chemokine production and improved antioxidant capacity [35].

Methods and subjects

According to the Czech Statistical Institute, there were 10694000 residents in the Czech Republic as of March 31, 2021 (100 %) (https://www.czso.cz/csu/czso/ari/population-change-1st-quarter-of-2021, accessed November 2021). From this total population, the Institute of Health Information and Statistics of

the Ministry of Health of the Czech Republic (https://onemocneni-aktualne.mzcr.cz/covid-19, accessed November 2021) identified 1665070 persons (15.6 %) infected with SARS-CoV-2 between 1 April 2020 and 30 June 2021. The daily counts of residents infected with the SARS-CoV-2 virus with three distinct pandemic peaks are shown in **Fig. 2.** The course of the disease was classified as grade 1 (asymptomatic, mild), grade 2 (moderate course requiring hospital care and/or oxygen therapy), grade 3 (severe, patients in the intensive care unit using artificial lung ventilation and/or extracorporeal membrane oxygenation), and grade 4 (death). The data was obtained from a publicly available database thus ethical consent was not required.

During the same time period we evaluated 1032 patients treated with amiodarone. The reason patients were treated with amiodarone was cardiac arrhythmia, and the patients took the drug for months or longer. The patients were from the General University Hospital in Prague (n = 695) and from the University Hospital Královské Vinohrady, Prague (n = 337). In this cohort, 35 people (3.4 %) with SARS-CoV-2 were identified. A classification of SARS-CoV-2 according to the severity of the disease was performed in the same way as in the general population of the Czech Republic.

Data analysis

The data concerning the entire population of the Czech Republic, which were downloaded from publicly available databases, did not contain information on the age and sex of individual persons suffering from SARS-CoV-2 disease, but allowed patients to be classified according to SARS-CoV-2 severity classification. Lotus 1-2-3 from the IBM Corporation, USA was used for this purpose. Data on both age and sex and severity of SARS-CoV-2 disease were available in hospital patients taking amiodarone. The arithmetic mean and standard deviation of these patients were calculated using the NCSS 2004 computer program (Number Cruncher Statistical Systems, Kaysville, Utah, USA).

Results

Of the 10694000 Czech residents during 1 April 2020 and 30 June 2021 1665070 persons (15.6 %) were diagnosed with SARS-CoV-2. Approximately 15 % of those infected were age of 65. Grade 1 infection

was reported in 7.6 %, grade 2 in 5.7 % and grade 3 occurred in 2 % of the infected cases/patients. Unfortunately 0.3 % of the patients with SARS-CoV-2 died (grade 4). The results are shown in **Tab. 1**.

Of the 1032 patients treated with amiodarone, only 3.4 % (35 patients) were diagnosed with SARS-CoV-2. Of those 1.5 % (15 patients) had a grade 1 infection, 1.4 % (14 patients) had a grade 2, 0.1 % (1 patient) had grade 3 and 0.5 % (5 patients) died (grade 4). The higher severity of disease was evident in the older population. More detailed data on the age and representation of men and women are given in **Tab. 1**.

Discussion

SARS-CoV-2 infection has different infection cycle characteristics. Virus replication in host cells is particularly important for the early phase of SARS-CoV-2. The late phase is characterized by an increase in cytokines with subsequent cellular apoptosis [36]. Amiodarone and its major metabolite DEA prevent coronavirus infection at concentrations similar to those found in the blood of patients treated for arrhythmias [26]. Other studies have shown that amiodarone can also effectively inhibit Ebola virus entry in vitro by interfering with the endocytosis pathway and by inhibiting proteolysis [26, 37, 38]. Unfortunately, other than case reports we did not find clinical studies describing the effects of amiodarone on SARS-CoV-2.

Antiviral assays using native SARS-CoV-2 virus in Vero E6 cells confirmed that amiodarone significantly inhibited SARS-CoV-2 replication, thereby reducing the viral RNA load of the supernatant with a promising level of activity [39]. Therefore, SARS-CoV-2 protein S-targeted inhibitors may demonstrate potential for treatment by preventing the entry of the virus [40-42].

It is evident that in the time period between 1 Apr 2020 to 30 June 2021 there is a clear difference between the groups of patients treated with amiodarone, where only 3.4 % patients were diagnosed with SARS-CoV-2 infection, and the population where 15.6 % were diagnosed with SARS-CoV-2 infection. Data on patients treated with amiodarone are on average 5 times more favorable, regardless of age and comorbidities. The disease caused by SARS-CoV-2 was expected to be more severe in residents of the Czech Republic than that seen in the hospitalized patients treated with amiodarone. Thus, it suggests that amiodarone can be beneficial with its antiviral effects affecting SARS-CoV-2.

Not only amiodarone, but also other substances, including naturally occurring agents, can influence the course of the SARS-CoV-2 disease. Androgens may play an important role, as androgen deficiency may be a risk factor for the severity of COVID-19. This is due to the fact that androgens are capable of inducing genomic anti-inflammatory and non-genomic hypotensive responses. On the contrary, elevated levels of androgens increase the activity of protease TMPRSS2, which fundamentally affects the penetration of the SARS-CoV-2 into host cells [43, 44]. The antiviral activity of amiodarone is likely to be due to interference with the endocytic pathway, but other mechanisms of action cannot be ruled out [45]. The safety and efficacy of amiodarone in patients with SARS-CoV-2 have yet to be investigated, and drug interactions with other therapies (e.g., hydroxychloroquine, lopinavir/ritonavir, atazanavir and darunavir/cobicistat) are major issues [46].

Conclusion

Our results suggest that amiodarone is likely to reduce SARS-CoV-2 virus replication and that due to its anti-inflammatory and antioxidant properties it can have a beneficial effect on the complications caused by SARS-CoV-2 virus. Additionally, inorganic iodine released from amiodarone can be converted to hypoiodite (IO^-) with known antiviral activity.

Acknowledgment

This work was supported by MH CZ - DRO (Institute of Endocrinology - EÚ, 00023761)

Author contributions

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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Table 1. Comparison of SARS-CoV-2 infection in the general population of the Czech Republic and in patients treated with amiodarone at two hospitals in Prague. The classification of the disease is explained in detail in the methods and subjects section. SD = standard deviation, n = number of residents in the Czech Republic or patients treated with amiodarone.

Population of the Czech Republic				**Hospital patients treated with amiodarone**					
	Disease clasification	**n**	**%**		**n**	**%**	**Age (years) (mean±SD)**	**Men**	**Women**
Czech population		10694000	**100**	**Hospital patients with amiodarone**	1032	**100**	69.7±13.0	627	405
Patients with SARS-CoV-2		1665070	**15.6**	**Patients with SARS-CoV-2 and amiodarone**	35	**3.4**	72.0±11.3	21	14
	1 (mild)	810472	**7.6**		15	**1.5**	68.8±12.2	7	8
	2 (moderate)	614301	**5.7**		14	**1.4**	72.1±10.8	10	4
	3 (severe)	213321	**2.0**		1	**0.1**	73.0	1	-
	4 (died)	26976	**0.3**		5	**0.5**	81.2±5.9	3	2

Figure 1. Amiodarone and its major metabolite N-desethylamiodarone (DEA).

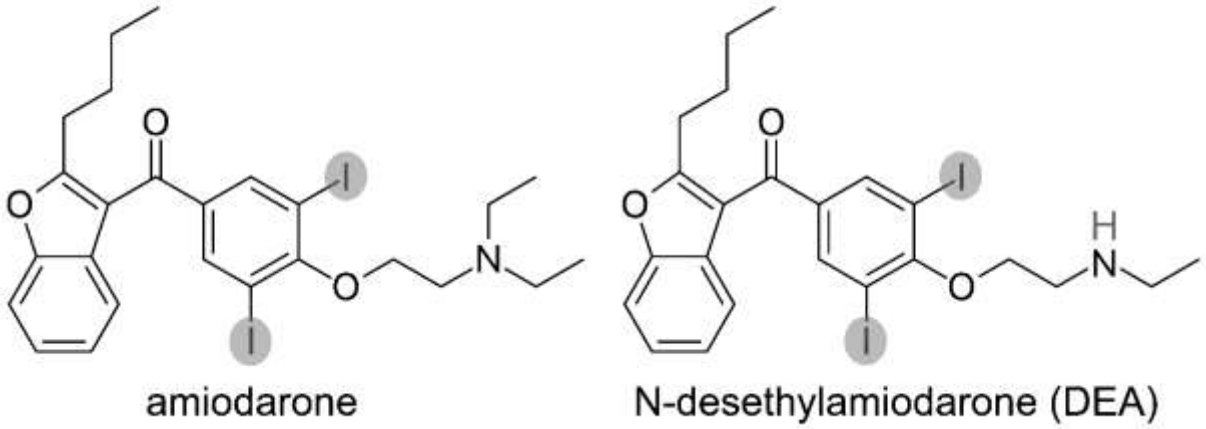

Figure 2. Daily counts of newly infected residents of the Czech Republic with the SARS-CoV-2 virus in the period from 1 April 2020 to 30 June 2021.