The efficacy of amantadine hydrochloride in the treatment of COVID-19 - a single-center observation study

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Short Report

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Abstract

Introduction: Coronavirus disease 19 (COVID-19) rapidly spread worldwide. The search for effective measures to counter the development and effects of the pandemic includes: identifying the disease pathogen, introducing methods of reducing its transmission, building the population immunity, and the search for a cure, both among the new and already-known substances with potential antivirus activity such as amantadine hydrochloride.

Study objectives: The study's aim is an observational single-center analysis of confirmed COVID-19 cases treated with amantadine in ambulatory settings.

Patients and methods: The group of 55 patients with confirmed COVID-19 diagnosis was treated in ambulatory settings by amantadine with a treatment schema. A retrospective analysis was based on symptoms, hospitalization, and number of deaths.

Results: The mean age of the patients was 55.9 years (*SD*=15), and most patients were male (60%). Despite the majority of patients 64% (n=35) suffering from comorbidities and 53% (n=29) of patients having been diagnosed with pneumonia, none of them died, and only four had required hospitalization in the course of COVID-19. Clinical stabilization was achieved in 91% (n=50) of patients within 48 hours after the first dose of amantadine with further improvement; additionally, all patients experienced remission of COVID-19. In total, 93% (n=51) of patients did not require hospitalization during the treatment.

Conclusions: The data may suggest that amantadine hydrochloride shows efficacy in preventing hospitalization and deaths in patients with COVID-19. At the same time, it emphasizes that daily monitoring of the patient and regular examination are important in the case of SARS-CoV-2 infection dynamics.

Introduction

The developing coronavirus pandemic has resulted in over two million infections and tens of thousands of deaths in Poland until the time of writing. COVID-19 which is caused by SARS-CoV-2, often manifests as a respiratory syndrome with high fever, coughing, shortness of breath and, in severe cases, leads to acute respiratory failure and can result in death. Growing knowledge concerning SARS-CoV-2 has led to the implementation of different substances against COVID-19 such as hydroxychloroquine, according to the World Health Organization [1], but we still need to work intensively on the treatment options that could be effective in COVID-19 treatment. Therefore, efforts should be made to continue research on implementing new substances for the treatment of COVID-19, and to work on new applications of already known antiviral active compounds.

Amantadine is a drug used in a standard dose of 200 mg/day (2 x 100 mg), usually well-tolerated [2], ensuring the effectiveness of therapy in the currently approved indications (Parkinson's disease,

dyskinesia, influenza). In individual cases, usually obese or poorly responding to drug patients (Parkinson's disease) there is a need to increase the dose to 300 mg-400 mg/day. In neurology, higher doses are used to increase the therapeutic effect, e.g., brain injuries, 400 mg per day for a week are used, which allows faster treatment effects [3]. Additionally in other cases, the temporary use of higher doses ultimately resulted in an improvement in health in 89% of respondents [4]. Those double-blind, randomized, placebo-controlled studies did not indicate a difference in adverse events compared to the control group. At the same time, there are studies suggesting positive results of increased doses in antiviral therapies, up to 400 mg/day [5, 6]. In 2016 amantadine was tested against dengue virus infection (DENV) at 300 mg/day, proving full remission 2 days after starting the treatment [7].

From the GP perspective amantadine proved to be effective against influenza for the past 30 years, using a 2x100 mg scheme daily for 4-6 days. The first studies in early 2020 suggested similarities between influenza and SARS-CoV-2 antibodies [8]. At the same time, first experiences proved to have positive effects, receiving remission 6-8 days after amantadine introduction. Due to the intensivity of disease (many patients reported losing 1 kg of weight per day) and rapid complications caused by COVID-19, another scheme was considered. Additionally, recent in vitro structural studies have shown the affinity of the amantadine cation to the interior of viroporin E and its nonchemoselective (nonspecific) attachment to the amino acids of the ion channel interior [9].

These results lead to the protocol described below suggesting that amantadine at higher doses could be both safe and beneficial as an anti-COVID-19 drug. In the study below, we present observations of the effectiveness and safety of amantadine hydrochloride based on 55 cases treated with its higher doses in the course of COVID-19.

Patients And Methods

The patients were not intentionally selected for this study – patients were admitted to the pulmonology outpatient department with various disease severities and times from the onset of symptoms. Patients under observation were admitted to the clinic in Przemyśl, Poland, between August 1st, 2020 and November 30th, 2020, and most of them were residents of the Podkarpackie Voivodeship; they were treated on an outpatient basis (only one case was admitted to the hospital and required oxygen therapy). The patients were consulted both in the clinic and over the phone, the latter in case of having to cover longer distances to the clinic, or the lack of possibility of another form of consultation (their GP did not treat them with amantadine or the treatment was not available because of the overload of the health service caused by the pandemic). Each patient was obliged to inform their health status daily and was under doctoral supervision.

Within the study, the data from 100 patients were collected, out of which 55% were RT-PCR positive, 9% were negative and 36% did not undergo RT-PCR. Only patients with positive RT-PCR results were further investigated.

During the treatment, two control points were defined to analyze its effectiveness. The first was stabilization, i.e., the moment when the disease and present symptoms stopped progressing (collected symptoms are available at Table 2). The second was subjective remission, defined as the moment starting persistent lack of evidence of COVID-19 disease as reported by patients (clinical remission of most symptoms).

The aim of a general practitioner (GP) was to start the treatment as early as possible to avoid complications. Three variants were used, and their objectives and protocol are presented further below.

Variant 1 – acute and fulminant course

The protocol is as follows:

- 200 mg over the first hour
- next dose (100 mg) to be administered every 6 hours, for 48 to 72 hours, depending on the patient's condition.

After clinical improvement, the dose was reduced to 2x100 mg a day.

Variant 2 – elderly patients with a decreased metabolism

In the case of a patient's slower metabolism, a dose of 100 mg was administered every 8 hours for 2-3 days. Then, the dosage was reduced in accordance with the adopted pattern.

Variant 3

Patients with significant comorbidities had received the doses adjusted individually (based on the variants described above) depending on their medical condition and the course of the diseases. The maintained doses were continued as long as necessary and adjusted individually.

Maintenance doses were administered for a minimum of 7-8 days and sometimes even 10-14 days, depending on the length of the disease, symptom severity and disease severity at the time of treatment initiation. The distribution of patients taking the particular dose (i.e. relevant variant) is presented in Fig. 1.

Results

A total of 55 patients were enrolled, of which 22 were women (40%) and 33 were men (60%). The age range was between 10 and 90 years (mean age was 55.9 years, standard deviation: 15), and the mean BMI was 28.1 (*SD* = 3.7). A detailed evaluation of the general health condition in relation to comorbidities was performed. The detailed data concerning the study group are presented in Table 1 and Table 2.

Table 1. The structure of the study group

Metrical and anthropometric data		Total
		n=55
Age, years	Mean (*SD*)	55.9 (15)
	< 60	31
	≥ 60	24
Sex	Female	22
	Male	33
BMI	Mean (*SD*)	28.1 (3.7)
	Normal weight	11
	Overweight	27
	Obesity	17
Comorbidities	Total (patients having at least one)	35
	Arterial hypertension	22
	Asthma and lung diseases	3
	Diabetes	5
	Cholesterol	4
	Thyroid disease	3
	Coronary disease	4
	Other	12

SD (standard deviation), BMI – body mass index

Table 2. Summary of the diagnosed disease symptoms among COVID-19 patients who tested positive by RT-PCR before starting the treatment

Symptom of the disease	Total
	n=55 (100%)
Body temperature below 36°C	14 (25.5%)
Body temperature above 38°C	44 (80%)
Cough	43 (78.2%)
Dyspnoea	27 (49.1%)
Tightness in the chest	23 (41.9%)
Back pain	35 (63.6%)
Body pain	44 (80%)
Diarrhoea	26 (47.2%)
Fatigue	53 (96.4%)
Loss of appetite	42 (76.4%)
Loss/disorder of taste and/or smell	38 (69.1%)
Number of symptoms/ mean (*SD*)	7.1 (1.9)
Diagnosed pneumonia	29 (52.7%)

SD (standard deviation)

The case group has an overrepresentation of severe cases in comparison to the world mean where 10-22% of cases are reported to develop pneumonia [10-14]. Within the group, 53% of cases of pneumonia were diagnosed (based on available methods for GP such as auscultation and laboratory and radiological tests), which is more than three times greater than the mean. Additionally, 64% of persons within the group had at least one comorbidity, while 45% were 60 years old or older. Additionally, in the same group, 80% of patients were overweight, out of whom 31% were obese; such persons are burdened with a 113% greater risk of hospital admission in the case of COVID-19 [15]. During the treatment, 43 patients (78%) received antibiotic therapy, of which 21 orally (38%) and 22 intramuscularly (40%), i.e. based on the clinical condition and pneumonia progression.

In the described group of patients, the introduction of amantadine into the therapy was usually (median) made on the eighth day after the disease symptoms developed (between day 2 and day 30 from the onset of symptoms, with a mean of 8.8 days and *SD* = 4.6). The frequency of the amantadine dosage used in subsequent days of treatment is presented in Fig. 1.

The potential side effects were analyzed. Adverse effects were reported in 5 cases (9% of all cases), yet these effects due to mild severity did not affect the dosage scheme; these were: insomnia (1), nausea (2), and vertigo (2). The amantadine dosage scheme was changed in 6 cases (11% of the total number of patients) because of: misunderstanding of the dosage by the patient (2), arrhythmia (1), disease progression (1), diarrhea (1), and lack of appetite (1).

The relations of the selected parameters connected with the onset of the disease as a function of the moment of amantadine introduction to the treatment are presented in Fig. 2 and Fig. 3. The data in those figures form clusters of cases that present semilinear rising patterns of increased concentration (interquartile range equal to 1 and 4, respectively). The observed trends are created by the cases near the centers of clusters and thus are not artifacts caused by outliers. Moreover, the separate analyses of observations below and above the respective medians lead to analogous results. Minima and maxima of linear regressions of those subgroups create narrowing windows within which the analyzed relation can be expected (grayed areas in Fig. 2 and Fig. 3). This can suggest that upward trends exist in the dependencies between the day of introduction of amantadine to the patient's treatment and the number of doses until the stabilization of the patient state and remission of the COVID-19 disease.

Discussion

From the moment of treatment introduction, stabilization occurred within 24 hours in 69% of patients, and within 48 hours in 91% of patients. Between 24 and 48 hours full remission of disease symptoms occurred in 43% of cases. In total, 93% of patients did not require hospital admission during the treatment. None of the patients died and by the end of the treatment, all patients experienced remission of COVID-19.

Despite a high rate of pneumonia in the group of treated patients (53%), only one person was treated in the hospital (oxygen therapy), after amantadine was introduced. Three other people were referred to the hospital for pneumonia treatment. None of the patients died. As of the completion of the observation, none of the patients sought medical assistance with post COVID-19 syndrome (the condition two months after the end of treatment). Exemplary X-rays of the patient made before the treatment and during treatment are presented in Fig. 4.

One of early COVID-19 studies showed that survival rates for patients with pneumonia can be as low as 55% [10]. Even though it was conducted at early stages of the pandemic when hospitals did not use currently accessible drugs and procedures, it can be easily compared to the ambulatory treatment regime in Poland that follows no recommendations for particular treatment [16].

Groups of both our study and the one cited above can be compared since they have similar mean ages (57 years). In the cited article, 37% of patients had comorbidities, 22% had pneumonia, and the mortality rate was 13%. In the studied group subject to this article, 64% of patients had comorbidities, 53% had pneumonia, and 80% of patients were overweight (as mentioned earlier, such persons are burdened with a 113% greater risk of hospital admission in the case of COVID-19) [15], but none have died, and just 7%

required hospitalization. This may suggest that treatment with amantadine hydrochloride can reduce the risk of death and hospitalization level.

Remarks concerning the use of the considered variants and observations

If an evident improvement does not occur after 2-3 days and no complete stabilization of the patient's condition is achieved, it may be suspected that complications, such as pneumonia, have already developed. Such patients must be carefully examined, and lung auscultation is absolutely necessary. In doubtful cases, CT (computer tomography) or at least an X-ray must be performed, as they might reveal inflammatory lesions that are not identified upon a stethoscope examination. If lesions are found during auscultation, antibiotic therapy is required with antibiotics administered intramuscularly or intravenously plus low molecular weight heparin. Steroids are administered according to the patient's condition.

In many patients blood pressure drops or transient cardiovascular failure might occur at the breakthrough moment after the introduction of amantadine treatment, i.e. on 3-4 day. Patients may not develop high temperature and the disease symptoms begin to resolve, but at the same time, some poor tolerance of exercise may occur – even walking which lasts a maximum of 1-2 days.

Limitations of the study

Within the analysis performed by this study, attention should be paid to its significant limitations, which include: the lack of study randomization, the low number of the study population, the lack of blinding and control groups and the lack of concrete endpoints for the evaluation of the efficacy of amantadine. The final outcome results were not confirmed with the presence of IgM and IgG antibodies against COVID-19 after the completion of the treatment.

The use of antibiotics and other therapies may also distort the results of the analysis. Antibiotic treatment was not a standard in the study group, and all patients did not receive identical therapy. In some cases it was introduced empirically by other primary care physicians.

The most important limitation we acknowledge out of the ones listed above is lack of randomization. Randomized trials are standard clinical studies, as they improve the credibility of the results, particularly when factors with strong prognostic significance may affect the endpoints. In this case, such a factor may be the presence of the coexistence of pneumonia and/or the use of antibiotic therapy. On the other hand, this observational analysis was fully retrospective, and post factum randomization was not possible. It can also be noticed that randomized trials may also raise some reservations of ethical nature, in particular in the period of coronavirus, when the patient's benefit from a given therapy (even an experimental one) is unquestionable in the opinion of the supervising physician. This type of problem is discussed in the work of K. Bielecki [17].

The second limitation of the work presented here is the lack of controlled conditions and the lack of blinding in the study. This could have affected the result of the study, as some patients were convinced of the efficacy of the medication and thus they reported for treatment on purpose (they even travelled large

distances to get it). Therefore the placebo effect cannot be excluded. It is also important that some of the patients expected (had high hopes) that the medication would help them – hence the possibility of "therapeutic misconception". Such a misconception might also have occurred among the patients who administered the medication and evaluated/registered the course of the disease. This may be the source of errors in the evaluation of the condition of the patients that could not be detected or avoided without double blinding of the study.

It must also be stressed that the analysis was not planned before the commencement of the treatment. As a result, the post-hoc construction of the study might have been subconsciously made in such a way that could prove the expected thesis on the basis of the possessed data. Additionally, there were no precisely defined control points, such as: the avoidance of pneumonia and the lack of the necessity of hospitalization, including respiratory therapy. The lack of patient mortality also poses limitations to the study caused by expediency.

Finally, all the patients could not have been guaranteed one uniform standard of treatment, its methodology and the control of the treatment effects, because of their place of residence and/or the type of consultation they were subject to (face-to-face or on the phone).

Conclusions

The global problem caused by the occurrence of COVID-19 initiated a race against time in the search for an effective vaccination and cure. Amantadine is a medication known since the 1960s that was previously approved in the treatment and prophylaxis of influenza A on account of its antiviral activity. Its molecular targets are, among others, the protein of the ion channel and M2 viroporin. However currently, there are no recommendations to use amantadine for this indication, even though the first reports concerning the possibilities of the effective use of amantadine in the treatment of COVID-19 were already presented in 2020 [18-20].

Within this work, the known and postulated mechanisms inhibiting the replication of SARS-CoV-2 with the use of amantadine, as well as the results of the observation of the efficacy of amantadine treatment on 55 patients with COVID-19 within a medical outpatient practice (primary healthcare), were analyzed.

The patients were qualified for the treatment of COVID-19 with amantadine on the basis of their patient history and physical examination comprising, among others, of the moment of the typical COVID-19 symptom occurrence and their duration. Amantadine treatment regimen and duration were documented, while medication dosage was determined by the intensity of the symptoms, patient age and comorbidities. All patients were monitored on a daily basis via telephone consultation. In 91% of patients, stabilization was achieved within 48 hours of the introduction of the considered therapy, while within 72 hours, in 73% of cases the health condition improved (remission of symptoms). In general, despite full-symptomatic COVID-19 cases, 93% of patients treated with amantadine did not require hospitalization.

The safety evaluation considered the possibility of developing adverse effects. Only in five cases were mild and transient adverse effects observed, which did not have any effect on the change in the dosage.

The presented analysis and real-life observation may contribute to the hypothesis that the introduction of amantadine hydrochloride may shorten the duration of COVID-19 symptoms and decrease the risk of developing complications such as pneumonia, significantly reducing the rate of hospitalization. It may also be concluded that the benefit of the use of amantadine can exceed the risk of adverse effects (which resolve after drug discontinuation) and a relatively well-understood mechanism of action of the drug allows avoidance of pharmacokinetic interactions.

As a result of the above, it can be hypothesized that amantadine may be an inexpensive and easily available medication effective in the early stages of SARS-CoV-2 infection that can also reduce the hospitalization rate. Therefore, it may be justified to carry out a prospective, randomized and double-blinded clinical study with the use of placebo, concerning the effectiveness and safety of the use of amantadine in the early stages of COVID-19 disease.

Declarations

Conflict of interest: none declared

Ethics statement: The processed registry contains strictly deidentified patient data, who agreed to participate in this study. The Bioethics Council at the Medical University of Silesia in Katowice, Poland, approved this retrospective study and waived the need for written informed consent from the participants.

Contributions: WB proposed the amantadine hydrochloride treatment scheme. JB and MSW prepared the literature review. All authors participated in the concept of the study and draft of the manuscript. JB collected the data and analyzed it with SK and GAA. All authors interpreted the data, and revised and approved the final version of the manuscript. MF presented the study protocol to the Bioethics Council at the Medical University of Silesia in Katowice.

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Figures

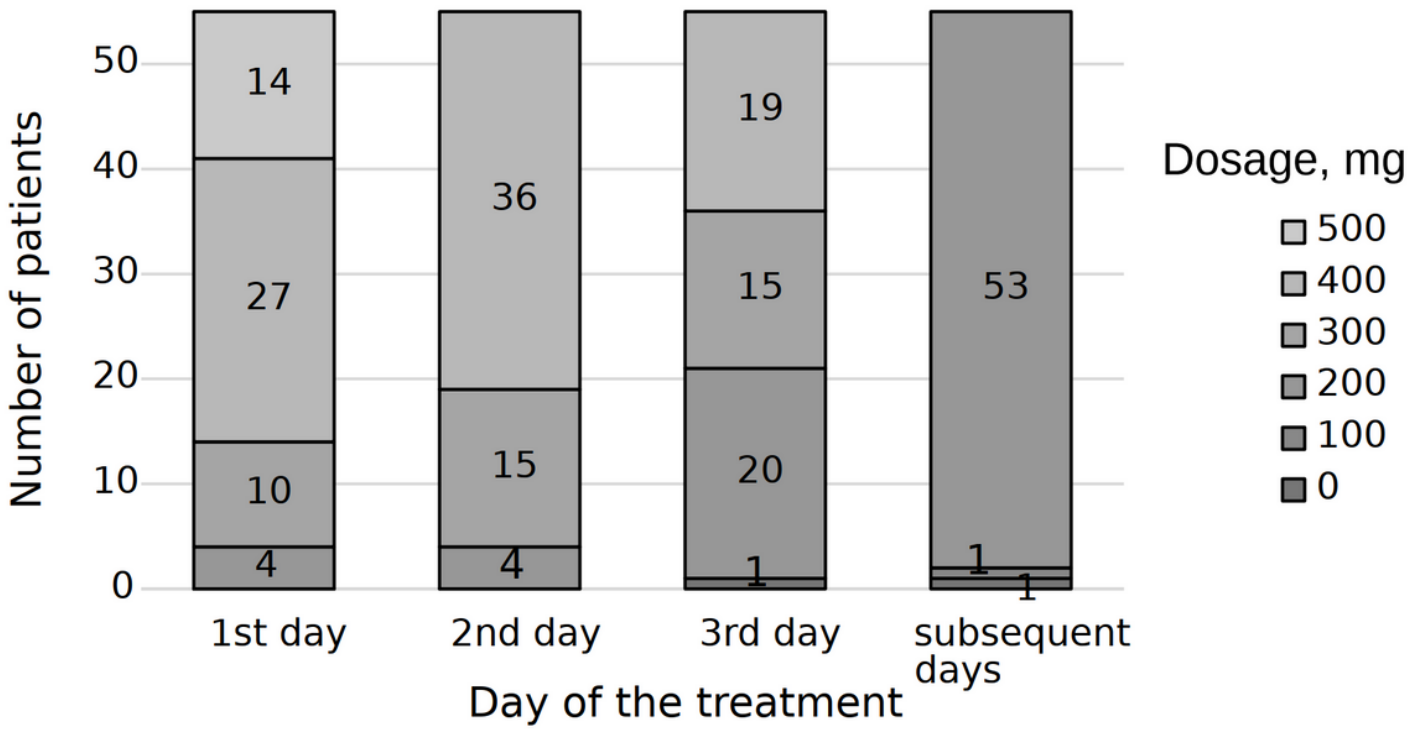

Figure 1

The distribution of the frequency of amantadine dosage in the first days of the treatment.

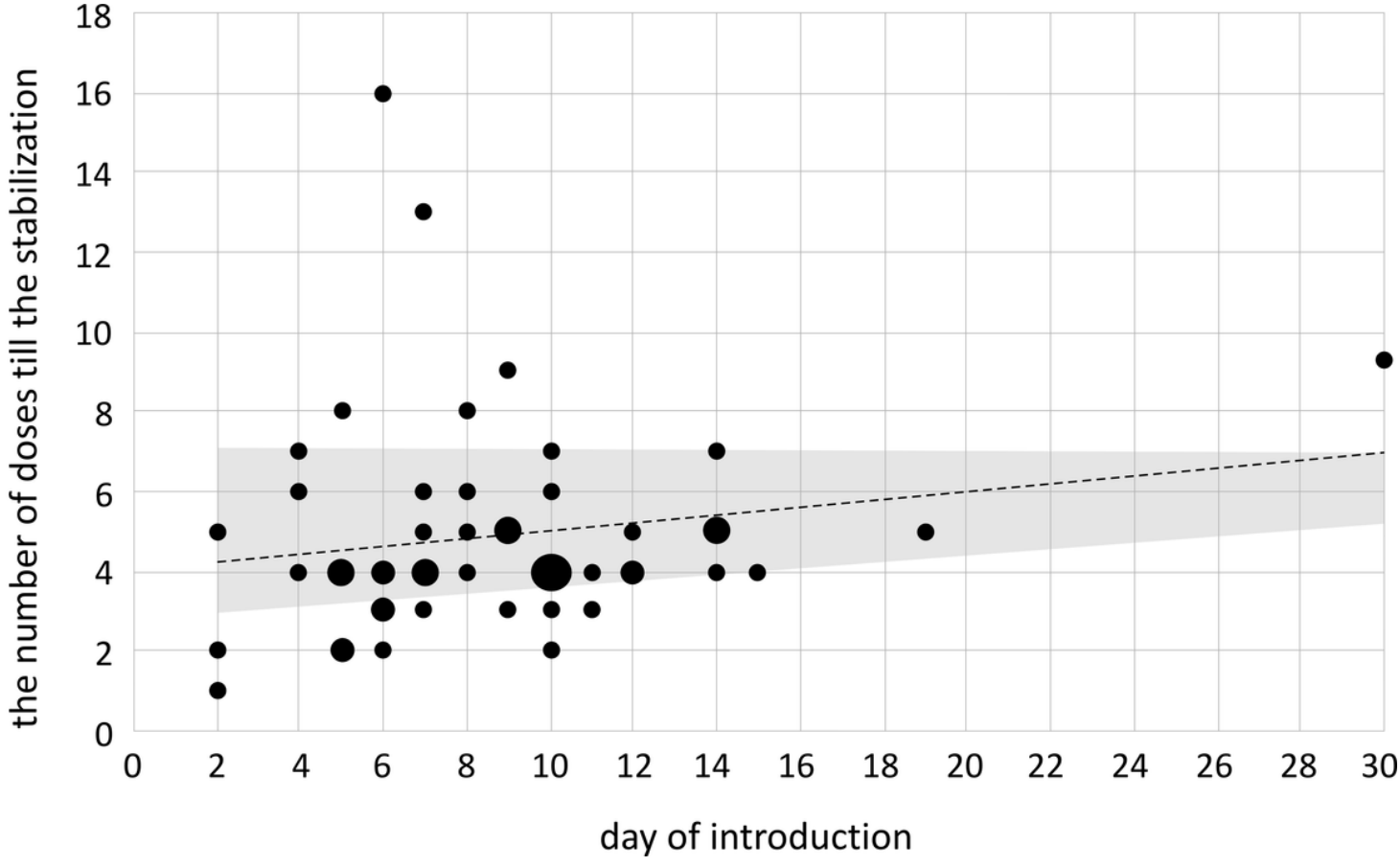

Figure 2

Aggregate the number of doses (1 dose - 100 mg) in the therapy until the moment of stabilization of the patient state as a function of the moment of introduction of amantadine hydrochloride to the treatment for COVID-19. The relative area of dots represents the number of cases (range 1-5). The grayed area is set by the minima and maxima of linear regression for groups of points below and above the median. The dashed line represents the linear regression for the whole observed group.

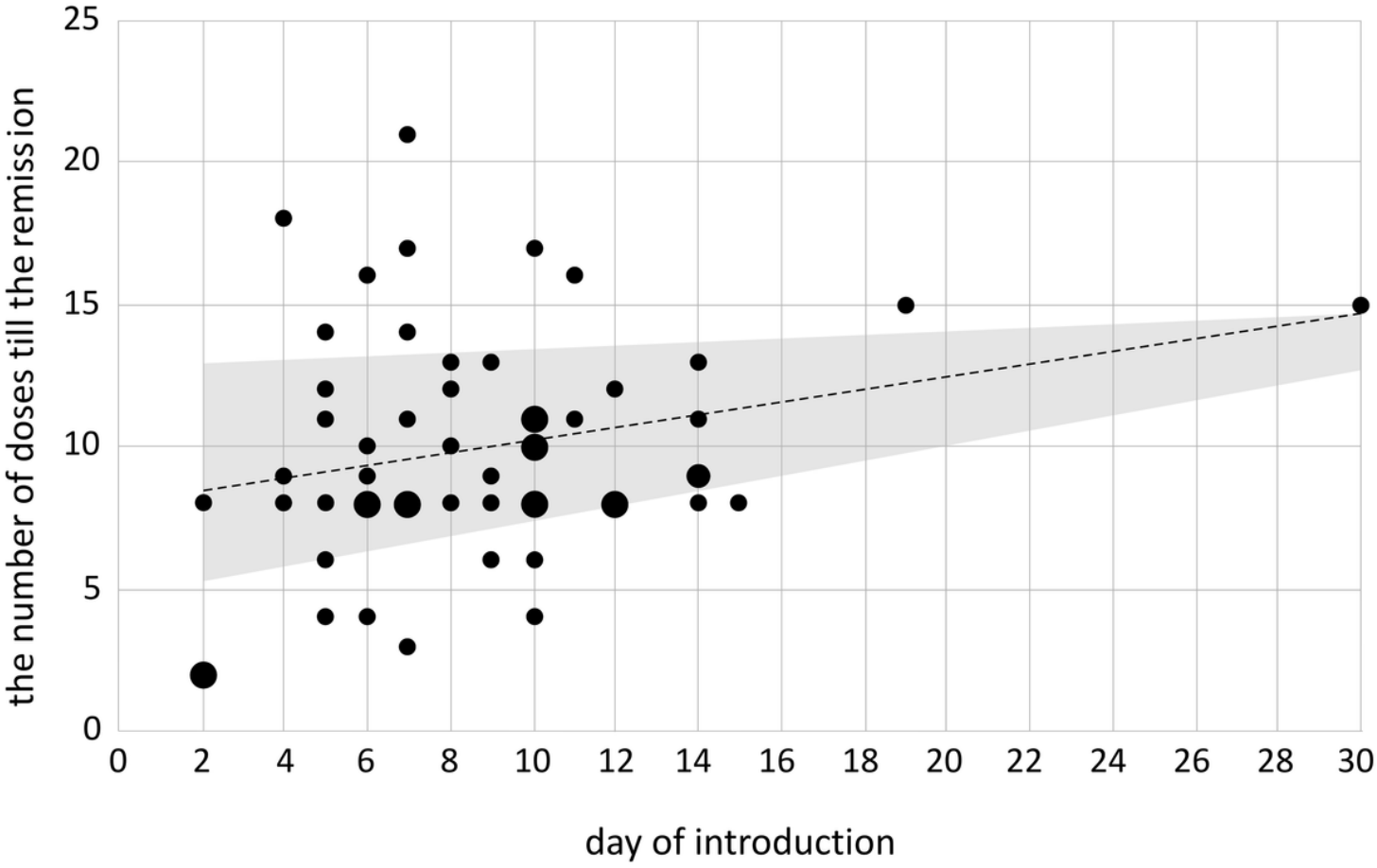

Figure 3

Aggregate the number of doses (1 dose - 100 mg) in the therapy until the moment of remission of symptoms of COVID-19 as a function of the moment of introduction of amantadine hydrochloride to the treatment. The relative area of dots represents the number of cases (range 1-2). The grayed area is set by the minima and maxima of regression for points below and above the median. The dashed line represents the linear regression for the whole observed group.

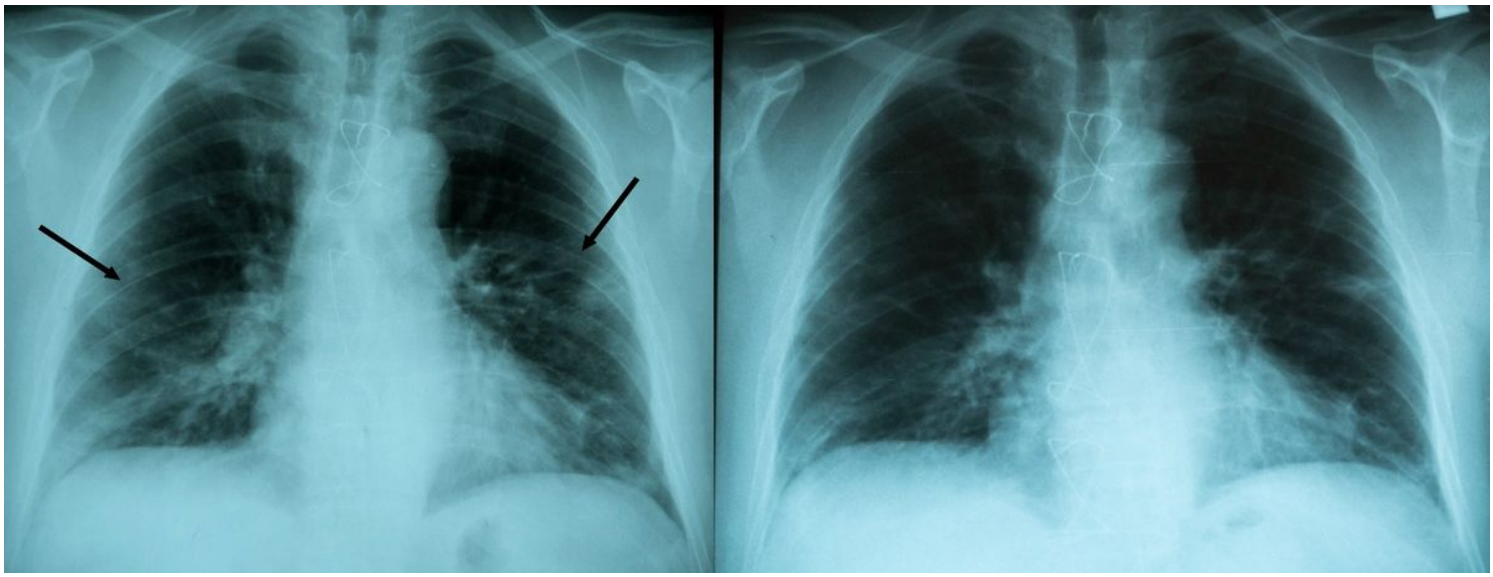

Figure 4

X-ray image of the lungs of a male patient in the mid-50s with obesity who was diagnosed with diabetes. The left photo shows the lungs before the start of amantadine therapy on the seventh day of fully symptomatic COVID-19 with a diagnosed active pneumonia caused by the SARS-CoV-2 virus. The right photo was taken on the fourth day of treatment. Radiological description: “a clear regress of the lesions, in particular the densification and ground-glass opacities in the peripheries of the inferior part of the right lung and in the peripheries of the middle part of the left lung. Less clear fibrotic and atelectatic strands supra-diaphragmatically in the left lung. Less distended hilar vessels and perihilar segments of the veins in the superior lobes.”