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Adverse drug reactions in patients with COVID-19 in Brazil: analysis of spontaneous notifications of the Brazilian pharmacovigilance system

Reações adversas a medicamentos em pacientes com COVID-19 no Brasil: análise das notificações espontâneas do sistema de farmacovigilância brasileiro

Reacciones adversas a medicamentos en pacientes con COVID-19 en Brasil: análisis de las notificaciones espontáneas del sistema de farmacovigilancia brasileño

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Abstract

In March 2020, the World Health Organization announced the new COVID-19 pandemic, which represented a challenge for health services and professionals. An effective treatment against this disease has not yet been developed; as such, several drugs are used without evidence of efficacy, which in some cases may lead to unwanted events. This is a cross-sectional study with the objective of evaluating adverse drug reactions (ADRs) in patients with COVID-19, identified between March 1 and August 15, 2020, in Brazil, as well as assessing the factors associated with the emergence of severe reactions. To compare the proportions of samples related to the notifier, patient, drugs and adverse events, we used Fisher's chi-square and exact nonparametric tests; and to compare the means of the data with normal distribution, we used the Student's t-test and Mann-Whitney's test. A multivariate logistic regression analysis was also performed, estimating the crude and adjusted odds ratio (OR) by the Stata software, version 10.0. A total of 631 ADRs were identified in 402 patients. The main drugs were hydroxychloroquine (59.5%), azithromycin (9.8%) and chloroquine (5.2%). The reactions manifested primarily in the cardiac system (38.8%), gastrointestinal system (14.4%), skin tissue (12.2%) and hepatic system (8.9%). Chloroquine (OR = 5.4; 95%CI: 1.9-15.6) and hydroxychloroquine (OR = 2.1; 95CI%: 1.2-3.6) were the only drugs associated with severe ADR. Our findings provide support for better practices in pharmacovigilance, contributing to effective and secure regulatory decision-making by the Brazilian Health Regulatory Agency, patients and society as a whole.

Coronavirus Infections; Chloroquine; Hydroxychloroquine; Pharmacoepidemiology; Patient Safety

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Introduction

On December 31, 2019, the World Health Organization (WHO) was notified of a new respiratory viral disease identified in Wuhan, China. On March 12, 2020, WHO declared that the world was facing a new pandemic. Genetic sequencing has suggested that it was a betacoronavirus linked to the SARS virus (SARS-CoV-2) [1], which causes the coronavirus disease 2019 (COVID-19). This virus binds to the enzyme ECA2 [2] and has great power of dissemination among humans.

Data from WHO on August 15, 2020, confirmed 21,026,758 cases of COVID-19, with 755,786 deaths worldwide. The United States and Brazil are the countries with the highest number of confirmed cases of this disease and deaths in the world (World Health Organization. WHO coronavirus disease (COVID-19) dashboard. https://covid19.who.int/, accessed on 15/Aug/2020). The pandemic puts great pressure on health systems and has significant impact on public health and global economy [2,3,4]. Up to that date, in Brazil, there have been 277,107 hospitalizations of people with COVID-19 (Ministério da Saúde. COVID-19: painel coronavírus. https://covid.saude.gov.br, accessed on 15/Aug/2020).

Preliminary data from in vitro studies identified antiviral activities of chloroquine and hydroxychloroquine, and drugs associated with macrolide antibiotics, such as azithromycin. These drugs are recommended in some countries as therapeutic approaches against SARS-CoV-2. Although they have indication for other diseases, the use in this pandemic is still experimental; even compassionate use may pose health risks, due to the potential to cause adverse reactions (especially cardiotoxicity) [4,5,6].

Adverse drug reactions (ADRs) are a serious public health problem and contribute to increased morbidity and mortality as well as costs for both patients and health systems [7]. ADRs can prolong the time of hospitalization of the patient, further aggravating the search for beds for new infected patients. Considering the limited amount of safety information for the treatment of COVID-19, this study aims to evaluate the adverse reactions identified in patients with the disease. This was carried out according to characteristics of patients, medications and reactions, as well as the identification of factors associated with the emergence of severe ADRs in these people.

Methodology

This study follows the guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) initiative.

Study design and population

This is a cross-sectional study, with descriptive-exploratory and analytical stages, using as data source individual case safety reports (ICSR) forwarded to the National Center for Monitoring of Medicines (CNMM) of the Brazilian Health Regulatory Agency (Anvisa).

The population consisted of COVID-19 patients who presented ADRs and were registered in the Brazilian pharmacovigilance system between March 1st, 2020, and August 15, 2020. The reports were tracked on the system using the words "COVID-19", "Coronavirus", "SARS-Cov", "Pneumonia", "Hydroxychloroquine", "Chloroquine", in the title of the notification and also by therapeutic indication of the drugs, according to the Medical Dictionary for Regulatory Activities (MedDRA), version 23 [8], with the terms "COVID-19", "suspected COVID-19", and "treatment of COVID-19". All reports were reviewed before their inclusion in the study.

Causality was assessed using the WHO-UMC (Uppsala Monitoring Center) method [9,10]. All drugs with the status of "interaction" in the reports were considered suspect, according to the ICH E2B guide (R3) [9]. The severity of ADRs was classified according to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH, Geneva, Switzerland) guide, which considers as severe ADRs any reaction that results in death, threat to life, causing hospitalization or prolonging hospitalization, resulting in disability, persistent or significant, or congenital anomaly [11].

Database and structural information arrangements.

The data source evaluated was VigiBase (https://www.who-umc.org/vigibase/vigibase/), a global database for receiving ICSR from countries that participate in the WHO drug monitoring program. This system was developed and maintained on behalf of WHO by the Uppsala Monitoring Center in Sweden [12].

Anvisa in 2019 declared VigiFlow (https://www.who-umc.org/global-pharmacovigilance/vigiflow/) as the official ADR notification system and adopted MedDRA as the standard dictionary of medical terms for these adverse reactions. In Brazil, this system was named VigiMed (http://antigo.anvisa.gov.br/vigimed). Thus, Anvisa complied with the ICH guideline that deals with data elements for transmission of adverse reactions (E2B guideline), and all concepts and methods used in this study, both for causality and severity assessment, are justified by the commitments of Anvisa, as a member of the ICH, and are used in its ADR-monitoring activities.

A report of a case of patients with ADR in VigiMed may generate several records in the database, depending on the number of drugs used and the reactions identified. For example, the ICSR of a patient who used three medications (A, B and C) and had two adverse reactions (X, Y) with the suspected drugs A and B, will create five records, with four drug-reaction pairs: two of drug A with each identified reaction (AX, AY), two of drug B (BX, BY), and one record for drug C as concomitant.

Each patient receives a unique ID and information on dosage, posology, or place of origin are repeated for each record created. Thus, the analyses can refer to the characteristics of the patient, notifier, drugs used and "drug-reaction" pairs, which are the reactions themselves. Due to the complexity of the data arrangements formed, the profile of patients, medications and drug-reactions pairs formed will be evaluated, since the analysis of severity, causality and outcome are based on the drug-reaction pair formed and not on the set of drugs used.

Inclusion and exclusion criteria

The ICSR of patients with COVID-19 reported in VigiMed during the study period were included, while those related to medication errors, ineffectiveness, or technical complaints of drugs wrongly inserted in VigiMed were excluded.

Study variables

The variables related to the characteristics of the notifier (state of residence, profession), patient (gender, age, number of drugs consumed, concomitant diseases), drugs involved (therapeutic class, cumulative dose, degree of suspicion) and ADRs (type, severity, causality) were evaluated. The drugs were classified according to the ATC (*Anatomical Therapeutical Chemical Classification System*) [13]. The ADRs were classified with the MedDRA terminology, version 23.0 [8], presented by system-organ-class (SOC) and preferred reaction terminology (PT).

Polypharmacy was defined as the consumption of five or more drugs [14]. To improve the completeness of the variables, the ICSR were evaluated individually and, whenever possible, the information absent in the database was completed from the data present in the text fields of the reports.

Statistical analyses

In the descriptive stage, the variables of interest were categorized and described using relative frequencies. The proportions of ADR were estimated using point estimates or 95% confidence intervals (95%CI). In the analytical stage, the data were submitted to non-conditional logistic regression, having as dependent variable "severe reaction (yes, no)," and as explanatory (independent) the variables gender, age group, presence of comorbidities and medications used. Any given case was considered "severe reaction" whenever it met the ICH severe reaction criterion [11]. For qualitative variables, we used the Pearson's chi-square nonparametric tests when the sample sizes were large and Fisher's exact test when they were small. To compare means and medians of samples with normal distribu-

tion, the t-test was used; in turn, the Mann-Whitney's test was used in small samples or with non-homogeneous variances.

Crude and adjusted logistic regression models were estimated. In the bivariate analysis, variables considered to be candidates for multivariate analysis were identified as those with a level of statistical significance of $p < 0.20$. We adopted a more permissive value, in this preliminary stage for the p-value, so that all relevant variables could be examined after including and adjusting confounders. Then, with the stepwise method (backwards) the statistically irrelevant variables were excluded, until only those with statistical significance ($p < 0.05$) were in the final model. Adjusted odds ratio (OR) measurements and their respective 95%CI were estimated. All analysis was done with the Stata software, version 10 (http://www.stata.com).

Ethical aspects

The study was approved by the Ethics Research Committe (CEP) of Federal Universtity of Ceará (UFC), with approval opinion n. 4,083,486, and CAE n. 02066818.3.0000.5054.

Results

The research identified 1,138 ICSR of patients with COVID-19. After applying the established criteria, 736 ICSR (64.7%) were discarded, 574 (78%) by duplication of the research, 114 (15.4%) by other unidentified diseases and therapeutic indications, 48 (6.6%) medication error and technical complaint. A total of 402 ICSR, with 499 suspected drugs and 631 ADR in patients with COVID-19, were included in the analysis.

Pharmacists were the ones who most reported suspected cases (81.8%) and the physicians were the professionals with the lowest participation in the system, with only three cases (0.8%). A total of 71 hospitals distributed in 16 states of Brazil were responsible for sending the ICSR. Moreover, 1,247 drugs (3.1 drugs/patients) were reported, generating an average of 1.6 ADR/patient. The states that sent most cases were: São Paulo (53.4%), Rio de Janeiro (11.9%) and Rio Grande do Sul (9.2%). (Table 1).

The majority of ICSR were male (59.7%). The most affected age group was 45-64 years (36.8%), with mean age of 60.5 years ± 1.8 years. 53.3% of the patients presented other diseases or risk factors, such as hypertension (31.1%), diabetes (21.4%), cardiovascular diseases (12.9%), with concomitant use of up to four medications (81.6%) (Table 1).

Drugs used in therapy

In general, the most reported pharmacological groups in ICSR were: aminoquinolins (26.3%), macrolide antibiotics (10.8%), and antithrombotic agents (6.3%). The five most used groups represented 51.6% of all drugs used by the patients in the study (Table 2).

Among the drugs consumed, 748 (60.0%) were considered concomitant, 17 (1.4%) as drug interaction with other drugs and 482 (38.6%) suspected of causing the reactions. Among the drugs suspected/with interaction (n = 499), the most frequent (79.7%) were hydroxychloroquine (59.5%), azitromycin (9.8%), chloroquine (5.2%) and ceftriaxone with 3.2% (Table 2).

Among the total number of drugs suspected and interacting (n = 499), 319 (64%) were discontinued from therapy, 17 (3.4%) had the reduction of the administered dose and in 107 drugs (21.4%) the medical team kept the medicine without changing the dose (Table 2). As patients grew older, the medical decision to withdraw the suspected drug was more frequent.

General aspects of reported adverse reactions

The main groups, by SOC, according to the place of manifestation of the reaction in patients, were diseases and cardiac alterations (38.8%), followed by gastrointestinal diseases (14.4%), those related to the cutaneous and subcutaneous tissue (12.2%) and hepatobiliary diseases (8.9%) (Table 3).

Table 1

Characteristics of adverse drug reaction (ADR) notifications, according to the notifying professional, the State, sex and age group, pre-existing disease of patients and polypharmacy. Brazil, March 1st to August 15, 2020 (N = 402).

	n	%
Notifying professional		
Pharmacist	329	81.8
Physician	3	0.8
Other health professionals	66	16.4
Consumer/non-health professional	4	1.0
Total	402	100.0
State of the notification		
São Paulo	215	53.4
Rio de Janeiro	48	11.9
Rio Grande do Sul	37	9.2
Ceará	28	7.0
Pernambuco	16	4.0
Minas Gerais	14	3.4
Rio Grande do Norte	7	1.7
Federal District	7	1.7
Bahia	7	1.7
Maranhão	6	1.5
Paraná	6	1.5
Espírito Santo	3	0.8
Piauí	3	0.8
São Catarina	3	0.8
Goiás	1	0.3
Mato Grosso do Sul	1	0.3
Sex		
Male	162	40.3
Female	240	59.7
Age group (years) (n = 386) *		
0-17	2	0.5
18-44	75	19.4
45-64	142	36.8
65-74	72	18.7
> 74	95	24.6
Pre-existing conditions		
No	186	46.2
Yes	216	53.3
Patients using multiple medications **		
No	328	81.6
Yes	74	18.4

* 16 patients had their age ignored;

** Use of five or more concomitant medications.

Table 2

Characteristics of the notifications, according to pharmacological groups, suspected drugs and actions of the medical team. Brazil, March 1st to August 15, 2020.

Drugs used during hospitalization	n	%
Pharmacological groups *		
Aminoquinolines	328	26.3
Macrolide antibiotics	135	10.8
Antithrombotic agents	78	6.3
Beta-lactam antibacterials **	71	5.7
Systemic antivirals	32	2.6
Other groups	603	48.4
Total	1,247	100.0
Relation between the medication and the event		
Concomitant	748	60.0
Interaction	17	1.4
Suspected	482	38.6
Total	1,247	100.0
Interactive drugs or main suspected drugs		
Hydroxychloroquine	297	59.5
Azithromycin	49	9.8
Chloroquine	26	5.2
Ceftriaxone	16	3.2
Other drugs	111	22.2
Total	499	100.0
Action of the medical team in relation to the interactive drugs or suspected drugs		
Suspension of medication	319	64.0
No dose change	107	21.4
Dose reduction	17	3.4
Ignored	56	11.2
Total	499	100.0

* 4th ATC (*Anatomical Therapeutical Chemical Classification System*) [13] level;

** Penicillins excluded.

The causality assessment showed that 19.8% of the reactions were classified as probable, 67.4% as possible, 2.1% as unlikely and 10.6% as conditional, that is, indefinite due to the absence or low quality of information. Only one reaction (0.2%) was confirmed.

The analysis of factors associated with the presence of severe ADR in patients

In total, 352 (56.4%) reactions were classified as severe, 37.8% of which were cardiac ADR with "QT interval prolongation". Regarding the outcome, 393 reactions (62.3%) were resolved, 137 (21.7%) were recovering, and 68 (11.3%) reactions had their outcomes ignored. A total of 30 reactions resulted in death; however, it was not possible to assess whether the reaction was the underlying cause of death. Table 4 presents all the outcomes of the main reactions.

When evaluating the factors associated with the presence of severe ADR among patients with COVID-19, presented in Table 5, we identified that men (OR = 1.7; 95%CI: 1.1-2.6; p = 0.02) and those over 65 years (OR = 1.5; 95%CI: 1.01-2.6; p = 0.04) were more likely to present severe ADR when compared to the other reported cases.

Hydroxychloroquine (OR = 2.1; 95%CI: 1.2-3.6; p < 0.01) and chloroquine (OR = 5.4; 95%CI: 1.9-15.6; p < 0.01) were the only two drugs that were statistically associated with the presence of severe

Table 3

Distribution of the notified "drug-reaction" pairs, according to the Medical Dictionary for Regulatory Activities (MedDRA, version 23 [8]) classification (preferred reaction terminology – PT and system-organ-class – SOC). Brazil, March 1st, 2020 to August 15, 2020 (N = 631).

Main SOC and PT involved	Azitromycin n (%)	Chloroquine n (%)	Hydroxycloroquine n (%)	Ceftriaxione n (%)	Others n (%)	Total n (%)
Heart disease and investigations of cardiac changes (n = 245; 38.8%)						
QT interval prolongation	23 (41.1)	15 (48.4)	165 (44.4)	1 (4.8)	8 (5.3)	212 (33.6)
Tachycardia	1 (1.8)	-	10 (2.7)	-	4 (2.7)	15 (2.4)
Other heart disorders	2 (3.6)	3 (9.7)	12 (3.2)	-	1 (0.7)	18 (2.9)
Gastrointestinal disorders (n = 91, 14.4%)						
Diarrhea	10 (17.9)	-	24 (6.4)	2 (9.5)	11 (7.3)	47 (7.4)
Nausea	-	1 (3.2)	15 (4.0)	1 (4.8)	3 (2.0)	20 (3.2)
Other gastrointestinal disorders	1 (1.8)	1 (3.2)	16 (4.3)	-	6 (4.0)	24 (3.8)
Skin and subcutaneous tissue diseases (n = 77, 12.2%)						
Pruritus	-	2 (6.4)	4 (1.1)	3 (14.3)	30 (19.9)	39 (6.2)
Exanthema	4 (7.1)	2 (6.4)	5 (1.3)	5 (23.8)	11 (7.3)	27 (4.3)
Other skin disorders	1 (1.8)	-	-	1 (4.8)	7 (4.6)	9 (1.4)
Hepatobiliary disorders (n = 56, 8.9%)						
Increased transaminases	4 (7.1)	2 (6.4)	28 (7.5)	-	4 (2.7)	38 (6.0)
Hepatotoxicity	4 (7.1)	-	4 (1.1)	1 (4.8)	7 (4.6)	16 (2.5)
Other liver disorders	-	-	2 (0.5)	-	-	2 (0.3)
Diseases of the hematological and lymphatic systems (n = 44; 7.0%)						
Non-hemolytic anemias and medullary depression	-	-	15 (4.0)	1 (4.8)	2 (1.3)	18 (2.9)
Other hematological disorders	-	-	16 (4.3)	1 (4,.8)	9 (6.0)	26 (4.1)
Other SOC (n = 109, 18.2%)	6 (10.7)	5 (16.1)	56 (15.1)	5 (23.8)	46 (30.4)	118 (18.7)
Final total	56 (8.9)	31 (4.9)	372 (59.0)	21 (3.3)	151 (23.9)	631 (100.0)

ADR. Patients who used hydroxychloroquine were almost twice more likely to have severe ADR than patients who did not use this medication; critically, those who used chloroquine were almost six times more likely to have severe ADR compared to patients who did not use this medication (Table 5).

Analysis of cumulative doses until the onset of the first symptoms of ADR

Among the 631 reported reactions, 271 of them (42.9%) had information on the total dose administered until the reaction (cumulative dose) appeared. Patients who used chloroquine had the highest cumulative dose mean with 1,503.8mg. As for azitromycin, the mean was 1,464.7mg, and for hydroxychloroquine it was 1,393.8mg (Table 6).

The cumulative mean dose of patients who used hydroxychloroquine and died was 1,485.7mg (SD = 999.0), while for those who did not die was 1,399.0mg (SD = 904.3). For those who used chloroquine and died, the cumulative mean dose was 1,950mg (SD = 687.4) while for the group who did not die it was 1,456.8mg (SD = 864.7). Despite the differences between the means, they were not significant ($p > 0.05$) (Table 6).

Table 4

Distribution of "drug-reaction" pairs according to sex, severity of reaction, causality and outcome of the reaction in COVID-19 patients. Brazil, March 1st, 2020 to August 15, 2020 (N = 613).

Variables	QT interval prolongation n (%)	Diarrhea n (%)	Increase in AST and ALT n (%)	Pruritus n (%)	Anemia n (%)	Other n (%)
Sex						
Female	84 (32.2)	29 (11.1)	13 (5.0)	12 (4.6)	7 (2.7)	116 (44.4)
Male	128 (34.6)	18 (4.9) *	25 (6.8)	27 (7.3)	11 (3.0)	161 (43.5)
Age groups (years) **						
0-17	-	1 (33.3)	-	1 (33.3)	-	1 (33.3)
18-44s	26 (21.3)	7 (5.7)	5 (4.1)	9 (7.4)	3 (2.5)	72 (59.0)
45-64	68 (30.6)	18 (8.1)	20 (9.0)	3 (1.4)	8 (3.6)	105 (47.3)
65-74	46 (41.4)	12 (10.8)	5 (4.5)	4 (3.6)	2 (1.8)	42 (37.8)
> 74	65 (43.1) *	9 (6.0)	6 (4.0)	21 (13.9)	5 (3.3)	45 (29.8)
Severity of reaction ***						
Non-severe	78 (28.7)	29 (10.7) *	12 (4.4)	17 (6.2)	6 (2.2)	130 (47.8)
Severe	133 (37.8) *	17 (4.8)	26 (7.4)	21 (6.0)	12 (3.4)	143 (40.6)
Causality						
Defined	-	-	-	-	-	1 (100.0)
Probable	54 (43.2)	3 (2.4)	4 (3.2)	10 (8.0)	-	54 (43.2)
Possible	152 (35.8)	37 (8.7)	27 (6.4)	11 (2.6)	15 (3.5)	183 (43.1)
Improbable	-	6 (46.1)	1 (7.7)	-	-	6 (46.1)
Conditional	6 (9.0)	1 (1.4)	6 (9.0)	18 (26.9)	3 (4.4)	33 (49.2)
Reaction outcome						
Death	11 (36.7)	1 (3.3)	7 (23.3)	-	-	11 (36.7)
Fully recovered	140 (35.6)	39 (9.9)	10 (2.5)	12 (3.1)	13 (3.3)	179 (45.6)
Recovery in progress	33 (24.1)	5 (3.7)	15 (11.0)	25 (18.3)	4 (2.9)	55 (40.1)
Ignored	28 (39.4)	2 (2.8)	6 (8.4)	2 (2.8)	1 (1.4)	32 (45.1)

* p-value < 0.05 (Pearson's chi-squared test)

** 22 drug-reaction pairs without the patient's age classification;

*** 7 drug-reaction pairs without classification of the severity of the reaction.

Individual analysis of the main reported reactions

• QT interval prolongation

Extension of the QT interval was the most reported reaction among all ADRs, with 212 records (33.6%). The main drugs suspected of provoking this reaction were chloroquine (48.4%), hydroxychloroquine (44.4%) and azitromycin (41.1%) (Table 3).

In the percentage distribution of this reaction by age group, a positive gradient was observed, from 21.6% among patients aged 18-44 years, to 43.1% in patients aged 75 years and over. Regarding the distribution by sex, 128 of these reactions occurred in men (34.6%), and 84 in women (32.2%) (Table 4).

A significant proportion of these reactions were severe (n = 133; 37.8%) (Table 4). Two patients presented torsades de pointes after the use of hydroxychloroquine, causing prolonged hospitalizations and thus being classified as severe ADR.

Among the patients who had the length of the QT interval prolongation reported in the database (n = 118; 55.7%), the mean of this prolongation was 513.1ms, (SD = 55.1). A total of 71 patients (60.2%) had this measure above 500ms. When evaluating this ADR, we observed that the mean prolongation

Table 5

Factors associated with the presence of severe adverse drug reaction (ADR) in patients with COVID-19, derived from crude and adjusted logistic regression analysis. Brazil, March 1st, 2020 to August 15, 2020.

	Univariate analysis			Multiple analysis		
	OR	95%CI	p-value	OR	95%CI	p-value
Sex						
Female	Ref.					
Male	1.7	1.1-2.5	0.01	1.7	1.1-2.6	0.02
Polypharmacy						
< 5	Ref.					
> 5	1.1	0.6-1.9	0.61			
Age classification (years)						
< 65	Ref.					
> 65	1.5	1.01-2.3	0.04	1.5	1.01-2.4	0.04
Has concomitant diseases						
No	Ref.					
Yes	1.2	0.8-1.9	0.27			
Use of the medication:						
Azithromycin	0.8	0.6-1.3	0.43			
Chloroquine	2.9	1.1-7.4	0.02	5.4	1.9-15.6	< 0.01
Hydroxychloroquine	1.4	0.9-2.1	0.16	2.1	1.2-3.6	< 0.01
Ceftriaxone sodium	1.1	0.6-1.9	0.86			
Other medication	0.7	0.4-1.4	0.36			
Concomitant diseases						
Liver diseases	0.4	0.03-4.5	0.46			
Hypertension	1.3	0.8-2.0	0.24			
Diabetes	1.0	0.6-1.7	0.84			
Gastrointestinal diseases	1.6	0.3-8.9	0.58			
Heart diseases	1.4	0.8-2.5	0.30			
Obesity	1.4	0.7-2.7	0.33			
Dyslipidemias	1.2	0.5-2.7	0.63			
Respiratory diseases	2.1	0.8-5.6	0.12			
Kidney diseases	0.6	0.3-1.4	0.26			
Smoking habit	1.2	0.2-7.4	0.81			
Neoplasias	0,6	0,2-1,8	0,32			

95%CI: 95% confidence interval; OR: odds ratio; Ref.: reference.

in patients using azitromycin was 511.7ms (SD = 42.1), while for those using chloroquine it was 505.4ms (SD = 36.7) and for those using hydroxychloroquine it was 512ms (SD = 56.5) (Table 6).

The patients who used hydroxychloroquine and had a QT interval under 500ms had an average cumulative dose of 1,148.5mg, while patients who had QT interval above 500ms, the cumulative dose for this same drug was 1,662mg ($p < 0.01$). For both chloroquine and azitromycin, the behavior was similar; however, the difference between the means was not significant (Table 6).

Regarding the outcome of the reaction, it was found that 11 of these were classified as fatal, which represented 36.7% of all deaths in the study. Among these, nine cases were reported after the use of hydroxychloroquine (81.8%) and two after the use of chloroquine (18.2%). The mean QT interval prolongation among all patients who presented this ADR was 513.05ms (SD = 55.1), while in fatal cases for this same reaction it was 507.8ms (Table 6).

Table 6

Mean cumulative dose (in mg) and QT interval prolongation of COVID-19 patients who used the drugs hydroxychloroquine, chloroquine and azithromycin and presented adverse drug reactions (ADRs). Brazil, March 1st, 2020 to August 15, 2020.

Variables	Azitromycin (SD)	Chloroquine (SD)	Hydroxychloroquine (SD)
Mean cumulative dose	1,464.7 (681.8)	1,503.8 (833.9)	1,393.8 (891.5)
Mean cumulative dose of patients with non-fatal outcome	1,526.7 (704.5)	1,456.8 (864.7)	1,399.0 (904.3)
Cumulative mean dose of patients with fatal outcome	1,000.0 (-)	1,950.0 (687.4)	1,485.7 (999.0)
Mean cumulative dose of patients with QT interval under 500ms	1,333.3 (288.7)	525.0 (106.1)	1,148.5 (762.9)
Mean cumulative dose of patients with QT interval over 500ms	1,400.0 (883.1)	2,100.0 (1,430.9)	1,662.5 (1,167.0)
Mean QT interval prolongation (ms)	511.7 (42.1)	505.4 (36.7)	512.0 (56.5)
Mean prolongation of QT interval (ms) in fatal cases	-	-	507.8 (32.1)
Mean prolongation of the QT interval (ms) in fatal cases	510.8 (43.7)	491.8 (23.7)	514.7 (60.3)

SD: standard deviation.

- **Diarrhea**

The group of gastrointestinal diseases was the second SOC group with more reports of reactions (n = 91; 14.4%). In this group, diarrhea was the most reported ADR with 47 records (7.4%), with azitromycin (17.9%) and ceftriaxone (9.5%) being the main drugs suspected of causing these reactions (Table 3).

Women (11.1%) had more cases of diarrhea than men (4.9%; $p < 0.05$). Unlike the QT interval prolongation reaction, diarrhea was more often classified as non-severe (n = 29, 10.7%; $p < 0.05$) (Table 4). Men presented proportionally (n = 7; 38.9%) more episodes of severe diarrhea than women (n = 10; 35.7%), however, this difference was not significant ($p = 1.00$). The only case classified as "fatal" was in a 70-year-old male patient who used azitromycin.

Among the diarrhea reactions with information on the actions adopted (n = 29; 61.7%), in 13 of them the medical decision was to maintain drug therapy without any alteration (44.8%) and in 16 (55.2%) the doctor decided to suspend the suspect medication.

- **Pruritus**

Pruritus was the main ADR of the SOC of skin diseases, with 41 ICSRs (6.5%) (Table 3). The proportion of men who presented this ADR was higher than that of women, but without significant difference ($p = 0.15$); in men, however, the reactions were severe. Patients under 18 years of age and those aged 75 years and over were proportionally the most affected by this reaction with 33.3 and 13.9%, respectively (Table 4).

Among the main reactions identified, pruritus had the highest percentage of causality assessed as "conditional" with 26.9%. Vancomin (n = 4) and hydroxychloroquine (n = 4) were the most reported drugs suspected of causing itches.

In 27 itching reactions (69.2%), the decision of the medical team was to suspend the use of the suspected drug. One reaction resulted in a reduction in the dose of the suspected drug, and in seven there was was no change in drug therapy (data not presented).

- **Increase in transaminases (AST and ALT)**

Liver diseases and investigations were the fourth SOC group with the highest percentage of ADR, with a total of 56 reports (8.9%). The reaction "increase in transaminases" had the highest percentage in this group (n = 38; 6%). The main medicines suspected of provoking the reactions were: hydroxychloroquine (n = 28; 7.5%), azitromycin (n = 4; 7.3%) chloroquine (n = 2; 6.4%), (Table 3).

The most affected age group was 45-64 years (n = 20; 9%), followed by the 65-74 years group (n = 5; 3.6%). The increase in transaminases occurred more in men (n = 25; 6.8%) than women (n = 13; 5%), but this difference was not significant (p = 0.49). The percentage of reactions classified as severe was 7.4% (Table 4). Men (72%) had a higher proportion of severe reactions than women (61.5%), however, this difference was not significant (p = 0.71).

Regarding the outcome, seven reactions were fatal, which represented 23.3% of all deaths in the study, second only to the reaction "QT interval prolongation" (Table 4). Two reactions led to death after the use of hydroxychloroquine (28.6%), 2 with chloroquine (28.6%), 1 with azitromycin (14.3%).

Discussion

This is the first study of ADRs of patients with COVID-19, collected by the electronic pharmacovigilance system of Brazil. The research described 631 ADRs in 402 patients from March 1, 2020 to August 15, 2020. The main drugs suspected of causing the reactions were HDC (59.5%), azitromycin (9.8%) and chloroquine (5.2%). The most reported reactions were QT interval prolongation (33.6%), diarrhea (7.4%), itching (6.5%) and the increase in transaminases (6.0%). 56.4% of all reactions were classified as severe. After the treatment of ADRs, 62.3% were recovered. 87.2% of the reactions had the causal link established as probable or possible.

The characteristics of the participants were similar to other studies [4,5,15,16,17] with this same theme, with the prevalence of men, patients over 60 years of age, with concomitant diseases and using multiple drugs.

Pharmacists sent most case reports with 81.8%, while physicians only submitted 0.8% (n = 3) of the reports from the national base. This data was also found in a study from Ceará on COVID-19, where pharmacists were also the highest notifiers (98.8%) [15]. It is already notorious that doctors notify little (around 5%) to pharmacovigilance systems [9]. This majority participation of pharmacists may be explained, in part, by the greater engagement of these professionals in pharmacovigilance issues, as demonstrated in the results of attitude and practices studies in pharmacovigilance in Brazil [18] and in Ethiopia [19], with these professionals presenting better performances than the others. This data reinforces the importance of expanding pharmacovigilance training to all other health professionals.

In our study, 87.2% of the reactions were classified as probable or possible. In practice, few reactions are considered "defined" and this is due to the complexity of evaluating a causal relationship between a drug and an adverse reaction. This is because there are multiple approaches and different scenarios that can bring uncertainties regarding the causal link of the reaction, including the underlying disease itself (as a confounding factor), competing with the drug for the cause of the reaction [20].

The main sites of manifestation of the reactions we identified are similar to those verified in other studies of ADR in patients with COVID-19: cardiac, gastrointestinal, cutaneous and hepatobiliary systems [15,16,17,21,22]. Prolongation of the QT interval favors the appearance of cardiac arrhythmias, ventricular fibrillation, torsade de pointes and sudden cardiac death [16,22,23]. This reaction is common with chloroquine and hydroxychloroquine, and is dose-dependent on the concentration administered. QT intervals above 450ms in men and above 460ms in women are considered abnormal values. Our results showed that the mean QT interval exceeded 500ms for both sexes, which is already considered as a serious event [23].

A study with data from the French voluntary system of ADR notifications5 identified 131 cardiac reactions with 90 related to QT interval prolongation (68.7%), a lower percentage than that identified in our study (86.6%). An explanation for this fact may be due to the lower exposure of French patients to hydroxychloroquine and chloroquine, since the French government banned on May 27, 2020 the prescription of these drugs for treatment of COVID-19 [24].

Among the reactions with reported QT interval prolongation, 64.3% were above 500ms, a higher percentage than found in France (53.3%) [4] by the study CloroCovid-19 [5] and almost three times more than the study in a Dutch hospital (23%) [16]. Our results were also consistent with the literature, which describes that drug-induced QT interval prolongation caused by medications is largely dose-dependent [16]. Patients with QT interval over 500 ms had a higher cumulative dose than those with QT interval under 500ms, which was a result also found in the CloroCovid-19 study [5]. The data also

showed that the medical team was on alert, since in 81% of these reactions, the patient had the drug suspended from therapy.

Diarrhea was the second most reported ADR and had the drugs azitromycin and ceftriaxone as its greatest suspects; and in smaller proportion, hydroxychloroquine. The study in Hunan, China [21], also pointed to gastrointestinal diseases as the second major factor with diarrhea as the main ADR of this group.

Hepatobiliary diseases were the third most identified adverse reactions in our study, with the increase in transaminases as the main adverse reaction of this group. Current data from the literature indicate that 14.8% to 53.1% of patients with COVID-19 have this type of reaction [25]. The percentages found in our study (9.9%) was lower than in the study in Hunan (13.8%) [21] and by that identified in a study from Ceará (34%) [15].

Similar to gastrointestinal tract reactions, patients infected with SARS-CoV-2 may have elevated enzymes during the course of the disease [26]; however, the mechanism of hepatobiliary diseases in the pandemic is still poorly understood, and the lesions may be caused by viral infection in the hepatocyte, immune system-related injury or even drug hepatotoxicity (ADR). This is characteristic of the complexity of causality analysis, as was previously discussed.

One of the relevant points in a drug monitoring program is the possibility of providing additional drug safety information, which previously could not be visualized during pre-marketing clinical trials, especially rare adverse reactions. Drugs that have questionable or uncertain effectiveness/safety profile require careful surveillance, especially those not yet used on a large scale [9]. Antimalarial drugs have been used for many years in malaria-endemic regions worldwide including the Legal Amazon Region in Brazil. However, its large-scale use in other populations and for other purposes is not yet adequately evaluated and deserves great caution.

In consultation with the Anvisa-sanctioned hydroxychloroquine electronic leaflet (http://www.anvisa.gov.br/datavisa/fila_bula/index.asp, accessed on 15/Aug/2020) we observed that reactions such as changes in liver function tests are considered unusual. However, this information is based on results of clinical studies with already-approved therapeutic dosages – for example, in rheumatic diseases. This situation is quite different from our current one, which is use without indication in the drug leaflet (off-label). Greater awareness of liver effects for this medicine is necessary since the population currently exposed is very different from the population in the clinical study of this drug.

Multivariate regression analysis identified that patients aged 65 years or over with COVID-19 are more associated with severe ADR than those under that age. Studies indicate that older patients are more sensitive to the adverse effects of some medications, and as age increases so does the likelihood of severe reactions [27,28]. These results show us that the use of hydroxychloroquine and chloroquine in older patients can be particularly harmful, especially in the absence of proven efficacy for the disease at the rate.

Another finding our analysis was the identification of men with COVID-19 being more associated with severe ADR than women. In general, the literature points out that women are more susceptible to ADR than men [29]. The analysis of the general data of the pharmacovigilance system of Portugal in the 2009-2011 period found a higher incidence of severe ADR in men when compared to women [28]. One of our hypotheses to explain the association of severe ADR in men in our study may be due to the disease itself, which most severely affects the male gender, thus favoring polypharmacy in these patients. However, COVID-19 and its consequences are still little known, and greater monitoring of these severe ADRs is necessary to better understand this result. In general, our findings corroborate the results of other studies, especially those evaluating the safety of hydroxychloroquine and chloroquine [2,3,4,17], which identified the association of these drugs and severe ADR, leading to deaths.

Our study has some limitations. The data comes from a spontaneous surveillance system, so the results may have been underestimated. Studies claim that underreporting represents a major problem for ADR monitoring systems [30,31]. In our study we identified two points about this problem. The first was the finding of 11 silent states in VigiMed in relation to cases of ADR by COVID-19, which led to question on whether the absence of notification was due to the lack of ADR in patients, operational and structural difficulties faced in the states and municipalities or in fact, an underreporting of ADRs. The second confirms the hypothesis of underreporting, with the results from a study from Ceará on COVID-19 [15] that identified 182 cases of ADR in Ceará; however, 28 reports were only reported to

VigiMed. Another point that may also have influenced the lower number of VigiMed notifications, given the current epidemiological scenario, is the referral of ADRs from patients in clinical studies to the clinical research sector of Anvisa, where it has another information system.

ICSR may present a certain degree of uncertainty due to problems in the quality of information and local variability of notifying institutions and professionals; therefore, the probability that suspected ADR is related to the drug is not the same in all cases.

The increase in reports of ADR for some drugs may have been influenced by the COVID-19 pandemic. Thus, interpretations of effect data, and particularly those based on comparisons between medications, can be misleading.

This study, both with regard to language and content, is the responsibility of the authors and does not necessarily express the opinion of Anvisa, CNMM or WHO.

Conclusion

We describe the main ADRs of the drugs used in COVID-19 therapy in Brazil, which were spontaneously reported to Anvisa. The main sites of manifestation of ADRs were in the, cardiac, gastrointestinal, cutaneous tissues and hepatobiliary system. The drugs most involved in the reactions were hydroxychloroquine, chloroquine and azitromycin. Although it was not the objective of this study, the data suggests that a relevant degree of underreporting, which suggesting that the magnitude of ADRs in the analyzed context is higher than the expected. Most of the ADRs observed in this study have been previously described, however, in a completely different scenario from the current one and approved for the use of diseases that have undergone rigorous pre- and post-clinical tests with specific populations. The use of these drugs in this pandemic is experimental and so far the data available in the literature does not guarantee the safety and efficacy for COVID-19 treatment. Therefore, during these times of uncertainty, our results reinforce the importance of monitoring patients using drugs on an off-label strategy, as well as the immediate notification in VigiMed of the ADRs identified in the patients, and systematic analyses of the data by Anvisa. In addition, the study provides support for best practices in pharmacovigilance, which can contribute to effective and safe regulatory decision-making for patients and society as a whole, such as the revision of these drugs leaflets, based on the frequency and severity of ADRs, and elements that can facilitate the evaluation of the inclusion of new therapeutic indications based on a risk-benefit assessment.

Contributors

J. R. R. Melo participated in the conception and design, analysis and interpretation of the data and writing of the article; he was also responsible for all aspects of the work to ensure accuracy and integrity. E. C. Duarte and P. S. D. Arrais contributed in the analysis and interpretation of the data, critical review of the content and approval of the final version. M. V. Moraes, K. Fleck and A. S. N. Silva participated in the evaluation of the causality of reactions, critical review of the content and approval of the final version.

Additional informations

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Resumo

Em março de 2020, a Organização Mundial da Saúde anunciou a nova pandemia denominada de COVID-19, representando um desafio para os profissionais e serviços de saúde. Ainda não foi identificado um tratamento eficaz contra essa doença e vários fármacos são utilizados sem evidências de sua eficácia, que em alguns casos pode causar eventos indesejados. Esse é um estudo transversal com o objetivo de avaliar as reações adversas a medicamentos (RAMs) nos pacientes com COVID-19, identificadas entre 1º de março e 15 agosto de 2020 no Brasil, e os fatores associados ao surgimento de reações graves. Para comparar as proporções das amostras relacionadas ao notificador, paciente, fármacos e eventos adversos utilizamos os testes não paramétricos qui-quadrado e exato de Fisher, e para comparar as médias dos dados com a distribuição normal foi usado o teste t e de Mann-Whitney. Também foi realizada a análise de regressão logística multivariável, estimando as odds ratio *(OR) brutas e ajustadas pelo software Stata, versão 10.0. Foram identificadas 631 RAMs em 402 pacientes. Os medicamentos mais envolvidos foram hidroxicloroquina (59,5%), azitromicina (9,8%) e a cloroquina (5,2%). As reações se manifestaram prioritariamente no sistema cardíaco (38,8%), gastrointestinal (14,4%), tecido cutâneo (12,2%) e hepático (8,9%). A cloroquina (OR = 5,4; IC95%: 1,9-15,6) e a hidroxicloroquina (OR = 2,1; IC95%: 1,2-3,6) foram os únicos medicamentos associados a RAM grave. Nossos achados fornecem subsídios para melhores práticas em farmacovigilância, contribuindo para tomadas de decisões regulatórias efetivas e seguras pela Agência Nacional de Vigilância Sanitária, para os pacientes e toda a sociedade.*

Infecções por Coronavírus; Cloroquina; Hidroxicloroquina; Farmacoepidemiologia; Segurança do Paciente

Resumen

En marzo de 2020 la Organización Mundial de la Salud anunció la nueva pandemia denominada COVID-19, representando un desafío para los profesionales y servicios de salud. Todavía no se identificó un tratamiento eficaz contra esta enfermedad y varios fármacos se utilizan sin evidencias de su eficacia, que, en algunos casos, pueden causar eventos indeseados. Este es un estudio transversal, con el objetivo de evaluar las reacciones adversas a medicamentos (RAMs) en pacientes con COVID-19, identificadas desde el 1º de marzo al 15 agosto de 2020 en Brasil, y los factores asociados al surgimiento de reacciones graves. Para comparar las proporciones de las muestras relacionadas con el notificador, paciente, fármacos y eventos adversos, utilizamos los tests no paramétricos chi-cuadrado y exacto de Fisher, y para comparar las medias de los datos con la distribución normal, se utilizó el test t y de Mann-Whitney. También se realizó un análisis de regresión logística multivariable, estimando las odds ratio *(OR) brutas y ajustadas, mediante el software Stata, versión 10.0. Se identificaron 631 RAMs en 402 pacientes. Los medicamentos más implicados fueron: hidroxicloroquina (59,5%), azitromicina (9,8%) y la cloroquina (5,2%). Las reacciones se manifestaron prioritariamente en el sistema cardíaco (38,8%), gastrointestinal (14,4%), tejido cutáneo (12,2%) y hepático (8,9%). La cloroquina (OR = 5,4; IC95%: 1,9-15,6) e hidroxicloroquina (OR = 2,1; IC95%: 1,2-3,6) fueron los únicos medicamentos asociados a RAM grave. Nuestros resultados proporcionan apoyo para mejores prácticas en farmacovigilancia, contribuyendo a las tomas de decisiones regulatorias efectivas y seguras, por parte de la Agencia Nacional de Vigilancia Sanitaria, para los pacientes y toda la sociedad.*

Infecciones por Coronavirus; Cloroquina; Hidroxicloroquina; Farmacoepidemiología; Seguridad del Paciente

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