Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Therapies (2020) 75, 381—388

Available online at
SciVerse ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

LETTER TO EDITOR

Pharmacological characteristics of patients infected with SARS-Cov-2 admitted to Intensive Care Unit in South of France

Keywords COVID-19; Angiotensin converting enzyme inhibitors; Angiotensin II receptor blockers; Renin-angiotensin-aldosterone system; Drugs; Non-steroidal anti-inflammatory drugs

Abbreviations

ACEIs angiotensin converting enzyme inhibitors
ARB angiotensin II receptor blockers
COVID-19 coronavirus disease 2019
DDP4 dipeptidyl peptidase 4 inhibitors
GLP-1 agonists glucagon-like peptide-1 receptor agonists
ICU intensive care units
NSAIDs non-steroidal anti-inflammatory drugs
SARS-CoV-2 severe acute respiratory syndrome coronavirus 2

Introduction

Patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can develop coronavirus disease 2019 (COVID-19), which drives many patients to hospital and some of them in intensive care units (ICUs). Little information is available about the main characteristics of patients admitted to hospital for COVID-19. A retrospective cohort study in hospitalized Chinese patients found that a majority of patients were men with a median age of 56 years and a 28% mortality rate [1]. Another recent US study in 5700 patients found a median age of 63 years with mainly men (80.3%) and arterial hypertension (56.6%), obesity (41.7%) and diabetes (33.8%) as main comorbidities [2]. A case series of critically ill patients in Italy found that the majority were older men, requiring mechanical ventilation and high levels of positive end-expiratory pressure with 26% of mortality [3].

Besides these demographical and clinical characteristics, there are relatively few data about drugs previously used in patients admitted to ICUs. Because some drugs could interact with the SARS-Cov-2 replication, some authors suggested that these drug exposures could be beneficial or harmful for COVID-19 patients. Among the pharmacological hypotheses, non-steroidal anti-inflammatory drugs (NSAIDs), drugs acting on the renin-angiotensin-aldosterone system (angiotensin converting enzyme inhibitors [ACEIs] and angiotensin II receptor blockers [ARB] alias sartans) or incretin-based drugs (glucagon-like peptide-1 receptor agonists [GLP-1 agonists] and dipeptidyl peptidase 4 inhibitors [DDP-4 inhibitors]) were proposed as a potential factors modifying SARS-Cov-2 infectivity [4—6]. Therefore, there is an urgent need to assess what is the drug exposure of COVID-19 patients admitted to ICUs. Here, we described the demographics, baseline comorbidities, drug exposures and outcomes of the first COVID-19 patients admitted to Toulouse University Hospital ICUs.

Methods

This case series was conducted at Toulouse University Hospital in France between March 10, 2020 and April 21, 2020. All consecutive adult patients (≥18 years old) with nasal/throat swabs positive for SARS-CoV-2 by polymerase chain reaction admitted in the three intensive care units were included. Clinical outcomes were monitored until April 21, 2020, the final date of follow-up. Toulouse University Hospital institutional review board approved the project (n° RnIPH 2020-50).

Data were collected from the ICCA (IntelliSpace Critical Care and Anesthesia, Philips) and ORBIS (Agfa Healthcare) softwares, which record all medical informations in Toulouse University Hospital inpatients. Patients were considered to have confirmed SARS-Cov-2 infection if the test result was positive or if it was negative but repeat testing was positive. Transfers from another regional or national French hospital to Toulouse University Hospital were merged and considered as a single visit. For patients with a readmission during the study period, data from the first admission are presented.

We registered the main demographic, medical comorbidities and home medications of the patients upon entry to the ICU. Demographics, body mass index and comorbidities were available for all admitted patients. Home medications were reported based on the admission clinical examination. We collected outcomes including length of stay, invasive mechanical ventilation, discharge and mortality. Outcomes were not available for all patients at study end because they had not completed their ICU course. Data about medications after admission in ICUs were not registered (since it was not the goal of our study).

Results

The results are presented in Table 1.

Table 1 Main characteristics of the 96 the patients upon entry to the ICU (intensive care unit).

	With intubation[a]	Without intubation[a]	Total[a]
Patients, *n* (%)	71 (79.0%)	20 (22.0%)	96 (100%)
Women, *n* (%)	14 (19.7%)	[c]	20 (20.8%)
Age, mean (min-max)	63.4 (20-85)	63.8 (34-89)	63.4 (20-89)
Comorbidities, *n* (%)[b]			
Cardiovascular disease			
Arterial hypertension	32 (45.1%)	7 (35.0%)	43 (44.8%)
Rhythmic Heart disease	5 (7.0%)	[c]	6 (6.3%)
Other cardiovascular diseases	10 (14.1%)	5 (25.0%)	16 (16.7%)
Chronic respiratory disease			
Asthma	6 (8.5%)	0	6 (6.3%)
Chronic obstructive pulmonary disease	[c]	[c]	5 (5.2%)
Kidney disease (or kidney transplant)	7 (9.9%)	[c]	10 (10.4%)
Metabolic disorders			
Overweight or Obesity	51 (71.8%)	10 (50%)	64 (66.6%)
Body mass index, median (min-max)	28.1 (20-47)	26.6 (19-42)	28.0 (19-47)
Dyslipidaemia disorders	12 (16.9%)	[c]	15 (15.6%)
Diabetes	16 (22.5%)	7 (35.0%)	27 (28.1%)
Cancer (solid or hematologic)	6 (8.5%)	[c]	10 (10.4%)
Current smokers	[c]	[c]	6 (6.3%)
Total Comorbidities			
1	12 (16.9%)	[c]	13 (13.5%)
≥2	54 (76.1%)	15 (75.0%)	74 (77.1%)
Median (min-max)	3 (0-7)	3 (0-5)	3 (0-7)
Drug exposure before ICU admission			
Paracetamol	24 (33.8%)	[c]	31 (32.1%)
Nonsteroidal anti-inflammatory drugs	5 (7%)	0	6 (6.3%)
Corticosteroid drugs	11 (15.5%)	[c]	13 (13.5%)
Other immunosuppressant drugs	5 (7.0%)	[c]	6 (6.3%)
Cardiovascular drugs			
ACEIs	6 (8.5%)	[c]	12 (12.5%)
ARBs	20 (28.2%)	[c]	23 (24.0%)
Diuretics	10 (14.1%)	[c]	15 (15.6)
CCBs	11 (15.5%)	[c]	13 (13.5%)
Beta-blockers	9 (12.9%)	[c]	14 (14.6%)
Statins	6 (8.5%)	[c]	11 (11.5%)
Antiplatelet drugs	8 (11.3%)	[c]	10 (10.4%)
Anti-hyperglycaemic drugs			
Metformin	10 (14.1%)	[c]	16 (16.7%)
Glicazide	[c]	[c]	5 (5.4%)
DDP4 inhibitors	5 (7.0%)	[c]	10 (10.4%)
Insulin	6 (8.5%)	[c]	11 (11.5%)
PPIs	8 (11.3%)	[c]	12 (12.5%)
Beta2 adrenergic receptor agonists	5 (7.0%)	[c]	9 (9.4%)
Benzodiazepine	5 (7.0%)	[c]	7 (7.3%)
Total drugs			
None	10 (14.1%)	[c]	12 (12.5%)
[1-3]	31 (43.7%)	9 (45%)	42 (43.8%)
≥4	30 (32.2%)	9 (55%)	42 (43.8%)
Median (min-max)	3 (0-14)	3 (0-8)	3 (0-14)
Time between first symptoms and ICU admission, median (days)	9 (1-37)	7 (0-20)	8 (0-37)
Hospitalisation time in ICU, median (days)	14 (3-33)	3 (0-13)	10 (1-33)
Death	8 (11.3%)	[c]	9 (9.3%)

ARBs: angiotensin II receptor blockers; ACEIs: angiotensin converting enzyme inhibitors; CCBs: calcium channel blockers; ICU: intensive care unit; PPIs: proton pump inhibitors.

[a] The clinical outcomes were not available for 5 patients on the April 21, 2020, as they were still hospitalised.

[b] There were less than 5 patients with auto-immune diseases, liver disease or depression.

[c] Number of patients <5.

Baseline characteristics

During this 6-week period, 96 patients were admitted in intensive care units in Toulouse University Hospital. They were mainly men (79.2%) with mean age 63 years. We found that 87 patients (91%) have at least one comorbidity with a median value of 3. The most common comorbidities were overweight or obesity followed by arterial hypertension and diabetes mellitus. Drugs taken by the patients before hospital admission were mainly paracetamol followed by ARBs and metformin. Exposure to ACEIs was two times lower than that to ARBs.

Outcomes and associated drugs

During this period, 71 patients were intubated during their resuscitation stay, 70 left the unit and 9 deaths occurred. Deaths were observed in 6 men, mean age 68 years (range 36-88) after a mean follow-up in intensive care units of 7.3 days (range 2-19 days). All, except two who suffered from only overweight or obesity, had at least another previous medical history (1 patient with asthma, 1 pulmonary embolism, 1 dyslipidaemia plus myocardial infarction, 1 leukaemia, 1 arterial hypertension, 1 myeloma plus breast cancer, 1 bone dysplasia). Among patients who died in ICU, 3 patients were exposed to ARBs, 3 to corticosteroids or immunosuppressant drugs: none were exposed to ACEIs, NSAIDs or DDP4 inhibitors.

Overweight or obesity were found in 71.8% of patients intubated versus 50% patients without intubation. The rate of intubation for patients with hypertension not exposed to ACEI or ARB was 70%, 60% for patients with ACEIs and 95% with ARBs. The rate of intubation for patients with diabetes not exposed to DDP-4 inhibitors was 81% versus 43% for those exposed to DDP-4 inhibitors. Due to the small sample, no statistical analyses were performed.

Discussion

The present study was performed to investigate the main clinical characteristics of COVID-19 patients admitted to ICU in Toulouse University Hospital (South Western, France) in March-April 2020 with a special focus on the main drugs received by the patients before admission. Several interesting points should be discussed.

First, we found that the main characteristic of the patients was presence of overweight-obesity in more than 2 patients out of 3: among them, 8 out of 10 were males. Moreover, the three first diseases associated to COVID-19 infection were arterial hypertension (around 1 patient out of 2) followed by diabetes (almost 1 patient out of 3) and other cardiovascular diseases (other than arterial hypertension; around 1 patient out of 6). These results are in agreement with previous studies published all around the world [1—3,7].

Second, we investigated home drugs in COVID-19 patients admitted to an ICU. The 3 first drugs found in the admitted patients were paracetamol (1 patient out of 3) followed by ARB (1 patient out of 4) and metformin (1 patient out of 6). The fact that paracetamol was in first place before NSAIDs is probably explained by the campaign carried out at the beginning of the infection about the potential risks of NSAIDs (4). Of course, due to the prevalence of cardiovascular diseases, ACEIs, ARBs, diuretics, beta-blocking agents and calcium channel inhibitors were widely found in this study. Among drugs acting on the renin-angiotensin system, ARBs were prescribed twice as much as ACEIs. It is interesting to underline that no death was observed in patients treated by ACEIs. While in our sample of patients with hypertension, we found a higher rate of intubation among patients exposed to ARBs (95%) compared to patients with ACEIs (60%), no conclusion can be made. In fact, today, there is no clear evidence neither for a deleterious nor a favorable effect of ACEI/ARB in this situation. Several randomized trials are in course to examine more precisely these potent issues or benefits [5].

In fact, we were unable to test putative statistical differences between the two groups as the power was to small and some confounding factors have to take into account in statistical analyses (age, sex, comorbidities). However, our observational study suggests potential differences between ARBs and ACEIs for the risk of intubation in COVID-19 patients. A recent observational study, involving patients who had been hospitalized in 11 countries on three continents, found that use of ACEIs may be associated with a lower risk of in-hospital death than non use (OR = 0.33, 95% CI, 0.20 to 0.54) while for ARBs, odds ratio was 0.23 (95% CI, 0.87 to 1.74) versus non-use [8]. In addition in our sample of COVID-19 patients with diabetes, a lower rate of intubation was observed in patients treated by DPP4-inhibitors (43%) compared to those not exposed (81%).

The present work suffers from some mandatory shortcomings due to the collection method used. Data were collected through software analysis and it was not possible to directly verify the data by interviewing patients directly since they were in the ICU. Our study is only a descriptive one. It is thus not possible to conclude about associated factors. This is particularly the case for smoking (only found in around 1 patient out of 16), for which a possible protective effect is currently discussed [9]. Since our work is a descriptive study, it also probably suffers from the indication bias (as well as for the lack of comparator). This work should be completed by other further investigations performed on larger French cohorts. However, this study, which reflects a particular situation in a university hospital in France, offers interesting perspectives for future research in the field of COVID-19 infection, particularly for future pharmacoepidemiological studies, since it is the first performed in France in such patients.

In conclusion, our study shows that patients admitted to intensive care units are mainly men suffering from overweight-obesity, arterial hypertension and chronically treated by cardiovascular drugs (more ARBs than ACEIs) and antihyperglycemic drugs.

Acknowledgements

The authors acknowledge, first all other health care professionals in the intensive care unit who managed the patients, as well as Mrs Leila Chebane who helped to the collection of data.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395(10229):1054—62.
[2] Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA 2020, http://dx.doi.org/10.1001/jama.2020.6775.
[3] Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA 2020, http://dx.doi.org/10.1001/jama.2020.5394.
[4] Micallef J, Soeiro T, Jonville-Béra AP, on behalf of the French Society of Pharmacology and Therapeutics. Non-steroidal anti-inflammatory drugs, pharmacology, and COVID-19 infection. Therapies 2020, http://dx.doi.org/10.1016/j.therap.2020.05.003 [in press], https://www.sciencedirect.com/science/article/pii/S0040595720300925. [Accessed May 12, 2020].
[5] Aronson JK, Ferner RE. Drugs and the renin-angiotensin system in Covid-19. BMJ 2020;369:m1313, http://dx.doi.org/10.1136/bmj.m1313.
[6] Strollo R, Pozzilli P. DPP4 inhibition: preventing SARS-CoV-2 infection and/or progression of COVID-19? Diabetes Metab Res Rev 2020, http://dx.doi.org/10.1002/dmrr.3330.
[7] Myers LC, Parodi SM, Escobar GJ, Liu VX. Characteristics of hospitalized adults with COVID-19 in an integrated health care system in California. JAMA 2020, http://dx.doi.org/10.1001/jama.2020.7202.
[8] Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular disease, drug therapy and mortality in Covid-19. N Engl J Med 2020, http://dx.doi.org/10.1056/NEJMoa2007621.
[9] Berlin I, Thomas D, Le Faou AL, Cornuz J. COVID-19 and smoking. Nicotine Tob Res 2020, http://dx.doi.org/10.1093/ntr/ntaa059 [pii: ntaa059].

François Montastruc[a,b,*], Charles Romano[c], Jean-Louis Montastruc[a,b], Stein Silva[c], Thierry Seguin[c], Vincent Minville[c], Bernard Georges[c], Béatrice Riu-Poulenc[c], Olivier Fourcade[c]

[a] *Department of Medical and Clinical Pharmacology, Centre of PharmacoVigilance and Pharmacoepidemiology, Toulouse University Hospital, Faculty of Medicine, 31000 Toulouse, France*

[b] *Inserm, UMR 1027 Pharmacoepidemiology, Assessment of Drug Utilization and Drug Safety, CIC 1426 - University Paul-Sabatier, 31000 Toulouse, France*

[c] *Anestesia and Critical Care Medicine Department, Intensive Care Unit, Toulouse University Hospital, 31000 Toulouse, France*

* Corresponding author at: Department of Medical and Clinical Pharmacology, Faculty of Medicine, 37, allées Jules-Guesde, 31000 Toulouse, France.
E-mail address: francois.montastruc@univ-tlse3.fr (F. Montastruc)

Received 6 May 2020;
accepted 12 May 2020
Available online 15 May 2020

https://doi.org/10.1016/j.therap.2020.05.005

Chloroquine and hydroxychloroquine during pregnancy: What do we know?

Keywords Hydroxychloroquine; Chloroquine; Covid-19; Pregnancy

Chloroquine and hydroxychloroquine are currently highly broadcasted as medications for severe Covid-19 infection although, to date, the efficiency data are very limited.

What do we know about the safety of these medications in pregnant women?

Chloroquine and hydroxychloroquine cross the placenta.

The volume of distribution of these medications is very high and potentially worrying for pregnant women and their half-lives are long; 10 to 30 days for chloroquine and 30 to 60 days for hydroxychloroquine, which leads to prolonged exposure after stopping these drugs. Thus, a woman who takes and stops one of these drugs before pregnancy can therefore be exposed during the upcoming pregnancy.

More data on safety during pregnancy are available about chloroquine, an old medication widely used in the general population as antimalarial than about hydroxychloroquine which is currently indicated for some autoimmune diseases such as lupus or rheumatoid arthritis.

First, experimental studies (in mice and monkeys) have shown that chloroquine could accumulate in the eyes, ears and adrenals. At very high doses (>250 mg/kg), microphthalmia and anophthalmia have been reported in rats. More recently, in ''in vitro'' and ''in vivo'' experiments, chloroquine caused genetic mutations and chromosomal damage (summary of product characteristics of Nivaquine®).

In humans, three studies on 169, 130 and 774 [1—3] women exposed to chloroquine during the 1st trimester of their pregnancy did not suggest an increase in the risks of congenital anomalies, in utero death or low birth weight.

Regarding hydroxychloroquine, two meta-analysis including 8 and 6 studies were published in 2015 and 2018 [4,5]. Their conclusion are rather reassuring about the risks of teratogenicity, termination of pregnancy and prematurity. However, according to the authors, these data should be interpreted with caution because the studies included in these meta-analyses, only small numbers of pregnant women (9 to 383 pregnant women) and were often observational [6].

Due to already described animal observations and rare but severe ocular adverse effects of both chloroquine and hydroxychloroquine in treated patients (retinal damage, sometimes irreversible, after several years of exposure), several case-studies have focused on the potential risk of prenatal exposure to chloroquine and hydroxychloroquine on eye development. Two cases of retinal degeneration