

Coronavirus Pandemic

Nitazoxanide against COVID-19 in three explorative scenarios

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Abstract

Introduction: Nitazoxanide has shown efficacy in vitro against coronavirus infections (MERS, SARS, SARS-CoV-2). The aim of this report is to describe the results of treating COVID-19 positive patients with nitazoxanide in three clinical settings: pregnancy/puerperium, hospitalized patients in an Internal Medicine Service and in an ambulatory setting.

Methodology: This was a prospective follow-up and report of COVID-19 cases in three different situations, pregnant women, hospitalized patients receiving medical attention in an Internal Medicine Service and ambulatory patients residing in Toluca City, and Mexico City.

Results: The experience with a first group of 20 women, pregnant (17) or in immediate puerperium (3) was successful in 18 cases with two unfortunate deaths. The five cases treated in an Internal Medicine service showed a positive outcome with two patients weaned from mechanical ventilation. Of the remaining 16 patients treated in an ambulatory setting, all got cured. Nitazoxanide seems to be useful against SARS-CoV-2, not only in an early intervention but also in critical condition as well as in pregnancy without undesired effects for the babies. As an adjunctive therapy budesonide was used that seems to contribute to the clinical improvement.

Conclusions: Nitazoxanide could be useful against COVID-19 as a safe and available regimen to be tested in a massive way immediately.

Key words: Ambulatory treatment; internal medicine; nitazoxanide; pregnancy; SARS-CoV-2.

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Introduction

The Coronavirus disease 2019 (COVID-19) caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has evolved into a global pandemic [1]. This disease shows a broad spectrum of illness, mostly mild but a small percentage with serious disease, sometimes requiring intensive treatment. The mortality in the serious illness subgroup is high [2] and gets even higher if the patients end up needing mechanical ventilation [3]. In such critical and desperate situations, physicians are faced with the challenge to take difficult decisions but always with the best interests of the patients in the fore [4,5]. Unfortunately, there is currently no widely accepted standard of care in the pharmacologic management of patients with COVID-19 [6] and repurposing of existing drugs [7] seems to be the only plausible option

for the majority of the worldwide population with scarce resources.

Just over five months after the emergence of this variety of beta-coronaviruses, four facts are relevant. Firstly, the high contagiousness with disaggregation of the family nucleus due to the death of one or more affected family members, especially those with risk factors and the unusual impact on morbidity and mortality on health personnel; taking into consideration that we are still in an ascending phase of infections in Mexico. Secondly, we are witnessing the crushing of the world's global economy with the greatest impact on countries that traditionally have weak economies, such as the majority, including ours. The third issue is that the vast majority of products that are being tested against COVID-19 are far away from being able to be used in most nations due to their low availability and

high cost; and finally, the lack of an effective vaccine makes it mandatory to expand the repertoire of therapies against this virus.

Given the reasoning above, it is very valid to identify new therapeutic alternatives with drugs that have demonstrated antiviral activity *in vitro* [8], have a good safety profile, and cost-benefit analysis that justifies their use in large population in multiple age groups including pregnant women. Nitazoxanide (NTZ), a medicine used in Mexico for many years as an antiparasitic [9] with a very low cost and easily available throughout the territory, fits this profile. This medicine is within the basic schemes of drugs of several healthcare institutions and has an extensive safety record spanning decades.

Another anti-parasitic drug, ivermectin, has recently proposed for use in patients with Covid-19, but has the drawback that it cannot be used in pregnant women or in children [10]. Thus, the fundamental objective of this report is to reposition NTZ as a valid option against SARS-CoV-2 with a role similar to that of oseltamivir against influenza.

Nitazoxanide (NTZ), 2-(acetyloxy)-N-(5-nitro-2-thiazolyl) benzamide, is a broad-spectrum anti-infective drug that markedly modulates the survival, growth, and proliferation of a range of extracellular and intracellular protozoa, helminths, anaerobic and microaerophilic bacteria, in addition to viruses [11]. Besides, NTZ has also been shown to have anti-inflammatory properties [12].

NTZ has demonstrated *in vitro* activity against other coronavirus such as SARS-CoV-1, SARS-CoV-2, MERS-CoV [13] and murine coronavirus [14]. Based on these multiple *in vitro and* animal data, it is thought that NTZ may also have in-vivo activity against SARS-CoV-2. As a matter of fact, adverse effects associated with this drug have been investigated and are uncommon [15]. For instance, patients may experience discoloration of urine, diarrhea, dizziness, gastroesophageal reflux disease, skin rash, or urticaria and less than 1% may experience more severe symptoms, including anorexia, flatulence, increased appetite, enlarged salivary glands and dizziness [16]

Although the *in vitro* activity of NTZ against SARS-CoV-2 is encouraging, more data is clearly needed to determine its role in the management of COVID-19. Surprisingly, data is limited regarding the efficacy of NTZ against human coronavirus. There are several publications that posit activity against COVID-19 either used alone [17] or combined with other drugs [12], but unfortunately its potential usefulness has been largely ignored. Here we present the experience with NTZ in three circumstances: in pregnant, acutely ill hospitalized and in ambulatory patients.

Methodology

This was a prospective follow-up and report of COVID-19 cases in three different situations, pregnant women seen at the “Mónica Pretelini Sáenz” Maternal-Perinatal Hospital (HMPMPS), hospitalized patients receiving medical attention in the Internal Medicine

Table 1. General characteristics of the three groups.

Variable	Pregnant women (N = 20)	Hospitalized patients in an Internal Medicine Service (N = 5)	Ambulatory patients (N = 16)
BMI (kg/m ²)	27.8 ± 5.1	32.5 ± 6.5	28.8 ± 4.1
Dyspnea (%)	60	100	43.8
Fever (%)	75	80	43.8
Headache (%)	35	100	81.3
Cough (%)	45	100	68.8
Sore throat (%)	5	40	37.5
Joint pain (%)	25	100	62.5
Muscle pain (%)	25	80	62.5
Thoracic pain (%)	0	20	31.3
Nasal discharge (%)	10	0	50
Conjunctivitis (%)	0	40	6.3
Disgeusia/ageusia (%)	0	20	37.5
Anosmia (%)	0	0	37.5
MBP (mmHg)	89.2 ± 7.9	81.2 ± 3.6	89.3 ± 9.3
Heart rate (beats per minute) (bpm)	101.2 ± 21.6	75 ± 10	98.7 ± 23.8
Respiratory rate (breaths per minute)	22.8 ± 2.8	24.2 ± 2	22.2 ± 3.1
Temperature (°C)	37.7 ± 1.0	37.2 ± 1	37.9 ± 1.1
O ₂ saturation (%)	87.4 ± 8.3	78.8 ± 2.7	87.9 ± 6.3

MBP: Mean Blood Pressure.

Service of the “Dr. Nicolás San Juan” General Hospital (both the hospitals are affiliated to the Health Institute of the State of Mexico, (ISEM)) and ambulatory patients from two cities - Toluca City and Mexico City.

All patients were positive for SARS-CoV-2 by quantitative RT-PCR (qRT-PCR) from the respiratory tract. The information regarding COVID-19 symptomatology, anthropometric variables, blood pressure, comorbid conditions, the type of treatment were documented in an Excel sheet designed specifically for this report.

The blood tests in the groups that were seen in the Hospital, were taken after a fasting period of eight hours at minimum and processed following the indications of the International Federation of Clinical Chemistry (IFCC). This was a zero-risk study and the consent form was waived as the information was obtained from clinical files during routine use. In all cases the anonymity of the patients was preserved.

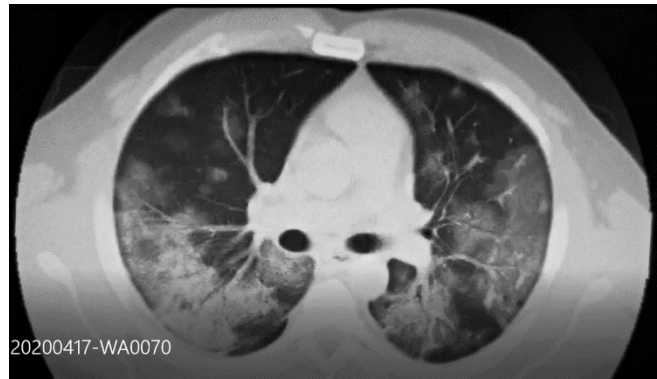
Results

The experience with the first group of 20 women who were pregnant (17) or in immediate puerperium (3) is showed in Table 1. The mean age of the patients was of 25.5 ± 4.6 years old with an important variability in the hospital stay, being anywhere from 1 to 30 days. The time with COVID-19 symptomatology before arriving at our hospital was 2.5 days (range 1-7), one death occurred due to delay in medical care (the patient was with respiratory symptoms for almost one week before arriving to our Hospital).

The cause to arrive at the Third Level medical attention was COVID-19 symptoms in half of the patients, obstetrical hemorrhage in three cases, preeclampsia in two cases and in one case: fetal tachycardia, cervicovaginitis, unfavorable cervix, preterm delivery and pelvic fetus presentation.

In fact, in this group there were two deaths, in one case for unknown reasons the drug was not administered over one weekend, but in both deaths the Computed Tomography (CT) evidenced severe lung lesion (Figure 1). On an average, the most common presenting symptom in pregnant/puerperal patients

Figure 1. Thoracic computed tomography of one of patients that died.



were fever (75%), dyspnea (60%) and cough (45%). All patients were given oxygen support and empirical antibiotic treatment based on clarithromycin and levofloxacin.

The obstetrical data in this patient series is as follows: mean gestations: 2.2 (range 1-5), vaginal deliveries: 0.5 (range 0-2), abortions: 0.3 (range 0-1), cesareans: 1.2 (range 0-3). Five women were still pregnant when they were discharged from the hospital, twelve babies were healthy and without any COVID-19 symptoms, unfortunately, two babies lost their moms. There were three fetal loses due to: ectopic pregnancy, fetal death at 16 weeks of pregnancy and a postnatal death from prematurity complications. Remarkably, one of the successful pregnancies was a woman with Hodgkin lymphoma.

Although most of the women had a normal BMI, there were two with obesity, registering 37.1 and 35.6 each. Two patients presented with preeclampsia. Importantly, 30% of the pregnant women developed transitory diarrhea after beginning the NTZ, but not enough to stop the treatment.

In the case of hospitalized patients, in this initial approach we prescribed the drug to only five patients, three males and two females (mean age 45.2 ± 13.5 years old) as an off-label use while thinking about initiating a randomized trial. In this respect, the response was quite promising, with two patients (a man

Table 2. Laboratory values of the pregnant women and hospitalized patient in an Internal Medicine Service.

Variable	Pregnant women (N = 20)	Hospitalized patients in an Internal Medicine Service (N = 5)
Hemoglobin (g/dL)	12.4 ± 2.4	14.5 ± 2.1
Hematocrit (%)	36.4 ± 6.6	42.4 ± 6.9
Leucocytes (cells/mm ³)	10930.0 ± 5564.2	5484 ± 893
Lymphocytes (cells/mm ³)	1706.5 ± 1986.9	747 ± 286.3
Platelets (cells/mm ³)	202300 ± 65531.9	330599.8 ± 30778.3

and a woman) in mechanical ventilation who were able to be weaned off of ventilatory support after six days in both cases. They developed ventilator associated pneumonia and were treated with levofloxacin.

Patient characteristics in this group – two patients were obesity grade II (BMI 39.4), two were overweight. Other comorbid conditions were Type 2 Diabetes Mellitus (T2DM) and Chronic Obstructive Pulmonary Disease (COPD). All these hospitalized patients received enoxaparin and paracetamol.

It calls to our attention that 100% of the patients referred dyspnea, headache, cough and joint pain, and 80% had fever. Eight patients had overweight, four with obesity grade I, two with obesity grade II and only two had normal weight.

In the third scenario with ambulatory patients, our first experience was with 16 patients (mean age 47.8 ± 16.9), eight men and eight women. In this cohort, two patients had grade II obesity, four had grade I obesity, eight were overweight and only one case per gender had normal weight. The most frequent symptom was headache at 81.3% and the next joint and muscle pain at 62.5%. Comorbidities were two patients with T2DM and one with hypertension and COPD.

Discussion

The regular NTZ antiparasitic dose is 500 mg twice a day. The anti-viral dose however is different [18]. Previously, long-acting NTZ 600 mg was used twice daily for 5 days, in a study in patients with acute uncomplicated influenza with minor adverse effects [19] and shown to reduce the duration of symptoms. However, based on the pharmacokinetic of this drug [20], the dose used in this case series report has been of 500 mg every 6 hours [18].

Interestingly, a previous review publication included only 64 pregnant women in the analysis of 13 papers [21]; that is relatively few as in this initial approach, the set of patients started with 20 women, with a mortality of 10%.

In order of frequency, the main symptoms reported by pregnant women were different from those reported by Huang *et al.* for general population: fever (69.2%), dyspnea (61.5%) and cough (46.2%) [22]. This difference might be attributed to the physiological changes during pregnancy that confuse women and probably the dyspnea is underestimated.

As expected, pregnant women were more anemic than the patients hospitalized in an Internal Medicine Service. By contrast, the group in the Internal Medicine service had lymphopenia at half the level for the reference value of our population.

The fact that in the Internal Medicine Service 100% of the patients had lymphopenia, which contrasts percentages reported by other groups, for example, 63% described by Huang [22], probably is telling that our patients were in a more critical condition when looking for in-hospital care.

Another point to consider is the importance of the chest CT [23]. Due to the large number of cases of COVID-19 that overwhelms the diagnostic system in Mexico, it is not possible to delay treatment while waiting for a PCR result, and the tomographic image is of great help in making a decision.

No less important than the early administration of NTZ is the addition of steroids in selected patients. 100% of the hospitalized patients (pregnant women and those of the Internal Medicine Service) received Clexane (enoxaparin) 40 mg S.C. once daily. In the ambulatory group 13 (81.25%) patients received Zinc at a dose of 220 mg/day as a complementary treatment based for its immunomodulatory effects [24].

The low mortality in this small clinical experience in relation to the national and international data can be explained in part due to the age of young adults. Another issue to be analyzed is the early intervention with NTZ, which could be critical factor to reduce adverse outcome.

Conclusion

The author humbly suggests NTZ could be useful against COVID-19 as a safe and viable treatment option to be tested in a massive way immediately. Finally, authors question whether the treatment against COVID-19 has always been with us, and if so, how many lives could have been saved with a more organized, inclusive and coordinated way to evaluate several schemes taking into account previous data against other coronavirus (SARS and MERS). A lesson to learn from for future pandemics.

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Authors' contributions

JMC, MRFF, LPC and JCBG: conceptualization, literature review. JMF and MJVC: data managing, patients follow-up. LCA: medical attention of the pregnant/puerperal women.

SDM: medical attention of the patients attended in an Internal Medicine Service. RRC: critical review and in charge of medical attention. SP: intellectual discussion, english edition and review of the final manuscript. HMC: data managing, draft writing and final edition of the manuscript.

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