"TREATMENT WITH BISMUTH SUBCITRATE IN FRAGILE PATIENTS WITH SARS-CoV-2 INFECTION AND DIARRHEA NOT FITTING FOR TRANSFER TO ACUTE HOSPITAL "

Protocol number: COVID-19-BISMUTH

Date: 14 April 2020

Investigational Drugs: Bismuth Subcitrate

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ABBREVIATIONS:

COVID-19 Coronavirus disease 2019

RT-PCR Reversal-transcriptase polymerase chain reaction

SARS-Cov-2 Severe acute respiratory syndrome coronavirus 2

ICU Intensive Care Unit

IECm Committee on Ethics and Research Involving Medicinal Products

1.Introduction:

In the course of the current pandemic caused by the spread and replication of SARS-Cov-2, respiratory symptoms dominate the clinical picture of the disease. However, a significant percentage of patients with COVID-19 infection present with gastrointestinal symptoms, such as anorexia, vomiting, diarrhea and abdominal pain, which are not always associated with respiratory symptoms or clinics. This percentage, according to current medical literature, ranges from 34% to 60%. Our study wants to focus basically on patients whose main symptom is diarrhea and because of their characteristics of fragility and associated comorbidities are not candidates for referral to acute hospital or aggressive therapies; therefore we speak of a fragile and multipathological patient admitted to a social-health hospital or a residential center.

Bismuth colloidal compounds such as bismuth subsalicylate are anti-diarrheal drugs whose mechanism of action is combined: on the one hand, it stimulates the absorption of fluids and electrolytes through the intestinal wall by inhibiting the secretion of chloride, and on the other hand when hydrolyzed to salicylic acid, it inhibits the synthesis of prostaglandins responsible for intestinal inflammation and hypermotility. They also have antimicrobial effects since they bind to the whole toxins of some bacteria such as E. Coli, through the products of the intestinal reaction (bismuth oxychloride and bismuth hydroxide). Its action is anti-secretory and antimicrobial.

Clinical guidelines describe bismuth subsalicylate as a drug indicated in the treatment of moderate diarrhea and common digestive disorders, such as heartburn, and currently also indicated as an adjuvant in the treatment of Helicobacter Pylorii.

In the context of the SARS-CoV-2 pandemic, a prioritisation of the use of health resources is established. This implies that frail, elderly patients with chronic diseases who, in addition, are often admitted to centres with a high incidence of COVID-19, do not have access to mechanical ventilation, and therefore still have higher mortality. Diarrhea is a major problem in these patients, so we have reported a prospective study in which the main

objective is to determine the efficacy of bismuth subcitrate treatment in COVID-19 patients with acute diarrhea.

The colloidal bismuth compound that we will use in our study is bismuth subcitrate, which is marketed in Spain and is currently considered a promising new line of therapy for irritable bowel syndrome.

Patients with bleeding ulcers, renal failure, hemophilia or hypersensitivity to salicylates have contraindicated colloidal bismuth subcitrate. It should be used with caution in patients with liver failure, may lengthen Prothrombin Time if the patient receives anticoagulants, interferes with the action of uricosurics in the treatment of gout and may cause hypoglycemia by a mechanism independent of insulin. A common side effect is blackening of the stool and tongue and a less frequent side effect is constipation.

2. Objectives

Main objective

To determine the efficacy of bismuth subcitrate in the treatment of diarrhea as the main symptom of COVID 19 disease, in the group of fragile patients with associated comorbidities and not candidates for invasive therapy or acute hospital referral.

Secondary objectives

To analyze the intensity of the diarrhea and if the concomitant pathology influences the evolution and treatment with bismuth compounds.

3. Type of clinical trial and design

Prospective, single-arm, open study in non-referral acute hospital or ICU patients infected with SARS-CoV-2 whose predominant clinical condition is diarrhea. Patients admitted to socio-medical hospitals and residential centres.

Recruitment will take place in the following hospital units:

Francolí Hospital Convalescent Service: Dr. Jacqueline Cimerman, Dr. Eugenia Sopena , Dr. Elena Moltó and Dr. Rami Quanetta.

Residential centres in Tarragona: Dr. Laura Canadell and Dr. Ferrán Bejarano.

All this with the help and support of the Pharmacy Service of the Joan XXIII Hospital: Dr. Laura Canadell

The recruitment period will be immediate to the approval of the study and depending on the results our intention would be to maintain it as a therapeutic option of the secret diarrhea in the elderly and frail patient.

4. Study population

To be eligible for the study, patients must meet all of the inclusion criteria and none of the exclusion criteria. Patients will receive the proposal for inclusion in the study at the Hospital Sociosanitario Francolí and Residential Centres in Tarragona. The main criterion to enter the study is the presence of diarrhea as a clinical manifestation of COVID-19 disease, in fragile patients, with pluripathology that the responsible doctor considers that in these moments of pandemic and health saturation, the patient is not a candidate for referral to a specific acute hospital.

4.1 Inclusion criteria

Patients infected by SARS-CoV-2 diagnosed by RT-PCR that are not suitable for ICU measures (geriatric patients with fragility criteria) and that suffer diarrhea.

2. Acceptance of the participation in the study by the patient or family, in the case of having associated cognitive impairment or not being competent patients for decision making.

4.2. Exclusion criteria

1. Patients with formal contraindications for treatment with bismuth colloidal compounds, such as the presence of previous renal failure, bleeding ulcers, hemophilia or hypersensitivity to salicylates.

5. Description of the treatment

Patients will be treated with bismuth colloidal subcitrate (trade name: Gastrodenol®) from the day they have more than two clearly liquid stools or a total number of stools per day greater than 3 between liquid and pasty.

Gastrodenol: 120 mg tablets: two tablets every 12 hours, half an hour before breakfast and dinner on an empty stomach. The treatment will be completed 48 hours after the cessation of diarrhoea.

6. Statistical analysis

Sample size: In the experience at the Hospital Sociosanitario Francolí, currently COVID-19 patients with diarrhea can have up to 8 days with more than two liquid diarrhea stools per day. We will consider the treatment to be effective if it can reduce this figure to 4 days. To detect the difference we will need to include a minimum of 32 patients with an alpha 0.05 and beta 0.20 risk.

Endpoints: Main: To determine the efficacy of bismuth colloidal compounds in fragile and pluripathological patients, with diagnosis of COVID19 and presence of diarrhea. The number of diarrheal stools per day and the number of days with stools will be analysed.

Secondary: To analyze if the concomitant pathology influences the evolution of the patient, through the calculation of the Charlson Index.

Analysis of the results:

Quantitative variables will be described by means and standard deviation (if they follow a normal distribution) or by median and range. Qualitative variables will be described by percentages and 95% confidence intervals.

7. Ethical aspects

The study will be carried out in accordance with the Helsinki Declaration (Fortaleza Version 2013). Prior to the inclusion of patients, the study must be approved by an IRB.

The consent of the patient or the patient's immediate family (or guardian in the case of patients with cognitive impairment or who are unable to make this decision) is required for participation in the clinical trial. The special circumstances of the coronavirus pandemic mean that written informed consent cannot be sought from the patient or family. The frail patient with S-Cov-2 diarrhoea is in a situation of general weakness and isolation that makes it difficult to obtain written informed consent, as well as advising minimum contact through paper or pen between the patient and health personnel. On the other hand, we will also not have personal access to family members with whom we only have telephone contact.

It is planned to request verbal consent from the patient (in the absence of dementia or other legal incapacity) or from the family or legal guardian (in the case of dementia or other legal incapacity), in the presence of a witness and to leave a written record of this fact during the clinical course. The written consent shall be requested to be signed at a later point in time when the patient's clinical condition and the circumstances of epidemiological isolation permit.

The study will be carried out in accordance with the laws on the confidentiality of personal data: the Organic Law 3/2018 on the Protection of Personal Data and guarantees of digital rights and the RG (EU) on the protection of personal data RGPD 2016/679.

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