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Study of the application of the 12-hour N-Acetylcysteine protocol in the emergency service for paracetamol overdose

A multicentre, non-inferiority, randomized, open label, controlled clinical trial

Final degree project
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Quiero dedicarles este trabajo a mis padres, Mª José y mis hermanas. Gracias por no haber dejado nunca de creer en mí. Sé que muchas veces el camino ha sido difícil para todos, pero con vuestro esfuerzo y afecto habéis estado ahí, por eso hoy os escribo estas palabras de agradecimiento.

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“If you can make one heap of all your winnings
And risk it on one turn of pitch-and-toss,
And lose, and start again at your beginnings
And never breathe a word about your loss;
If you can force your heart and nerve and sinew
To serve your turn long after they are gone,
And so, hold on when there is nothing in you
Except the Will which says to them: ‘Hold on!’”

Rudyard Kipling

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ABSTRACT

Background

Paracetamol is commonly used worldwide. It is the first step on the World Health Organization (WHO) pain ladder and is currently recommended as first-line pharmacological therapy for acute and chronic painful conditions. Paracetamol is the main drug causing acute liver failure in countries as in United Kingdom (UK) and United States (US), the incidence is 70% and 46% respectively. In Spain, the incidence is lower than in the aforementioned countries, at 2,2% of cases of paracetamol overdose. The paracetamol overdose can be acute (single dose greater than 7.5 to 10 grams) or chronic (repeated dose). The hepatotoxicity per paracetamol is caused by an accumulation of metabolite toxic NAPQI and glutathione stores depleted. The clinical course of hepatotoxicity it can be asymptomatic to a hepatic encephalopathy caused by hepatitis fulminant. The treatment of paracetamol is an N-acetylcysteine (antidote) for 21 hours.

Objectives

The main purpose of this study is to compare the incidence of hepatotoxicity in patients with paracetamol overdose between NAC protocol 12 hours vs. NAC protocol 21 hours. In addition, this study will compare the incidence of adverse effects and hospital length of stay in both groups.

Design

This study is designed as a non-inferiority, randomized, parallel group controlled, open-label clinical trial will be performed among different hospitals of Catalonia, Madrid and Andalusia.

Method

Patients enrolled in this study will be randomized in two groups (A and B). The group A (n= 235) will receive therapy A which consist a standard protocol of NAC for 21 hours, while the group B (n=235) will receive therapy B which consist a modified protocol of NAC for 12 hours.

Main outcome will be the hepatotoxicity caused by paracetamol, which will measure with parameters of laboratory (include ATL, INR, PT). This outcome is defined as a 50% increase in ALT after 21 h post-treatment compared with the admission value overall; ALT > 1000, INR > 1.5 and Quick time >20% at 21 h vs 12h post-treatment.

The follow-up will be done the hospital length of stay in the emergency service of patient, according to her/his clinical situation (includes symptoms and the laboratory tests) and her/his response to treatment.

Keywords: Paracetamol, overdose, antidote, hepatotoxicity, N-acetylcysteine, adverse effect

ABBREVIATIONS

ºC: Grade centigrade
AEMPS: Agencia Española del Medicamento y Productos Sanitarios
AIDS: Acquired immune deficiency syndrome
AIF: apoptosis-inducing factor
AFL: Acute Failure Liver
ALP: Alkaline phosphatase
ALT: Alanine aminotransferase
AST: Aspartate aminotransferase
BCL-2: B cell Lymphoma 2
BMI: Body Mass Index
BP: Blood pressure
BUN: Blood urea nitrogen
CIOMS: Council for International Organizations of Medical Scientists
Cm: Centimetre
CNS: Central Nervous System
COX: Cyclooxygenase
CYP: Cytochrome
DAMPs: Damage-associated molecular patterns
DILI: Drug induced liver injury
E.g.: Example
EKG: Electrocardiogram
FBC: Full blood count
GIT: Gastrointestinal
GGT: Gamma-glutamyl transferase
Gr: Gram
GSH: Glutathione
GST: Glutathione-S-transferases
H: hour
HE: Hepatic encephalopathy
HR: Heart rate
ICU: Intensive care unit
ID: Identity
Ig: Immunoglobulin
iNOS: Inducible nitric oxide synthase
INR: International Normalized ratio
IU: International Unit
IV: Intravenous
Kg: Kilogram
L: Litre
Lpm: Latidos por minute
Mcg: Microgram
MHE: Minimal hepatic encephalopathy
Mg: Milligram
Ml: Millilitre
Mmhg: Millimetre of mercury
Mmol: Millimole
MT: Methyltransferase
NAC: N-Acetylcysteine
NAPQI: N-acetyl-p-benzoquinoneimine
NAT: N-acetyltransferase
NIHSS: National Institute of Health Stroke Scale
O_2: Oxygen
PT: Prothrombin time
ROS: Reactive oxygen species
Rpm: Respiraciones por minute
RR: Respiratory rate
RUCAM: Roussel Uclaf Causality Assessment Method
SULT: Sulfotransferases
Tª: Temperature
TLRs: Toll-like receptors
UDP: Uridine 5'-diphospho-glucuronosyltransferase
UGT: UDP- glucuronosyltransferases
UK: Unite Kingdom
US: Unite States
WHO: Wold Health Organization

1. INTRODUCTION

1.1. DEFINITION AND EPIDEMIOLOGY

Liver intoxication can occur because of chemical agents (abuse of drugs, natural or industrial products) or physical agents. A paracetamol overdose is considered a chemical liver intoxication, and it can be produced because of acute, subacute or chronic overdose. (1,2)

- Acute paracetamol overdose is defined as a single ingestion of greater than 7,5 to 10 grams, occurring within a period of 8 hours or less.
- Subacute paracetamol overdose is defined as ingestion of repeated toxic dose.
- Chronic paracetamol overdose is considered a repeated supratherapeutic ingestion during vary days.

There is little data about the incidence of hepatotoxicity, and most it is related with DILI (3,4) (drug induced liver injury). Since its introduction in the 1950s, its use has increased as an analgesic, and it is also relatively safer compared to other NSAIDs in relation to adverse effects such as high gastrointestinal bleeding or increased blood pressure, among others. However, paracetamol can cause hepatotoxicity when an overdose occurs.(5) The paracetamol (acetaminophen) is commonly used worldwide. It is the first step on the World Health Organization (WHO) pain ladder and is currently recommended as first-line pharmacological therapy by a variety of international guidelines for a multitude of acute and chronic painful conditions. (6)

Paracetamol is considered one of the drugs that are currently sold most in Spain and many countries around the world, under medical prescription, although it can be accessed for sale without such prescription. (7–10). According to the “Annual Report of the National Health System” of 2016 (11) , paracetamol is the second active principle with the highest number of annual containers (36.5 million) during 2015. (11)

In developed countries such as the United Kingdom (UK) or United States (US), the paracetamol overdose, either accidental or with suicidal intent, causes 70% and 46% of cases of ALF (acute liver failure), respectively. (7) In Spain the incidence is lower than in the aforementioned countries, at 2,2% of cases of acute liver failure. This data was collected through a study carried out in Barcelona, which concluded that for every 106

inhabitants/year of cases of severe acute toxic liver disease 7,4 cases required hospital admission (1,12). In a study of the Hospital de la Paz (Madrid), 80% of patients with chronic paracetamol poisoning at toxic doses presented hepatotoxicity and 37.5% of these patients with acute liver failure criteria (13).

In the elderly, it is one of the most prescribed drugs to treat pain, usually chronic. This population is usually people with pluripatology that causes a higher risk of paracetamol poisoning. In addition, the elderly has a physiological alteration of age-specific liver metabolism. Therefore, some of the drugs they take can interact in the metabolism of paracetamol thus increasing the risk of toxicity. (14)

In the paediatric population, paracetamol is one of the most commonly used drugs as an antipyretic and analgesic, and the one that causes the most poisonings, most of them being accidental due to overdosing, and in a minimal part due to an autolysis attempt. (15,16)

Responsible agents

The Barcelona study of ALF in Spain (12) concluded that the first cause of ALF was hepatitis B virus (37%) followed by drug or toxic reactions (Of 19,5%, only 2,2% was caused by paracetamol), the last group was miscellaneous (11,6%). It is important to note that 32% was of unknown cause (cryptogenic/indeterminate liver failure).

1.2. PROPERTIES PHARMACOLOGICALS OF PARACETAMOL

1.2.1. Introduction of pharmacokinetics

When drugs are taken the organism needs to carry out different phases to eliminate the drug. The phases are absorption, distribution, metabolism (we focus on this, see Pharmacokinetics of Paracetamol section) and elimination ***(Annex 1, figure 1).***

The metabolism of drugs (initially hydrophobic product) it is necessary to turn it into more hydrophilic products, that facilitate elimination (renal excretion). During the process of metabolism, we can observe two different reactions:

- Phase I: produces reactions of oxidation, reduction and hydrolytic reactions. These reactions are produced by enzymes, which **change the biological property of drugs**. The results of these reactions are inactivated drugs. The main enzymes

are **cytochrome P450 (CYP-450)**, monooxygenases containing flavins and epoxide hydrolase. The enzymes CYP-450 are from a large family. There are seventy-four families of gens three of which (CYP1, CYP2 and CYP3) participate in metabolising drugs in human livers. The mechanism depends on a complex cycle, but the outcome is the addition of O_2 atom to the drug to form an oxidized substrate, also other O_2 atoms are turned into water. Sometimes the consumption of O_2 is higher than the amount of oxidized substrate, which is generated, thus an **"active oxygen"** or **O_2^-** is produced. The "active oxygen" can also be called **reactive oxygen species (ROS)** and can **produce oxidative stress**, which is harmful for the cellular physiology (see below).(17–19)

- Phase II: the enzymes participate in conjugation reactions and produce an **inactivated metabolite** (from phase I). This allows the decrease of pharmacological activity and toxicity (it is important to understand the toxicity of paracetamol). Thus, it gets metabolised and is easier to eliminate. The main enzymes are:
    - Sulfotransferases (SULT): adds a group of sulphate
    - UDP - glucuronosyltransferases (UGT): adds a glucuronic acid *(UDP: Uridine 5'-diphospho-glucuronosyltransferase)*
    - **Glutathione-S-transferases (GST): adds a glutathione.** It will be responsible for neutralizing the intermediate toxin from the drugs, the result is decreased pharmacological and toxic activity (see below). (19)
    - N-acetyltransferase (NAT): adds a group of acetyls
    - Methyltransferase (MT): adds a group of methyl (18–20)

1.2.2. Dosage of Paracetamol

Therapeutic dose of oral paracetamol in adults is 1g/6-8 hours with a maximum of 4 gram per day. In children over 10 kg the dose is 15 mg/kg/dose, and in children under 10kg the dose is 7,5mg/kg/dose given every 4 or 6 hours ***(Annex 2,Table 1).*** (21)

The toxic dose may vary among individuals according to baseline glutathione levels and other factors.

- The toxic dose is considered to be **150 mg/kg in children, 125 mg / kg in adults** (equals to 7,5gr) (22), and **100 mg / kg in adults with risk factors** (chronic

alcoholism, cachexia or enzymatic induction, ***table 2***) (8,23). Thus, in the clinical practice the minimum toxic dose is 6 gr in adults and doses of over 20-25 gr are potentially fatal. (24)

1.2.3. Pharmacodynamics of Paracetamol

Paracetamol is a derivative of aminophenol and it is a drug effective for the treatment of pain and fever. Paracetamol can be administered in different forms (oral, rectal or intravenous), also it can be associated with other agents/drugs like analgesics (including opioids), antitussive, antihistamine or nasal decongestants. (7,8)

It is believed that paracetamol increases the pain threshold because it **inhibits the prostaglandins synthesis**, through the blocking of cyclooxygenases in the Central Nervous System (exactly COX-3).

Also, paracetamol stimulates the activity of the descending serotoninergic pathway, which blocks the transmission of nociceptive signals to the spinal cord from peripheral tissues. The anti-thermal action is related to the inhibition of prostaglandin 1 synthesis on the hypothalamus, which is in charge of thermoregulation. (24)

1.2.4. Pharmacokinetics of Paracetamol

Paracetamol is absorbed from the gastrointestinal tract, and the **peak concentration** of paracetamol in **plasma** is reached between **30 to 60 minutes** after oral administration. The presence of food may delay absorption.

When paracetamol reaches the bowel, it binds with plasmatic proteins until it reaches the liver, where the metabolism occurs. The time to achieve maximum effect is 1 to 3 hours.

Metabolism of paracetamol occurs within hepatic microsomes. With therapeutic doses the drug reaches the liver and the following occurs:

- **90%** of the paracetamol, through the reactions in phase II, are transformed into **sulfate and glucuronide conjugates** pathway SULT and UGT (see above), which are **non-metabolic toxins** and are excreted in the urine. (2)
- The other **5-10%** of paracetamol is metabolized by the oxidative pathway (reaction of phase I) CYP being mainly **CYP2E1** and in less proportion also

CYP3A4, CYP246 and CYP1A2. The outcome is an intermediate **N-acetyl-p-benzoquinoneimine (NAPQI)**, which is rapidly **conjugated** with hepatic **glutathione** (GSH), forming **nontoxic cysteine** and **mercaptate** compounds that are excreted in the urine. (23,25)

- Less than 5% is excreted in the urine unchanged.

However, when toxic doses of paracetamol are taken, **sulfation and the glucuronidation pathway begin to be saturated**. Thus, unlike described above, almost all the paracetamol is metabolized by CYP (oxidative pathway and CYP2E1 predominates), which results in **increased NAPQI formation *(Figure 2)*.** The CYP2E1 is localized in endoplasmic reticulum also within mitochondria, which is important as there are some studies which have demonstrated that **mitochondrial CYP2E1** is able to **cause oxidative stress and cytotoxicity** after exposure to paracetamol overdose (26,27). So, when hepatic **glutathione stores are depleted** (approximately 70 to 80 %), the **concentration of NAPQI is higher**, and it can produce cellular and hepatic injury for different mechanisms.

- NAPQI react to cellular proteins to form adducts (covalent bonds). (2)
- GHS depletion generates **oxidative stress** (ROS and other toxic free radicals), that produce **intracellular toxicity and hepatocellular centrilobular necrosis** (28,29). High doses of the drug that exceed the protective effect of glutathione will determine the increase in the toxic metabolite that produces in zona III or centrilobular necrosis.(30)
- **Activation of the innate immune system**, after hours of massive hepatocyte death. The Kupffer cells[1] respond by secreting proinflammatory cytokines and chemokines that drive a systemic inflammatory response. This response from Kupffer cells can extend the zone of hepatic injury. (2,26) In normal conditions there is a balance between the generation of inflammatory response and protective response.

[1] Kupffer cells are part of the functional structural unit of the liver, they are tissue macrophages that are located in the hepatic sinusoidal lumen. Which makes them the first cells of the mononuclear phagocytic system that comes into contact with the immunoreactive material that comes from the absorption of the gastrointestinal tract. It plays an important role in the body's defence mechanisms.

Elimination half-life is between 1,5 to 3 hours after ingesting a therapeutic dose, but this may be delayed beyond four hours when a toxic dose is taken, even if drugs which delay gastric emptying (eg, opiates or anticholinergic agents) are taken. (2,24,31)

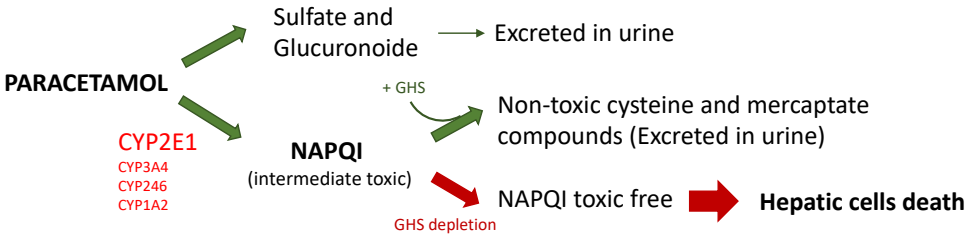

Figure 2. *Metabolism of paracetamol. Adapted from* (2,20)

The green arrows show the metabolism with a therapeutics doses, while the red arrows show the metabolism with a toxic's doses. GHS: glutathione. NAPQI: N-acetyl-p-benzoquinoneimine

1.2.5. Risk factors to increase the hepatotoxicity of paracetamol

A lot of risk factors can participate in the metabolism of paracetamol and can cause decreased capacity of glucuronidation or sulfation, depletion of glutathione stores, and even increase the activity of CYP, among other effects. ***(Table 2).*** (2)

- **Alcohol ingestion:** some alcohol is metabolized by CYP2E1 (system of oxidation) which may be altered after acute or chronic ingestion of alcohol.
    - Acute ingestion of alcohol: in situations of acute ingestion of alcohol coupled with paracetamol overdose, there occurs competition for CYP2E1. Thus, there is a hypothesis that acute alcohol ingestion protects against liver damage, because the alcohol inhibits the CYP activity. (32)
    - Chronic ingestion of alcohol enhances and increases the synthesis and activity of CYP2E1 which results in the shunting of a greater fraction of paracetamol through the CYP2E1 pathway and enhanced generation of NAPQI. Chronic alcoholics may also have a decreased capacity to synthesize mitochondrial glutathione and they are not able to neutralize the excess NAPQI.
- **Nutritional status:** In a fasting or malnourished state, glucuronidation of paracetamol and the glutathione stores are reduced, this situation is associated with an increase of CYP metabolism, thus an over production of NAPQI. The result of this is a high risk of hepatotoxicity. Also, the fasting increases the

CYP2E1 activity at the same time as the glutathione store is depleted, which contributes to hepatotoxicity in alcoholics who take paracetamol.

- **Genetics:** if there is a genetic polymorphism of CYP and hepatic enzymes this results in variations in the way the drugs metabolise, thus it can facilitate hepatotoxicity.
- **Age:** older patients appear more likely to develop hepatotoxicity following acute overdose. Paracetamol is the most commonly used analgesic in older people, also the incidence of adverse reactions is two to three times higher and is attributed to the most frequent prescription, the concomitant use of multiple drugs and the indirect effects of intercurrent diseases. Due to alterations in the bioavailability and metabolism of drugs, the risk of association with dose-dependent reactions is higher in older patients. (14,33)

Table 2. Risk factors that increase the hepatic toxicity of paracetamol. Adapted from (23). See complementary in ***annex 3, figure 4.***

Decreased hepatic intracellular glutathione	Malnutrition AIDS Nervous anorexia Cystic fibrosis Chronic alcoholism Cachexia of any origin
Increased hepatic oxidative activity	Chronic alcoholism Usual treatment with carbamazepine, phenobarbital, isoniazid or rifampicin
	Some authors also include addiction to psychotropic drugs, parenteral drug use and treatment with other antiepileptic or tuberculostatic drugs (although it has only been demonstrated in those in the upper row).
Others	Homocystinuria Gilbert's syndrome Genetic polymorphism
AIDS: acquired immune deficiency syndrome	

1.2.6. Types of intoxications

The paracetamol overdose can produce acute overdose or subacute overdose. The difference between both is important, because the therapeutic management will be different in each case.

- **Acute intoxication:** define the patients who have **ingested a simple toxic dose** of paracetamol. A toxic dose is considered to be 150 mg/kg in children, 125 mg / kg in adults, and 100 mg/kg in adults with risk factors.
- **Subacute and chronic intoxication:** this term is reserved for patients who have **ingested fractional doses of paracetamol** (e.g. 12 g every 3-4 hours for 24, 48 or 72 hours), for a headache, odontalgia or any other reason. These patients can also develop a serious clinical manifestation and consult the emergency service for nausea, vomiting and abdominal pain and a severe hepatocellular injury can be detected at the emergency service. Chronic alcoholics are particularly susceptible to this problem. The chronic intoxication refers to intake of paracetamol for several days.

1.3. MECHANISM OF PARACETAMOL HEPATOTOXICITY

It is well known that when the formation of NAPQI exceeds the capacity of GSH to eliminate this metabolite, NAPQI can react with protein sulfhydryl groups, which leads to the formation of protein adducts. During the early days, it was assumed that covalent binding of paracetamol to proteins was the direct cause of hepatocyte cell death (34,35), but today it is well established that the mitochondrial translocation of BAX is a very early event that induces hepatocyte death (36–38). BAX is one of the essential proteins of the mitochondrial apoptotic pathway or BCL2-regulated (B cell Lymphoma 2) pathway that triggers cell death (39). BAX together with BAK forms pores in the outer mitochondrial membrane that leads to the release of intermembrane proteins including cytochrome c, the second mitochondrial activator of caspases (smac), endonuclease G and apoptosis-inducing factor (AIF). Endonuclease G and AIF translocate to the nucleus and contribute to the nuclear DNA fragmentation and hepatocyte death (37). On the other hand, mitochondrial protein binding triggers an inhibition of the mitochondrial respiration, which causes a selective oxidant stress and peroxynitrite formation in the mitochondria. The oxidant stress and peroxynitrite are responsible for mitochondrial

DNA damage and the opening of the mitochondrial membrane permeability transition pore (MPT), which triggers the collapse of the membrane potential and cessation of ATP formation. The resulting mitochondrial swelling leads to the rupture of the outer membrane with the release of intermembrane proteins and subsequent nuclear DNA fragmentation (***Figure 3***) (40–42).

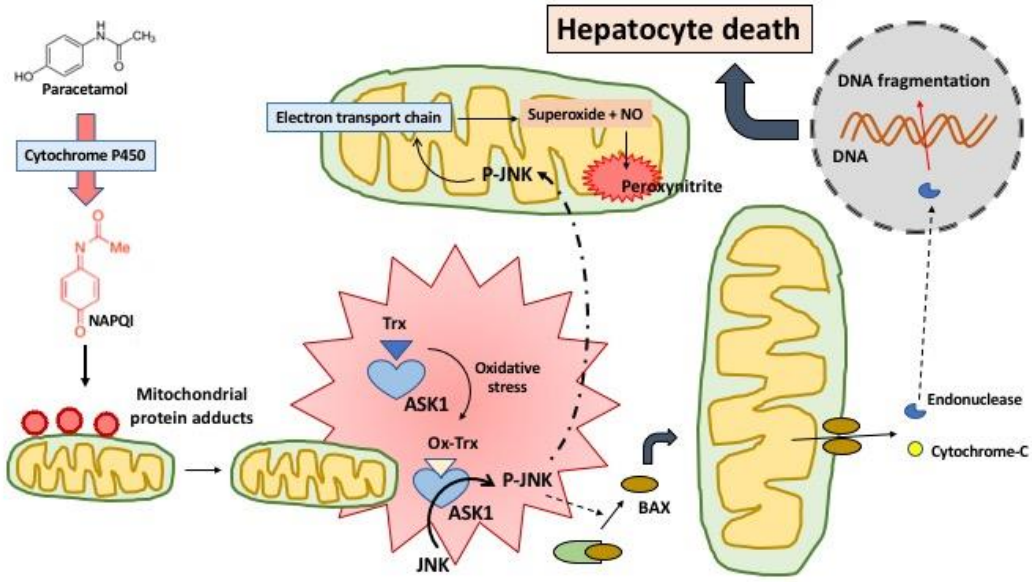

***Figure 3*.** Paracetamol-induced hepatocyte death**.**
Paracetamol metabolism through the cytochrome P450 enzyme results in generation of the reactive metabolite NAPQI, which forms adducts on mitochondrial proteins. The subsequent oxidative stress induces de phosphorylation of JNK (c-Jun N-terminal kinases), which release BAX which generates a pore, that allows the exit of endonuclease-G and cytochrome-C to the cytosol of the hepatocyte. Endonuclease translocates to the nucleus and begins DNA fragmentation, causing hepatocyte death. Also, phospho-JNK initiates signaling which compromises mitochondrial electron transport and amplifies the oxidative stress as well as generation of peroxynitrite. Adapted from (38).

DNA fragments act as damage-associated molecular patterns (DAMPs), that join toll-like receptors (TLRs) on macrophages and other cell types, triggering the formation of a number of cytokines and chemokines and initiating the recruitment of neutrophils and monocytes into the liver (43). The infiltration of these cells in the hepatic parenchyma, and the activation of resident macrophages of the liver (Kupffer cells) after paracetamol overdose, contribute to exert a protective effect of the liver injured by paracetamol overdose, limit toxicity by preventing excessive iNOS (inducible nitric oxide synthase) induction, by promoting cyto-protective gene expression and by supporting regeneration (43). It is well known that infiltrated M2 macrophages appear to be the most critical phagocytes for clearing necrotic cell debris and shutting down inflammation, promoting hepatocyte proliferation and liver regeneration (44).

1.4. TYPES OF INJURIES

The intoxication can produce different degrees of injury from an asymptomatic elevation of transaminases to severe acute liver failure (fulminant hepatitis). (1) Therapeutic toxicity can be produced by different mechanisms:

- Injuries from **indirect toxicity** which is produced by a toxic metabolic, such as a NAPQI in an overdose of paracetamol.
- **Idiosyncratic reactions**
- The possibility of influence of **genetic factors**, above all CYP 450 polymorphisms that can stimulate the hepatotoxicity.

Moreover, the paracetamol intoxication can produce different types of injury among which we can find **acute injury** (hepatocellular, cholestasis, mixed), **chronic injury** (steatosis, granulomas, chronic hepatitis, cirrhosis), and **vascular problems** (liver peliosis, venooclusive disease, Budd-Chiari syndrome).

It can be said that there is hepatotoxicity when there is suspicion of a drug and any abnormality is detected such as (29):

- Increased alanine aminotransferase (ALT) over five times the normal upper limit.
- Increased alkaline phosphatase (ALP) over twice the normal upper limit.
- Increased ALT over three times the normal upper limit and increased total serum bilirubin over twice the normal upper limit.

Depending on the type of injury, we can observe different types of injury at the pathological level, also there is a relation between levels of ALT and ALP (number of times above the normal upper limit)(1,29).

- **Hepatocellular injury:** relation ALT/ALP is greater or equal to 5. Histologically we can see variable degrees of **inflammation and necrosis**. The presence of **centrilobular** prevalence of **lesions** and the presence of inflammatory infiltrate rich in eosinophils suggests a toxic aetiology. As mentioned above the centrilobular necrosis is important in paracetamol overdose cases. Clinical presentation is mentioned in the clinical manifestations section.
- **Cholestasis injury:** relation ALT/ALP is greater or equal to 2. Histologically we can see cholestasis of hepatocytes and bile canaliculi dilated thrombus bile, with no

evidence of necrosis or inflammation. This leads to a benign course and complete recovery without sequelae. The main drugs involved in this type of injury are amoxicillin-clavulanic, macrolide antibiotic and phenothiazine, among others.

- **Mixed injury:** relation ALT/ALP is between 2 to 5. Histologically we can see characteristics of hepatocellular and cholestasis injuries.

1.5. CLINICAL MANIFESTATIONS

The acute toxicity of paracetamol is very serious, because as explained above the toxic metabolites (NAPQI) cannot be neutralized by glutathione and it increases the oxidative pathway, which can produce hepatic injury. Any risk factor ***(Table 2)*** can increase the risk of hepatoxicity. (23) The initial manifestations of paracetamol poisoning are often mild and nonspecific.

Hepatocellular insufficiency is characterized by the alteration of hepatocytic functions (synthesis, clearance, biliary secretion), which results in the **decrease** in plasma **concentrations of coagulation factors**, and therefore a **decrease in Quick time** (or prothrombin time – PT). (45) The clinical course of poisoning is often divided into four sequential stages ***(Table 3).***

Table 3*. Clinical course of paracetamol overdose.*

Stage	Symptomatology	Laboratory test
Stage I (0 to 24 h)	The patient is usually **asymptomatic** o can manifest malaise, nausea, vomiting, paleness and diaphoresis.	Serum **aminotransferase** concentrations are often **normal** but may increase as early as 8 to 12 hours after ingestion in severely poisoned patients. Sometimes decreased Quick time without increased transaminases can be observed. (2,23)
	It was observed in the Hospital Clinic de Barcelona that in elderly patients in particular, with very high overdoses (> 20 g) and serum paracetamol concentrations> 240 mcg / ml, they could enter a deep coma (Glasgow 6), hypotension , shock and electrocardiographic signs of myocardial ischemia, with a very poor short-term prognosis (6 hours after intake)(23). Also, in very high overdose (> 20 g) an elevated anion gap metabolic acidosis can be observed. (2)	

***Table 3**. Clinical course of paracetamol overdose (Continued)*

Stage II (24 to 72 h)	The patient can **continue** to be **asymptomatic** and appear to improve clinically. The patients develop **pain** in the **epigastric and right hypochondrium**, with **hepatomegaly** and hepatic tenderness. (8,46)	The first alteration is the **increase of transaminases** ALT>AST (aspartate aminotransferase, AST). In addition, there may be a **decrease in Quick time**, **antithrombin III and total bilirubin**. (2,47)
	Renal insufficiency is rare, only 2% of the intoxicated patients present it during this stage. It is usually associated with severe acute liver failure (see below) and manifests as **hepatorenal syndrome or acute tubular necrosis**. (48) Acute kidney injury is shown by elevations of blood urea nitrogen (BUN) and creatinine along with proteinuria, hematuria, and granular and epithelial cell casts on urinalysis. There may be pancreatitis, especially in cases associated with alcoholism. (2) The evolution of this stage can be towards normalization in 3 to 4 days, alternatively the patient will enter the next stage.	
Stage III (72 to 96 h)	The abnormalities of hepatic function peaks in the laboratory test and the hepatocellular failure is evidenced.	
	The **symptoms of stage I reappear** in conjunction with **jaundice**, confusion and other **symptoms of hepatic encephalopathy**, and a bleeding diathesis. The evolution of the patient can be favorable, but death most commonly occurs in this stage, usually from multiorgan system failure.	It can observe a **marked elevation in aminotransferases enzyme**s (which can sometimes exceed 10,000 IU/L), **hyperammonemia, function renal** affected, **prolongation of the Quick time, hypoglycemia, lactic acidosis**, and a total **bilirubin** concentration **above 4 mg/dL** (predominance of the indirect).
Stage IV (4-7 or 14 days)	**Progressive evolution towards hepatic and / or renal coma**. Patients who survive until this period begin the phase of clinical recovery, which begins on day 4 and is completed on the seventh day after intoxication. It can be extended up to 3 weeks or more if the patient has serious effects.	Progressive alteration or normalization in weeks.
	Histologic changes in the liver vary from cytolysis to **centrilobular necrosis**. The centrilobular region (zone III) is preferentially involved because it is the **area** of greatest **concentration of CYP2E1** and therefore the site of maximum production of NAPQI. Chronic liver failure is not a sequela of paracetamol poisoning.	

1.5.1 Severe acute liver failure and hepatic encephalopathy (HE)

This is also called fulminant hepatitis (4,49,50) and it is a rare syndrome. It is an uncommon and severe disease characterized by a rapid onset of severe hepatocellular failure in individuals without previous liver disease.(51) Although it also includes some chronic liver diseases (Wilson's disease, HBV reactivation in a non-cirrhotic liver,

chemotherapy-induced immunosuppression, acute Budd-Chiari syndrome and autoimmune hepatitis) that manifest acutely. Acceptable diagnostic criteria are: (52)

- Acute hepatitis.
- Evolution in less than 28 weeks.
- Onset of hepatic encephalopathy (HE) as clinical signs of liver failure.
- Prothrombin time (PT) reduction below 40% or INR ≥ 1.5 as a biological sign of liver failure.
- Previously healthy liver (with the exceptions described above).

The clinical manifestations of HE is very heterogeneous and oscillating. They can appear from few apparent changes, such as abnormal sleep rhythm or attention deficits, to liver coma situations. (53) The HE can be classified in different grades, according to the level of consciousness, neuropsychiatric symptoms and neurological symptoms. For evaluating the grade of HE, we can use West-Haven criteria ***(Table 4).***

Table 4. West-Haven criteria for hepatic encephalopathy. Adapted from (53)

Grade	Level of consciousness	Neuropsychiatric symptoms	Neurological symptoms
0	Normal	Normal	None
MHE	Normal	Alteration only evidenced in psychometric tests	None
1	Mild lack of awareness	Mood changes, inappropriate behavior, attention deficit, difficulty in developing ideas, irritability, altered sleep / wake patterns	Mild asterixis or tremor
2	Lethargic, apathy	Personality disorder, mild tempo-spatial disorientation	Obvious asterixis, bradylalia, Flapping
3	Somnolent	Impossibility of mental tasks, disorientation in time and space, amnesia, unintelligible speech, psychomotor agitation	Clonus, hyperreflexia, muscular stiffness
4	Coma	Not Assessable	Decerebrate posturing (by cranial hypertension)
MHE: Minimal hepatic encephalopathy			

1.6. DIAGNOSIS

The initial attention for patients on arrival at emergency services, includes (54):

- **Clinical situation**: constants and vital signs, symptoms and neurological, respiratory and cardiocirculatory estate.
- **Pathway or exposure to the drug**: Oral (most common), nasal, pulmonary, dermal, conjunctival, subcutaneously, intramuscularly or intravenously.
- **Type of toxic**
- **Interval**. Time from overdose until arrival at emergency service, if possible.

1.6.1. Anamnesis (2,29,33,55)

Most patients are conscious, so when they are attended at emergency services, they can give details about the intoxication. When the patient is unconscious, the anamnesis will be with family members, friends or someone who shared with the patient the last hours of apparent normality. It is important to make an early diagnosis, which includes the **identification of the causative drug** that is suspected and thus prevent the progression to more severe or chronic liver disease. The clinical objective is to discover that an adverse reaction to a specific drug is the cause of a certain injury, in addition, in some cases, when ingestion is interrupted recovery occurs.

The presence of specific symptoms can help us to orientate to etiology. In case of severe paracetamol overdose lactic acidosis (stage III) will present.

It is important to know:

- The time (**latency**) between the start of treatment of poisoning and the beginning of liver damage (by the suspected agent) is very variable.
- **Details of ingestion**: time of the ingestion, pattern of use (single or repeat doses), quantity ingested (in grams), additional ingestion of possible drugs or drug abuse (includes alcohol). If the patient does not know to tell us the exact dose, he/she can tell us how many pills he/she has taken. For this, we assume that every pill corresponds to 1 gram of paracetamol.
- **Exclude alternative causes *(Annex 4, table 5)*** and existence of comorbid conditions that may predispose the patient to the development of hepatic injury (eg, alcohol use, Gilbert's disease, anticonvulsant drug use, recent fasting).

- **Psychiatric history**. To determine possible suicidal intent.
- **Personal medical history**, which includes all diseases that the patient has (hepatopathies, autoimmune, asthma, atopy, etcetera).

The diagnostic etiological consists of establishing a **temporal relation** between **suspected toxic and hepatic injuries**. This can vary from hours to weeks or months. For this reason, the cause is often very difficult to determine. There exist different rating scales, that give points to different elements and, depending on the score obtained, the drug or toxic is considered to be a definitive, probable, possible, unlikely or excludable cause of the injury. The scale of CIOMS (Council for International Organizations of Medical Scientists) /RUCAM (Roussel Uclaf Causality Assessment Method) is used for hepatic lesions caused by a drug. In this scale the following is taken into account:

- Time to onset from the beginning of the drug/herb
- Course of ALT or ALP after cessation of the drug/herb. Percentage difference between ALT or ALP peak and normal upper limit.
- Risk factors: alcohol, pregnancy and age >55 years old
- Concomitant use of drug(s)/herb(s)
- Search for alternative causes

Total score and resulting causality grading: < 0, excluded; 1–2, unlikely; 3–5, possible; 6–8, probable; and >9, highly probable. (1,56)

1.6.2. Physical exploration (55):

Allows a medical practitioner to definitively establish a diagnostic hypothesis indicated previously by anamnesis, this also helps to determine the gravity of intoxication. It is very important to establish **degree of consciousness**, for that we can us Glasgow Scale (designed for cranial trauma) or National Institute of Health Stroke Scale (NIHSS, designed for non-traumatic comas).

NIHSS 0	ALERT. Normal level of consciousness.
NIHSS 1	SOMNOLENT. Patient wakes up and responds to verbal stimuli.
NIHSS 2	STUPOROUS. Patient wakes up and responds only to painful or repetitive stimuli.
NIHSS 3	COMA. Patient responds only with motor or autonomic reflexes or does not respond at all.

1.6.3. Laboratory (2,22,55)

Required serum studies:

- **Hemogram with leukocyte formula**
- **Liver function test**, which includes ALT, AST, total bilirubin (normal range is less than 1.2 mg/dL), alkaline phosphatase (ALP normal range is less than 120 UI/L) and gamma-glutamyl transferase (GGT normal range is less than 28 U/L in men and less than 18 in women).
    - The elevation of ALP, GGT and bilirubin may be due to cholestasis in advances stages (III-IV), when it can be appear an jaundice. (57)
- **Coagulation test**, which includes PT (such as Quick time) with international normalized ratio (INR).
- **Renal function test**, which includes electrolytes, creatinine and BUN (Blood urea nitrogen)
- **Glucose and acid-base balance**

Arterial blood gas and ammonia will be required in clinically compromised patients.

Laboratory evidence of hepatic injury including elevated transaminases and coagulopathy can be detected within 24h of ingestion. It has been suggested that the **aminotransferases are the first laboratory marker to become abnormal** following paracetamol ingestion. The markers for hepatotoxicity include ALT elevations and PT. (58). The liver is responsible of the synthesis of most of all coagulation factors, also it eliminates coagulation factors activated and regulates factor VIII metabolism. **Coagulation tests** are useful in acute liver diseases, because they allow you to specify the **degree of hepatocellular insufficiency**. The determination of Quick Time, it can be less than 20% in acute hepatopathies. If appear cholestasis it can be decreased due to vitamin K absorption deficit. (57). The PT, also reflected in INR measurement, is widely used as a marker of hepatic injury and synthetic dysfunction, as well as to monitor progress and recovery from paracetamol-induced liver toxicity. A typical normal range for PT is 11–14s (INR 1–1.3), but this can vary from laboratory to laboratory. Some **confounders affect the predictive value of the PT** in the development of hepatotoxicity. These include concurrent **anticoagulant** use, **pre-existing liver disease**, and the direct

inhibition of factor VII activity by paracetamol, all may prolong the PT. An initially elevated PT is less likely to predict those that will go on to develop hepatic injury.

An initial normal ALT or AST (typical normal range is less than 40 UI/L, this can vary from laboratory to laboratory) activity is a good indicator that hepatotoxicity is unlikely to develop, in patients treated with acetylcysteine. (59)

All patients with a clear history of paracetamol overdose have to undergo a **measurement of serum paracetamol concentration**. Blood collection for prognostic and therapeutic evaluation should only be done between 4 hours and 24 hours post-intake. In these cases, we can apply **Matthew and Rumack nomogram *(Figure 5)*** to **estimate risk of hepatotoxicity**, in adults with a single acute ingestion and time knowledge.

For patients who have ingested **repeated doses** during hours or days, the blood test cannot give results regarding hepatotoxicity, so we can **calculate the elimination half-life** of paracetamol. This calculation is a very faithful prognostic index of hepatotoxicity, especially when the time of ingestion or whether paracetamol has been ingested in fractional doses, is unknown. In both cases we cannot apply Matthew and Rumack nomogram.

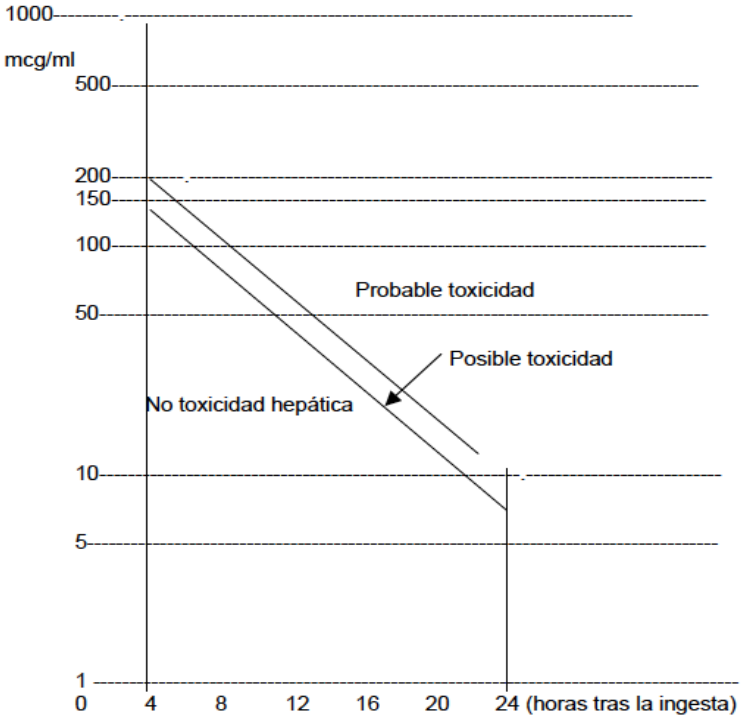

Figure 5. Matthew-Rumack nomogram (47)

The Matthew-Rumack nomogram interprets the paracetamol concentration (in micrograms per mL), in relation to time (in hours) after ingestion. The nomogram predicts potential toxicity beginning at 4 hours after ingestion up to 24 hours after ingestion. Serum concentrations drawn before four hours may not represent peak values and should not be used. **Concentrations measured 4-18 hours post-ingestion are most reliable.** (2,22)

Paracetamol detection in urine in children according to study (60), this detection allow discarding the ingestion of the drug in the previous 24 hours. Also, the detection of paracetamol in urine has a negative predictive value of 100%, so the authors conclude that a negative test allows to rule out the intake of paracetamol and it is not necessary determinate of serum paracetamol concentration.

1.6.4. Additional studies

They will be done always when arrives any type of poisoning to discard the ingestion of other toxics or even objects (e.g. batteries).

- **Thorax and/or abdomen X-ray** allows to detect an accumulation of ingestion of multiples pills on gastric chamber.
- **Electrocardiogram (EKG):** allows to detecting rhythm disorder, conduction disorder o repolarization disorder. It will be useful if there has been ingestion any cardiotoxic drug, also it can demonstrate cardiovascular complications such as a consequence of the drugs of abuse. (55)

1.7. TREATMENT

The treatment of paracetamol overdose in the emergency service of University Hospital Dr. Josep Trueta (Girona) is based on a guide of "Acute intoxication. Basis for a treatment on an emergency service" (23,54).

1.7.1 General measures

- **Monitoring of constant vitals** includes heart rate (HR), respiratory rate (RR), blood pressure (BP) and temperature (Tª). Assess the general state:
    - If there is vomiting, treatment will consist of ondansetron IV better than metoclopramide (It delays the gastric emptying, so the clinical course worsens).
    - If there is hypoglycemia, treatment will consist of glucose serum IV.
    - If there is severe renal failure, treatment will consist of hemodialysis.
    - If the PT is extended, treatment will consist of vitamin K IV.
- Hemodynamic status assessment (**ABC**)
    - **A – Airway**: checking that the airway is free. If there are signs or symptoms of airway obstruction the treatment may consist of manually

removing the foreign bodies, aspirating the secretions, placing a Goeddel cannula, hyper extending the neck or, ultimately, proceeding to tracheal intubation.

- **B – Breathing**: We can observe hypoventilation or in hypoxemia, where treatment consist of ventilatory support, that depends on the severity of the situation. Options range from oxygen therapy to orotracheal intubation. We apply ventilatory support in cases of paracetamol overdose that causes fulminant liver failure.
- **C – Circulation**: arterial hypotension is the most frequent cardiovascular manifestation.

- **Neurological assessment**. The affectation of Central Nervous System (CNS) can occur as a coma or/and seizure.

1.7.2. Gastric lavage (54)

Implemented when intake occurred **less than 2 hours**, of a toxic dose of a product which is absorbed by digestive mucosa.

When the patient is conscious, the objective of this treatment must be explained in order to obtain their consent and collaboration. This measure can apply in determined situations such as a patient in coma, also it can allow immediate use of activated charcoal.

It is not advised to implement gastric lavage at the same time as administering activated charcoal, but after this procedure the first dose of 25 gr of activated charcoal can be administrated.

The main complication is bronchoaspiration and thus aspiration pneumonia, and to decrease his risk in a coma situation the procedure will be carried out with tracheal intubation.

There are recommendations for performing a safe and effective gastric lavage. ***(Annex 5, table 6).***

1.7.3. Activated charcoal (25,54)

Can be used in a single dose, repeated dose or combined with other methods. Activated carbon is a very effective absorbent of many toxic products. It should be **administered** during the **2 hours following the intake**. It is used after ingesting a product which is absorbed by digestive mucosa and a toxic dose is ingested, and also that the substance can be absorbed by an activated charcoal.

- The dose recommended in **adults** is of **25g dissolved in 200mL of warm water**, and in **child is 1g/kg.**
- When the ingestion of drugs is more than 250 mg/Kg, we will administer a second dose of activated charcoal.
- The activated charcoal can be administered by oral route or nasogastric tube. This last point can be considered after gastric lavage and in cases of decreased consciousness.
- Main complication is vomiting and bronchoaspiration.
- Contraindications: after ingestion of caustic products, patients at risk of upper gastrointestinal bleeding or gastrointestinal perforation such as consequence of a recent digestive surgery or a severe previous gastrointestinal pathology.

1.8. SPECIFIC TREATMENT

The specific treatment in paracetamol overdose consists of NAC antidote IV, before its administration we should consider whether it is necessary or not.

Indication of NAC depends on:

- Grams of paracetamol ingested.
- Ingestion of acute single dose or repeated dose.
- Time that has passed since the overdose.
- Plasma concentration of paracetamol.
- Elimination half-life time of paracetamol.
- Risk factors ***(Table 2).***

Before the administration of NAC IV, a laboratory test will be done at 4 hours after ingestion of paracetamol. During the treatment with NAC IV, patient monitoring will be

necessary at 6 to 8 hours after the first laboratory test. Monitoring refers to the laboratory tests specified in the diagnostic section.

1.8.1. Evaluation after acute overdose

The risk of hepatotoxicity is best predicted by relating the time of ingestion to the concentration of paracetamol in the blood plasma. The **modified Rumack-Matthew nomogram** (4h concentration of 150 mg/L) is safe and efficient ***(Table 7).*** The patients with serum paracetamol concentrations above 150 mcg/mL at 4 hours and 10 mcg/mL at 16 hours are considered at "possible risk" for hepatotoxicity and treatment with NAC is standard. The lower limit of sensitivity of the method in most laboratories is 10 mcg/ml, thus that a concentration of "negative" paracetamol in a time interval greater than 16 hours would not be assessable, so if the ingested dose is toxic the patient has to be treated with NAC. The treatment line in the modified Rumack-Matthew Treatment nomogram is 25 percent lower than the original treatment ***(Figure 5)*** line ("probable hepatic toxicity"). This margin of safety was created to allow for variations in paracetamol measurements among laboratories and possible errors in the estimated time of ingestion. (2)

After an acute single overdose of paracetamol, we should determine the serum paracetamol concentration four hours after intake. According to ***Figure 6 (Organigram 1)*** we assess the presence or absent of risk factors and serum concentration. After that we apply nomogram “150” for patients without risk factors or nomogram “100” for patients with risk factors, so as to know if it the administration of NAC treatment is necessary.

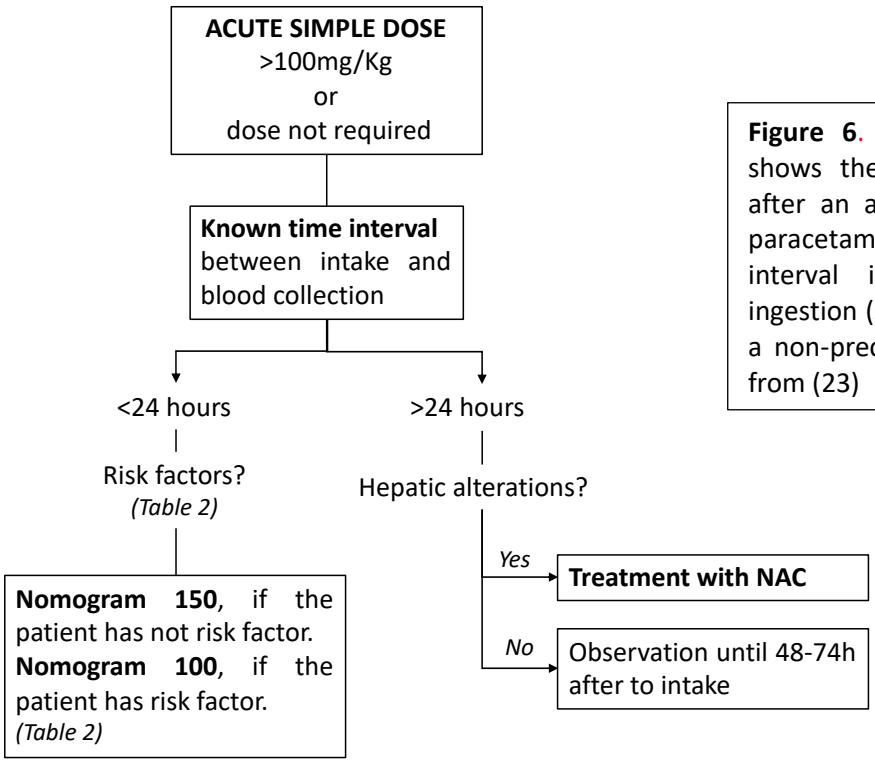

Figure 6. Organigram 1, that shows the attitude to follow after an acute intoxication by paracetamol, when the time interval is known between ingestion (single dose), valid for a non-preciable dose. Adapted from (23)

Table 7. Modified nomogram of Matthew-Rumack "150-100". Indications of treatment according to the levels of paracetamol in blood and time since ingestion. Adapted from (23)

Time that has passed since the ingestion (hours-h)	Administer NAC if the level of paracetamol in the blood is	
	Nomogram "150" in patients without risk factors (above)	Nomogram "100" in patients with risk factors
4h	> 150 mcg/ml [1]	> 100 mcg/ml
6h	> 100 mcg/ml	> 80 mcg/ml
8h	> 80 mcg/ml	> 60 mcg/ml
10h	> 50 mcg/ml	> 40 mcg/ml
12h	> 30 mcg/ml	> 25 mcg/ml
14h	> 20 mcg/ml	> 15 mcg/ml
16h	> 10 mcg/ml	> 8 mcg/ml
18h	> 7 mcg/ml	> 6 mcg/ml
20h	> 6 mcg/ml	> 5 mcg/ml
22h	> 5 mcg/ml	> 4 mcg/ml
24h	> 4 mcg/ml	> 3 mcg/ml

[1] *Mcg/mL (microgram/milliliter) = mg/mL (milligram/milliliter)*

1.8.2. Evaluation after acute overdose with unknown time interval and subacute overdose

In cases in which the time interval is unknown, but it is known that there has been a single dose ***(Figure 7, organigram 2)*** the paracetamol concentration must be measured immediately, also second measurement of the concentration of paracetamol in the blood should be made 2 hours later. The results of both measurements will be assessed with ***Table 8*** according to the elimination half-life of paracetamol.

In clinical practice it is simpler to obtain an estimation of half-life with a quotient between the first and second measurement of paracetamol concentration (mcg/mL). It can be affirmed that a patient with an elimination half-life greater than 4 hours, has a high probability of developing hepatotoxicity.

The above also applies in situation of subacute intoxication (e.g. 12 grams every 3 to 4 hours during 24, 48 or 72 hours), in these cases, we have to follow ***Figure 7 and use table 8*** to know if the administration of NAC is necessary.

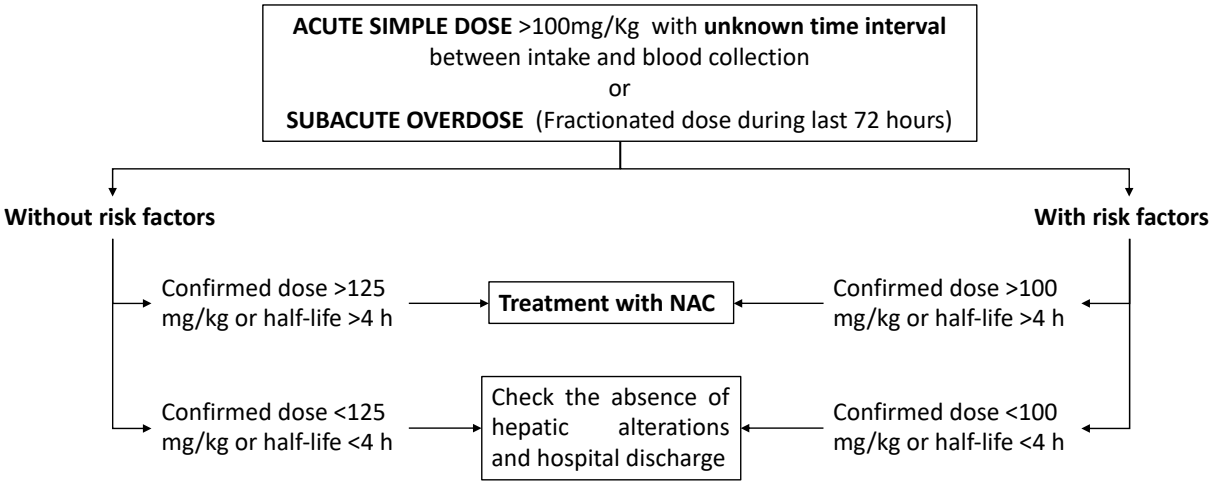

Figure 7. Organigram that shows the attitude to follow before an acute intoxication by paracetamol, when the time interval is unknown between ingestion (single dose), valid for a non-preciable dose and fractionated dose. Adapted from (23). *See risk factors in* ***Table 2.***

Table 8. Indications of treatment based on the elimination of paracetamol. Adapted from (23)

Time interval between 2 plasma paracetamol determinations	Quotient between both determinations	Elimination half-life time of paracetamol >4 hours
2 hours	≤ 1,4	INDICATION TO **ADMINISTRATE NAC**
3 hours	≤ 1,7	
4 hours	≤ 2,0	
5 hours	≤ 2,4	
6 hours	≤ 2,8	
7 hours	≤ 3,7	
8 hours	≤ 4,0	
9 hours	≤ 4,7	
10 hours	≤ 5,6	
11 hours	≤ 6,7	
12 hours	≤ 8,0	

An **empiric treatment with NAC IV** is done in cases of:

- Fractioned dose of paracetamol starts empirical treatment with NAC IV, request laboratory tests.
- A suspected single ingestion of greater than 150 mg/kg in children, 125 mg/kg in adults, and 100 mg/kg in adults with risk factors whom the serum paracetamol concentration will not be available. If 8 to 24h have passed since the ingestion, start empirical treatment with NAC IV, request laboratory tests (look in the diagnostic section).

In all cases above, after initiating the NAC IV a laboratory test will be done at 4 hours after ingestion, if the results are normal the treatment will be suspended, and the patient discharged. If an analytical alteration is observed, continue the treatment with NAC IV (47) and **laboratory test will be done at 6-8 hours after first laboratory test**. Again, if the results are normal, the patient will be discharged, and if they have altered the NAC IV will be continued until 21 hours of treatment.

1.8.3. Destination of the patient

- In "Hospital Universitari Dr. Josep Trueta of Girona" the hospital **discharge** procedure takes into count the **normalization of prothrombin time**, from the laboratory test realized at 6-8 hours after the first laboratory test. If the result is altered the treatment will continue.

  However, there are some studies that suggest **measuring the ALT** prior to stopping NAC and continuing treatment if the ALT is abnormal, as some patients will develop liver injury during the treatment period. Also, they suggest **remeasuring the serum paracetamol concentration** prior to stopping NAC to verify that the level is undetectable. (22,25)
- If there is a certainty that the intake is less than 150 mg / kg (children), 125 mg / kg (adult) without risk factors, or the intake is less than 100 mg / kg with risk factors, there is no possibility of toxicity and, therefore, the patient can be discharged from the hospital. If there is any doubt, a laboratory test must be realized.
- **Once the treatment is finished**, if the patient is in a **situation of toxic hepatitis** with hepatocellular insufficiency, the treatment with NAC of 150mg/kg/24h

must be continued in continuous **infusion** with 5% glucose serum, until there are biological signs of improvement (normalization of laboratory levels) or clinical worsening

- Patients in the **stage III** of clinical course with criteria of liver transplantation, have to be moved to the **ICU** (intensive care unit). In these patients, we will also do treatment with NAC IV although it seems unhelpful.
- All persons who have been **voluntarily intoxicated** require a suicide risk **assessment** by a hospital **psychiatrist**, if this specialist is not available, it is necessary to refer the patient to a specialist in a different hospital.

1.9. N-ACETYLCYSTEINE (NAC) (61)

1.9.1. Dosage and method of administration

The treatment should be **initiated within the first 8 hours** of paracetamol intake, because there are studies (62) which have shown that the risk of hepatotoxicity decreases in these cases. If the administration of NAC is done after 15 hours of the overdose of paracetamol, the risk of hepatotoxicity is higher.

The NAC is administered by intravenous (IV) perfusion with glucose serum of 5% and the **perfusion** should be done **slowly to decrease the risk of adverse effects**.

In case that it is no advised the 5% glucose serum, we can do the dilution with 0,9% of saline serum (sodium chloride). (61)

The treatment guideline in adults and teenagers (20-40kg) consist on three continuous perfusions with a total of 300mg/kg body weight of NAC IV during 21h of treatment:

- First infusion: initial dose of **150 mg/kg in 250 mL** of 5% glucose serum for **60 minutes.**
- Second infusion: **50 mg/kg in 500mL** of 5% glucose serum for **4 hours.**
- Third infusion: **100 mg/kg in 500 mL** of 5% glucose serum for **16 hours.**

The treatment in children $\leq$ 20kg the dose will be the same of adults, however the volume of solution to be infused should be modified taking into account the patient's age and body weight due to the possible risk of pulmonary vascular congestion due to fluid overload. (87)

- First infusion: initial dose of **150 mg/kg in 30 mL/Kg** of 5% glucose serum for **60 minutes.**
- Second infusion: **50 mg/kg in 70 mL/kg** of 5% glucose serum for **4 hours.**
- Third infusion: **100 mg/kg in 140 mL/kg** of 5% glucose serum for **16 hours.**

1.9.2. Other forms of administration of NAC

Modified (shorter) protocol over 12 hours(63)

- Loading dose: **100 mg/kg in 200 m**L of 5% glucose serum **over 2 h**
- Second infusion: **200 mg/kg in 1000mL** of 5% glucose serum over **10 h**

Two-bag acetylcysteine regimen(64)

- Loading dose**: 200 mg/kg in 500mL** of 0,9% saline serum over **4 h**
- Second infusion: **100 mg/kg in 1000 mL** of 0.9% saline serum over **16 h**

According to the guide "Acetaminophen (paracetamol) poisoning in adults: Treatment Acetaminophen" (available in UpToDate ©) (25):

The NAC is stopped once the INR is less than 1.3, the ALT concentration is less than 100 U/L (and not more than twice the admission value), and the serum paracetamol concentration is less than 20 mg/L (20 mcg/mL). If these criteria are not met, the final infusion rate is continued.

1.9.3. Pharmacodynamic properties

After the intake of a high dose of paracetamol the NAC can decrease the hepatotoxicity of NAPQI, through:

1. Main mechanism in initial phases: NAC acts as a **precursor on glutathione synthesis**, thus allowing the body to maintain enough glutathione to inactivate the NAPQI.
2. After 12 hours, most of the paracetamol has been metabolized by reactive metabolite (NAPQI). In this phase, the NAC acts by **decreasing oxidative thiols** groups produced by enzymes (Necessary to produce an oxidative stress).

When the treatment is initiated after 8 to 10 hours of overdose, the efficiency of NAC to prevent the hepatotoxicity is lower. But there is evidence that administration of NAC up to 24 hours after the ingestion can produce some benefits as it improves systemic hemodynamics and oxygen transport (the mechanism is unknown), so it decreases mortality and improves hepatic and cerebral function. (25)

1.9.4. Pharmacokinetic properties

After intravenous administration of NAC, plasma levels 300 to 900 mg/l have been observed within a short time of perfusion. The levels continue to fall at the end of perfusion, until 11 to 90 mg/L.

The NAC has an elimination half-life of 5,6 hours and approximately 30 percent of NAC is eliminated by the kidneys.

1.9.5. Adverse effects of NAC

Adverse effects usually occur between **15 and 60 minutes after the perfusion**, and in a lot of cases its effects disappear after stopping perfusion. When the adverse effects are under control, the treatment can be restarted with a lower perfusion rate (100mg/kg in 1 litre over 16 hours). There are studies (65–68) that specify that **nausea, vomiting and cutaneous systemic hypersensitivity reactions are the most commonly observed**. We must take into account that vomiting can also be secondary to the paracetamol overdose itself. (67)

Main adverse effects classified by system organs:

- Gastrointestinal (GTI) disorder: vomiting and nausea.
- Immunologic system disorder: anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, hypersensibility.
- Heart disorder: tachycardia, bradycardia.
- Vascular disorder: hypertension.
- Respiratory, thoracic and mediastinal disorders: bronchospasm, dyspnoea, stridor, coughing.
- Skin disorder: angioedema, urticaria, flushing, rash, itching, facial edema.
- Coagulation disorder: in some cases, an increase of prothrombin time has been observed (decreased prothrombin index and increased of INR), but in very few cases can we observe a decrease in prothrombin time.

Predefined clinical categories used for adverse effects (69):

- **Minimal** if patients had no reaction or mild GTI symptoms only with- out any specific treatment.

- **Moderate** if patients had GTI symptoms requiring temporary NAC infusion cessation, mild flushing, pruritus, mild chest pain, breathlessness, or peak expiratory flow rate (PEFR) 25–50% less than baseline (where available).
- **Severe** if NAC was stopped due to severe flushing, respiratory distress, moderate to severe chest pain, >50% reduction in PEFR from baseline (where avail- able), or hypotension (systolic blood pressure <90 mmHg or diastolic blood pressure <50 mmHg).

Immunologic system disorder (66,70):

Clinical features of anaphylactoid reactions are very similar to anaphylactic reactions. The difference between both is that **anaphylactic reactions** result after **re-exposure to an allergen**, which means specific **IgE** (immunoglobulin E) molecules stimulate the surface of mast cells and basophils. Mast cell degranulation causes a release of histamine and tryptase, the level of which correlates with clinical severity.

Anaphylactoid reactions are not IgE-mediated(71) and do not require previous exposure to the "allergen agent" (which in this case would be NAC). Furthermore, treatment with NAC can often be safely reintroduced without complication following a reaction. The **histamine** does appear to be an important **mediator**, for this reason higher histamine concentrations cause moderate to severe reactions, which **can be suppressed** with prior administration of a **H1 antagonist** (antihistaminic). This reaction can manifest as any type of sign or symptom aforementioned. It is important to highlight that these reactions are more prevalent in patients with a history of asthma and atopy. Treatment of anaphylactoid reactions are based on the treatment of anaphylaxis:

- **Stop the infusion of NAC**
- Administer **dexclorfeniramina IV** (Polaramine®). If the reaction is more severe it may be necessary to administer corticosteroids IV, and in the case of hypotension it may be necessary to administer epinephrine IV.
- **Restart a slower NAC IV infusion**. According to the data sheet of the NAC antidote (61) of the "Spanish Agency for Medicines and Health Products" (AEMPS), the infusion can usually be started again at an infusion rate of 50 mg / kg for 4 hours, followed by the final infusion of 100 mg / kg for 16 hours.

1.10. HEPATIC TRANSPLANTATION

This therapeutic option should be considered in all patients in the third clinical stage. Urgent transplant criteria in Severe acute liver failure(52): pH <7.3 regardless of the grade of encephalopathy, or the following 3 criteria: Grade III or IV encephalopathy, PT> 100 seconds (INR> 6.5) and Creatinine > 3.4 mg / dL.

1.11. PROGNOSIS

The immediately prognosis of hepatotoxic reactions depend on extension of necrosis. Variables such as: feminine gender, diabetes mellitus, decreased platelet count and low albumin levels and elevated total bilirubin and AST and an AST/ALT ratio >1.5, are independently associated with a poor short-term prognosis. (72)

According to the toxicology guide “Intoxicaciones agudas bases para el tratamiento en un servicio de urgencias” (23) the mortality rate in “Hospital Clinic de Barcelona” for hepatotoxicity caused by overdose paracetamol is zero. Although, there have been cases of severe hepatitis that have required NAC IV for 4-5 days.

According to another guide (25) the outcome of paracetamol intoxication is nearly always good if the antidote, N-acetylcysteine (NAC), is administered in a timely fashion. When fulminant hepatic failure and death occur from paracetamol poisoning, they result from a delay in seeking medical attention, unrecognition of poisoning, or the failure to administer appropriate therapy.

2. JUSTIFICATION

Paracetamol is one of the best-selling drugs in Spain currently under medical prescription, despite being accessible without such a prescription, according to the "Annual Report of the National Health System" of 2016 (11). Also, paracetamol is the second active principle with the highest number of containers sold annually (36.5 million).

Since paracetamol was introduced, in the 50s, its use has increased as an analgesic. In addition, it is safer compared with other nonsteroidal anti-inflammatory drugs (NSAIDs), especially regarding adverse effects (e.g. high gastrointestinal bleeding or increased blood pressure) (5,73,74). For this reason, it is one of the first drugs recommended by WHO for pain treatment both acute and chronic (6), and as such is one of the most consumed worldwide (7–10).

However, paracetamol in an overdose context can produce hepatotoxicity, causing AFL in some cases (3,4,6,27,38,50,74–77). Thus, early diagnosis and treatment is very important, according the study (13) especially in cases of chronic poisoning in which case it often takes longer to request medical assistance.

The current treatment protocol that is being carried out in Spanish hospitals, has a duration of 21 hours. It is based on the guide "Intoxicaciones Agudas. Bases para el tratamiento en un servicio de urgencias"(78). This treatment protocol is also used in other European Countries.

One of the main drawbacks of the current protocol are the adverse effects (62,68,69,71,79) related to the perfusion of the NAC antidote in the first hour of administration. The adverse effects that have been observed most frequently are nausea, vomiting and anaphylactoid reactions (68,69).

Bateman, Et.al (63) demonstrated an important reduction of adverse effects. This reduction was achieved by modifying the time of administration of standard protocol, the time was decreased from 21 hours to only 12 hours. In this study Bateman, Et. al demonstrated a reduction of 25% of anaphylactoid reactions and 29% of nauseas and vomiting in the patients who received the modified protocol for 12 hours. Following this study, others have been carried out that reaffirm the results (64,80,81). The clinical trial realized by Bateman, Et.al also concluded that medication errors and hospital stay were

reduced. Even so, it was not studied whether the modification of the protocol at 12 hours was more effective in preventing the development of paracetamol hepatotoxicity. This study aims to demonstrate that the application of modified protocol NAC 12 hours in Spanish hospitals, is more effective in preventing the occurrence of paracetamol hepatotoxicity. In addition, we want to corroborate that, effectively, a reduction in adverse effects and a reduction in hospital stay is achieved. For that, we will use as a guide the study of Bateman, Et.al. We will expand the sample, and we will also include people between 12 and 16 years old, that in the aforementioned study were not included.

In the case of a positive result its implementation should be assessed as a therapeutic protocol in Hospital Universitari Doctor Josep Trueta.

In conclusion, the paracetamol poisoning (overdose) is a situation of low incidence but is extremely severe in some cases. Meaning a continuous renovation of protocols is required, with the objective to decrease in number and severity its most important effect, which is hepatotoxicity. Thus, this protocol pursues that objective, intending to also demonstrate that this modification of the administration time will be beneficial in other aspects, such as the reduction of hospital stay, and the adverse effects derived from the antidote.

3. HYPOTHESIS

In patients with paracetamol overdose, the infusion of N-acetylcysteine (NAC) for 12 hours will be more effective in preventing hepatotoxicity than N-acetylcysteine (NAC) infusion for 21 hours.

4. OBJECTIVES

Main objective:

This study aims to compare the incidence of hepatotoxicity in patients with paracetamol overdose between NAC protocol 12 hours vs. NAC protocol 21 hours.

Secondary objectives:

This study aims to compare the incidence of adverse effects in patients with paracetamol overdose between NAC protocol 12 hours vs. NAC protocol 21 hours.

This study aims to compare the hospital length of stay in patients with paracetamol overdose between NAC protocol 12 hours vs. NAC protocol 21 hours.

5. METHODS AND MATERIAL

5.1. STUDY DESIGN

This study is designed as a **non-inferiority, randomized, parallel group controlled clinical trial**. It will be an **open-label** clinical trial because both the doctor and the patient will know if a perfusion of NAC 12h or NAC 21h protocol will be administered, which will be selected randomly.

Also, this study is designed to be **multicentre**. It will be set among the hospitals refence of Catalonia, Madrid and Andalucia, they are specified in ***Annex 6***.

In the "Hospital Universitari Doctor Josep Trueta" with 845.142 inhabitants as a reference population, there is an incidence of 8 to 10 cases per year, thus there is 1 case per 100.000 inhabitants. So, with a total population of 7,601,813 in Catalonia, the expected incidence would be 72 cases per year. If we take into account the population of Madrid, Andalucia and Catalonia, with a total of 22.673.813, the expected incidence would be 215 cases per year.

5.2. STUDY POPULATION

The study population will be all patients with either suspected or confirmed overdose of paracetamol, who arrive at the emergency service. We will know if the patient has an overdose of paracetamol through exhaustive anamnesis, which includes:

- The amount of paracetamol which has been taken, in grams. If the patient is not able to tell us the exact dose, he/she can tell us how many pills he/she has taken. For this, we assume that every pill corresponds to 1 gram of paracetamol.
- Type of intoxication, acute, subacute or chronic.

If the patient arrives at emergency service unconscious, we should do the anamnesis with a close relative, or the last person who saw the patient conscious.

Inclusion criteria:

- Age ≥12 years old
- Single paracetamol overdose >150 mg/kg in children, >125 mg/kg in adults (equals to 7,5gr), and >100 mg/kg in adults with risk factors.

- Repeat paracetamol overdose for 24 hours: >150 mg/kg in children, >125 mg/kg in adults (equals to 7,5gr), and >100 mg/kg in adults with risk factors

Exclusion criteria:

- Age <11 years old. We have considered these patients excluded because there are estimates which establishes that a child of 12 years old has approximately a weight of 40 kilograms, the treatment for children weighing less than 40 kg is different. (82,83)
- Blood concentrations of paracetamol below the level which necessitates this treatment, according to the nomogram 100-150 (The patient has not indication to receive the treatment with the NAC).
- Patients who deny informed consent.
- Patients with a paracetamol overdose taken more than 36 hours before help was sought. These patients are considered chronic paracetamol overdose cases, who have been taking high doses of paracetamol over a number of days.
- Patients with anticoagulant treatment.
- Patients with criteria of urgent transplant: pH <7.3 regardless of the grade of encephalopathy, or the following 3 criteria: Grade III or IV encephalopathy, prothrombin time > 100 seconds (INR> 6.5) and creatinine > 3.4 mg / dL.

Withdrawal criteria

Patients may discontinue their participation in the study at any time. The research doctor, in his or her opinion or judgment, may also withdraw a patient from the study if required by the patient´s clinical situation or if the patient does not comply with the protocol. The cause and justification of the withdrawal will be reflected in the study development. The treatment will also discontinue if any adverse effects appear at any time (See section: Adverse effects of NAC).

5.3. SAMPLE

5.3.1. Sample selection

The first stage consists on choose the hospitals that will participate in our study by **convenience**, so it will be an **intentional sampling**. We choose this type of sampling for practical reasons. So, assuming that patients in the different Catalan, Madrid and

Andalusians hospitals have similar baseline characteristics, so we do not think that choosing the hospitals by convenience will generate selection bias.

The second stage consists on choose the patient attended to emergency service in all these hospitals, it will be used a **non-probabilistic consecutive sampling** method.

The patients will be selected if they accomplish the inclusion and exclusion criteria, also the patient will have to accept an informed consent form. The sample will be composed of two groups **a control group and intervened (protocol) group**.

5.3.2. Sample size

In a **bilateral contrast** with an alpha significance level of 5% and a power of 80% assuming that the differences detected were moderate, we will need **235 patients per arm of the clinical trial** (total 470). The possibility of a 20% abandonment has been assumed.

Computations were carried out with the Prof. Dr. Marc Saez' software based on the library pwr of the free statistical environment R (version 3.6.2).

5.3.3. Time of recruitment

According to non-published data, the "Hospital Universitari de Girona Doctor Josep Trueta" attends around 8 to 10 people suffering paracetamol overdose per year. So, taking into account the patients attended per year, we estimate that the "Hospital Universitari de Girona Doctor Josep Trueta" (845.142 inhabitants as a reference population), it will attend on 3 years approximately 30 cases.

If, we consider the number of cases of paracetamol overdose in Catalonia according to inhabitants of reference (aforementioned), we can extrapolate these data to the Madrid and Andalusian hospitals which participate in the study. Thus, we estimate that in all hospitals attend approximately the necessary number of patients with paracetamol overdose per year. Therefore, we estimate that the **time of recruitment will last 33 months.**

To achieve more accuracy, this incidence will be assessed after the first 6 months of the study to confirm this conservative estimate and if it shows differences then the study duration will be recalculated.

5.4. VARIABLES AND METHODS OF MEASUREMENT

5.4.1. Study interventions

The independent variable is the **therapeutically intervention.** Both groups will be treated with a NAC IV antidote after to attend by doctor in emergency service with a confirm diagnosis of paracetamol overdose.

- **Group A** is a control group, it will receive an intravenous NAC for 21 hours, which is considerate a conventional treatment (identified as **therapy A**).
- **Group B** is an intervention group, it will receive an intravenous NAC for 12 hours, which is considerate a modified treatment (identified as **therapy B**).

It is a **dichotomous qualitative variable.**

5.4.1. Dependents variables *(Table 9)*

The main variable is the **paracetamol induced hepatoxicity.** It will be measured with parameters of laboratory test in each group:

- Concentration in plasma of ALT is a **continuous quantitative variable** expressed in Ul/L.
- Concentration in plasma of INR is a **continuous quantitative variable** expressed in numbers.
- Quick time is a **continuous quantitative variable** expressed in percentage.

All these parameters will be collected by a nurse during patient follow-up from the beginning to the end. The hepatotoxicity to be determinate as (84,85):

- Proportion of patients with a 50% increase in ALT after 21 h post-treatment with therapy A, compared with the admission value overall, and compared to those with therapy B post-treatment.
- Proportion of patients with ALT > 1000 at 21 h post-treatment with therapy A and compared to those with therapy B at 12h post-treatment.
- Proportion of patients with INR > 1.5 at 21h post-treatment with therapy A and compared to those with therapy B post-treatment.
- Proportion of patients with Quick time <20% at 21h post-treatment with therapy A and compared to those with therapy B post-treatment.

Blood samples for paracetamol concentration, INR, urea and electrolytes, creatinine, full blood count (FBC) and liver function tests (including ALT, AST, ALP, bilirubin and GGT) **will be obtained at baseline and 12 h and 21 h after initiation of NAC IV**. These samples were taken by nurse. Results will be collected by the research team, via the hospital electronic laboratory reporting system. Also, we will request at blood samples 6 hours after starting the treatment, such as control measure.

The nurse will use 3 types of tubs to recollect the blood sample: EDTA anticoagulant, a tube with sodium citrate and sterile tube without anticoagulant. All of these will be identified with the patient barcode label.

The secondary variables are related to **adverse effects** causing by NAC IV. The adverse effects usually occur between 15 and 60 minutes after the perfusion, and in a lot of cases its effects disappear after stopping perfusion. It will be measured as the occurrence of adverse events with therapy A and B compared to his/her situation before the start the NAC IV. We will take into account the main adverse effects, which are:

- Gastrointestinal: vomiting or nausea only or vomiting and nausea. It is a **dichotomous qualitative variable** (yes/no).
- Anaphylactoid reaction. It is a **dichotomous qualitative variable** (yes/no).
- Anaphylactic shock. It is a **dichotomous qualitative variable** (yes/no).
- Cutaneous symptoms: flushing, rash, urticaria, wheals, itch. It is a **dichotomous qualitative variable** (yes/no).
- Respiratory symptoms**:** bronchospasm, wheeze, dyspnea, shortness of breath. It is a **dichotomous qualitative variable** (yes/no).
- Heart rate disorder: tachycardia or bradycardia expressed in beats per minute. They are **dichotomous qualitative variable** (yes/no).
- Blood pressure disorder, it can be hypertension or hypotension expressed in mmHg. They are **dichotomous qualitative variables** (yes/no).

The gastrointestinal effects, anaphylactoid reaction, anaphylactic shock, cutaneous symptoms and respiratory symptoms will be measured by a physical examination. The heart rate and blood pressure will be measured with monitoring through automatic tensiometer (which will be the same for all patients).

Another secondary variable is the **hospital length of stay** during the administration of NAC IV. It is a **continuous quantitative variable**, and it will be measured through the **time expressed in hours**, and it will be registered in the clinical history of the computer database. We will into account the time of entry and exit.

5.4.3. Covariates *(Table 10)*

- Age: It is a **continuous quantitative variable**. It will be calculated through the date of event minus the date of birth obtained from the patient's ID card or another valid document. It will be measured in years.
- Gender: It is a **nominal qualitative variable** (Male/Female/Unknown). It will be collected from the patient's ID or another valid document during admission.
- Weight: It is a **continuous quantitative variable.** It will be measured with a scale and if it is not possible, we will try to ask to a close family member, or an approximate estimate will be made. It will be expressed in kilograms. When it is possible to measure the weight with a scale, it will be used the same for all patients, thus we will avoid a measurement error. The body weight is used and not BMI (Body Mass Index), due to the calculation of the dose of NAC is done with body weight.
- Low socioeconomic status: Low income, unemployment and non-college education are factors of low socioeconomic status, and they may also be confounding factors for paracetamol overdose. It is a **dichotomous qualitative variable**: presence or absence of low socioeconomic status. It will be collected from clinical history made by the doctor during emergency admission.
- Alcohol ingested: It is defined as an alcohol intake along with paracetamol overdose. It is a **dichotomous qualitative variable** (yes/no)**.** It will be collected from clinical history made by the doctor during emergency admission.
- Chronic alcohol (enolism): It is defined as a disease caused by excessive and prolonged consumption of alcoholic beverages that causes a state of psychic and physical dependence on alcohol. It is a **dichotomous qualitative variable (yes/no)**. It will be collected from clinical history made by the doctor during emergency admission. The chronic alcohol may be a confounding factor for

paracetamol overdose because as aforementioned in the introduction, this situation favours the production of NAPQI and thus the hepatotoxicity.

- Other drugs ingested: It is a **dichotomous qualitative variable:** presence or absence of drugs (include drugs of abuse). It will be collected from clinical history made by the doctor during emergency admission. It can be considered drugs which intake the patient for other diseases, or if there is an autolysis attempt, the drugs can be intake at the same time that paracetamol overdose.
- Time since the overdose: The time is a continuous quantitative variable. This variable will be expressed according to the number of patients that are included in each category. Thus "Time since overdose" variable will be categorized and therefore become **polytomous qualitative variable.**

This variable is related with the time passed after the overdose, so each category can be less than 8 hours, between 8 to 24 hours and over than 24 hours.

- The pattern of overdose can be single o fractioned, and it is a **dichotomous qualitative variable.** It will be collected from clinical history made by the doctor during emergency admission.
- Plasma paracetamol concentration: It is a **continuous quantitative variable.** It will be measured with a laboratory test realized by a nurse. It will be expressed in mg/dl, and it will be measured by laboratory test:
    - The first plasma paracetamol concentration in >4 hours post-ingestion in single overdose.
    - Mean serum paracetamol concentration mg/dL in acute overdose (Less than 24 h post-ingestion).
    - Plasma paracetamol concentration in fractioned overdose ingestion. It will be measured with two determinations of it in plasma separate into 2 hours. The average of the two concentrations will be made.
- Pre-existing liver disease: It is a **dichotomous qualitative variable** (yes/no). It will be collected from clinical history made by the doctor during emergency admission. Although, it can determine pre-existing of liver disease if there is any previously note in computerized clinical history.

It has been considered such as a covariate because it can be a confounder that affects the predictive value of the PT in the development of hepatotoxicity.

Table 9. Variables of study

Variable	Type	Categories of Values	Measure of instrument
Independent variable			
Therapeutical intervention	Dichotomous qualitative	Therapy A or therapy B	
Paracetamol induced hepatoxicity (main dependent variable)			
Concentration in plasma of ALT	Continuous quantitative	UI/L	Laboratory test
Concentration in plasma of INR	Continuous quantitative	Number	Laboratory test
Quick time	Continuous quantitative	%	Laboratory test
Adverse effects of NAC IV (secondary dependent variable)			
GIT: vomiting or nausea	Dichotomous qualitative	Yes/No	Physical examination
GIT: vomiting and nausea	Dichotomous qualitative	Yes/No	Physical examination
Anaphylactoid reaction	Dichotomous qualitative	Yes/No	Physical examination
Anaphylactic shock	Dichotomous qualitative	Yes/No	Physical examination
Cutaneous symptoms	Dichotomous qualitative	Yes/No	Physical examination
Respiratory symptoms	Dichotomous qualitative	Yes/No	Physical examination
Heart rate disorder	Dichotomous qualitative	Yes/No	Physical examination
Blood pressure disorder	Dichotomous qualitative	Yes/No	Physical examination
Hospital length of stay (secondary dependent variable)			
Hospital length of stay	Continuous quantitative	Number hours	Clinical history (database)

GIT: gastrointestinal

Table 10. Covariates

Variable	Type	Categories of Values	Measure of instrument
Age	Continuous quantitative	Number of years	Patient's ID card or other documentation
Gender	Nominal qualitative	Male/Female/Unknown	Patient's ID card or other documentation
Weight	Continuous quantitative	Kilograms	Scale (clinical examination)
Low socioeconomic status	Dichotomous qualitative	Presence or absence	Clinical history
Alcohol ingested	Dichotomous qualitative	Yes/No	Clinical history
Chronic alcohol (enolism)	Dichotomous qualitative	Yes/No	Clinical history
Other drugs ingested	Dichotomous qualitative	Presence or absence	Clinical history
Time since the overdose	Polytomous qualitative	Less than 8 hours Between 8 to 24 hours Over than 24 hours	Clinical history
Patter of overdose	Dichotomous qualitative	Single or fractioned overdose	Clinical history
Plasma paracetamol concentration	Continuous qualitative	Mg/dL	Laboratory test
Pre-existing liver disease	Dichotomous qualitative	Yes/No	Clinical history

5.7. RANDOMIZATION TECHNIQUE AND STUDY INTERVENTION

5.7.1. Randomization technique

The patients who participate in this clinical trial study after meeting all inclusion criteria and none of the exclusion criteria will be randomly assigned to one of two groups:

- **Group A:** a control group; the patients will be receiving a NAC IV protocol 21h (standard, **therapy A**).
- **Group B**: an intervention group; the patients will be receiving a NAC IV protocol 12h (**therapy B**).

With the randomized selection we avoid selection bias. This randomized clinical trial will be in a therapy A or B. The patient will always know that he/she will receive a treatment

with NAC IV, such as a responsible doctor. When a new patient arrives at emergency services and accepts to participate in this study, they will be **assigned randomly through a computer program** to group A (who will receive therapy A) or group B (who will receive therapy B).

5.7.2. Study intervention

Prior to this, the informed consent form will be signed by the patient, representative or legal guardian. Then, the patients will be assigned to group A or B and one of the two therapies (A or B) will be administered:

Group A: this group will receive intravenous **therapy with NAC for 21 hours** (therapy A). An experienced nurse (supervised by a responsible doctor) will administer conventional treatment with NAC IV after admission to study consisting of:

- A bolus of 150 mg/Kg in 250 ml of 5% glucose serum, over 60 minutes.
- 50 mg/Kg in 500 ml of 5% glucose serum, over 4 hours.
- 100 mg/Kg in 500 ml of 5% glucose serum, over 16 hours.

Group B: this group will receive intravenous **therapy with NAC for 12 hours** (therapy B). An experienced nurse (supervised by a responsible doctor) will administer conventional treatment with NAC IV after admission to study consisting of:

- A bolus of 100 mg/Kg in 200 ml of 5% glucose serum, over 2 hours.
- 200 mg/Kg in 1000 ml of 5% glucose serum, over 10 hours.

In both groups, we will take into account:

- The dose necessary for each patient will be calculated by a doctor, based on patient body weight, which will be measured by a nurse with a scale. When this is not possible, we will ask a close family member, or an approximate estimate will be made (most commonly in cases of patients who are unconscious).
- The dilution (NAC plus glucose serum) will be done by a nurse. After administering the first dose in each group, then the second dose will be administered by the same nurse.
- After administering the first dose, the patient will be observed for the first 15 to 60 minutes, for any reactions or adverse effects to the NAC.

5.8. METHOD OF DATA COLLECTION

All data will be collected prospectively during the **33 months** of the patient recruitment using **"Data Collection Sheet"** ***(Annex 7).*** The following procedure will be followed in each hospital which participates in our study.

In each patient attended to in the hospitals that participate in the study, according to information obtained with "Data Collection Sheet", a paracetamol overdose must be suspected. In case of suspected poisoning, we always have to rule out other causes, especially the concomitant ingestion of other drugs or drug abuse ***(Annex 4, Table 5).*** Once we have a definite diagnosis, and the patient fits all inclusion criteria and none of the exclusion criteria, he or she will be formally enrolled in the study.

Before joining the study, all patients will receive **"Information Sheet"** ***(Annex 8)*** describing the study and the doctor will ask them to participate in it, highlighting the confidentiality and the voluntary aspect to join. If the patient decides to participate, they will be asked to sign an **informed consent** form ***(Annex 8)*** to be included. In some cases, there will be a **reduced level of consciousness or cognitive impairment**, and in other cases a **loss of capacity** which is deemed to be **temporary** (alcohol, abuse drugs, etc.). In this situation as the patient will not be able to give his consent before the data collection due to the severity of his/her condition, the "Informed Consent" will be required from a **family member first-degree, representative or legal guardian** if they are present. Once the patient is conscious, we will ask him/her to sign an informed consent form ("re-consent"). If the **patient** is a **minor**, then the "Informed consent" will be required from his/her first-degree **family member or legal guardian.**

The informed consent forms and study information sheets will be available in Catalan, Spanish and English but only their Spanish version is annexed.

Once we consider that the patient meets all the inclusion and exclusion criteria and the informed consent form has be signed by the patient, as soon as possible, they will be randomly assigned a group, and they will begin the treatment with NAC IV according to the therapy group (A or B).

After filling out the data collection sheet, the **initial attention** for patients on arrival at emergency services, includes:

- Clinical situation: constants and vital signs, symptoms and neurological situation (includes the assess of consciousness).
- Hemodynamic status assessment: ABC (See the details in Treatment: general measures section).

Also, before administering the antidote treatment, the doctor will do a **laboratory test** (see the details in the laboratory test section on introduction) with acid-base balance, chest/abdominal X-Ray and EKG. Both last tests are very useful to assess the concomitant ingestion of other drugs or the abuse of drugs.

To evaluate our main dependent variable (hepatotoxicity), laboratory test parameters (ALT, INR, Quick time) will be measured at 4 hours after ingestion of paracetamol and 12 or 21 hours after the treatment is completed, these values will be compared between both groups, and with baseline values.

The **dose** necessary will be **calculated by a doctor**, and the **dilution** of NAC with 5% glucose serum will be done **by a trained nurse**, who will be administering it in "boxes" of emergency service. When the first bag of dilution is completed (administered as a bolus of perfusion), the second bag will be administered by a nurse and the same procedure will be repeated again for cases which need a third bag. It will **always** be the **same nurse** because she/he knows the patient and her/his clinical situation and, thus, **medication errors can be avoided.**

The patient remains in "boxes" until the treatment is finished at 12 hours or 21 hours. It is important for the first 15 to 60 minutes to assess if there are any adverse effects (See section: NAC, adverse effects) because this is when they most commonly appear. The adverse effects will be controlled during the patient´s length of stay at hospital in order to increase safety regarding the therapy's fulfilment by patient. If the drug is not-well tolerated, the NAC IV must be stopped, and the corresponding treatment will be administered, according to the type of adverse effect. This will be considered a withdrawal criteria (see section: 5.2. Study population).

Once the **treatment is finished**, if the **laboratory test is normal** (INR, ALT and Quick time within normal parameters), the treatment will be stopped, and the **patient will be discharged**. On the contrary, if the patient is in a **situation of toxic hepatitis** with hepatocellular insufficiency, the treatment with **NAC** of 150mg/kg/24h **must be**

continued in continuous infusion with 5% glucose serum, until there are biological signs of improvement (normalization of laboratory levels) or clinical worsening.

The **follow-up** will be done during the hospital stay of the patient, according to his/her clinical situation (includes symptoms and the laboratory tests) and his/her response to treatment. In cases, of **clinical worsening** (See section: Treatment), the patient will be **referred** to the **ICU**. When the patient is discharged the follow-up will be done by his/her primary attention doctor.

All the data obtained during the follow-up will be collected in a "Data Collection Sheet" and also, it will be entered into a computerized clinical history of the patient by the doctor. The doctor will also be in charge of collecting and annotating the necessary dose of NAC, adverse effects and their treatments, the results of the laboratory tests and the start and end of the treatment. The nurse will be in charge of collecting the information about constants and vital signs.

6. STATISTICAL PLAN AND STATISTICAL ANALYSIS

6.1. STATISTICAL PLAN

The statistical analysis describes the items that will be necessary for obtaining the results and to assess the data collected from each patient:

- Description of sample will be performed with covariates (age, gender, weight and low socioeconomic status), and also in relation with therapeutically intervention.
- Description of the main dependent variable (hepatotoxicity) according to the laboratory test values (ATL, INR, Quick time) at the end of the treatment, comparing it in both groups. Also, the values of this variable will be compared with baseline values pre-treatment. In addition, in both groups will be compared the main dependent variable (hepatotoxicity) with the intervention (therapy A or therapy B).
- Description of the main dependent variable (hepatotoxicity) according to covariates.
- Assess if there are any difference between both therapies A or B (independent variable) of intervention in both groups, according to covariates.
- Assess if there are any difference between both therapies of intervention according to the secondary dependent variable (hospital length of stay).

6.2. STATISTICAL ANALYSIS

The statistical analysis will be done using the Statistical Package for the Social Sciences (SPSS Windows®).

The patients will be receiving a treatment randomly, and I will wait that the therapy B will be better than therapy A. The descriptive analysis of the variables will be performed to compare the characteristics of the population of both groups (therapy A and therapy B).

The statistical analysis method used will be the **intention to treat analysis,** it would allow obtaining information on the effectiveness of the treatment from the clinical trial. The effect obtained is in real conditions, through the randomization of patients in both groups. So, if appear hepatotoxicity or any adverse effect they are not attributed to therapy received. In

this method all patients are included independently meet or not the entry criteria, if they leave the protocol or the treatment received.

Descriptive

The main dependent variable (hepatotoxicity: Concentration in plasma of ALT, INR and Quick time) will be described through **means and standard deviations**: median and interquartile range, according to the distribution of symmetric o asymmetric variables respectively, stratifying by intervention.

The secondary variables (adverse effects) I will summarize them by stratifying them by the control and intervention group through **contingency tables** (proportions per row).

The secondary variable (hospital length of stay) I will categorize them as **median** and **quartiles**.

I will be stratifying all these analysis by the covariates. In the case of the covariate of age, weight and plasma paracetamol concentration (continuous variables) I will categorize them as **quartiles**.

Bivariate

I will assess the relation between the main dependent variable and the therapeutical intervention through **T-student** and **U de Mann-Whitney**, depending on if the distribution of variables is symmetric or asymmetric respectively.

The relation between secondary dependents variables (adverse effects) and therapeutically intervention will be assessed through **chi-square test and Fisher's exact test** when the expected frequencies are less than 5.

I will assess the relation between the secondary dependent variable (hospital length of stay) and the therapeutical intervention through **U de Mann-Whitney**, depending on if the distribution of variables is symmetric or asymmetric respectively.

I will be stratifying all these analysis by the covariates. In the case of the covariate of age, weight and plasma paracetamol concentration (continuous variables) I will categorize them as **quartiles**.

Multivariate

As random there will be no confounders. However, such as additional analysis I will adjust the relations described above using multivariate models.

The main dependent variable will be estimated with a **linear regression models**, controlling for all covariates.

The secondary dependent variables will be estimate with **logistic regression models**, controlling for all covariates. The relation between hospital length of stay and independent variables will be adjusted through a Poisson distribution, controlling for the covariate.

7. LEGAL AND ETHICAL ASPECTS

This clinical trial will respect the medical ethics principles of human experimentation, according to the **World Medical Association Declaration of Helsinki (1964)** about the Ethical Principles for Medical Research Involving Humans Subjects.

Once this protocol will be finished, it will be sent to the **Clinical Research Ethics Comitte** (CEIC) to be evaluated and approved. According to the ***"Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos"*** the approbation of the protocol by the CEIC is mandatory to start clinical research. In this way, permission will also be solicited to the direction of each of our hospitals and the protocol will be sent to the ***"Asociación Española de Medicamentos y Productos Sanitarios"*** (AEMPS) to receive its authorization. After its approval, an application for a registry number to the European Union Drug Regulating Autorities Clinical Trials (EudraCT) will be also sought.

CEIC will be responsible to decide if our trial is considered an invasive procedure according to Ley 14/2007 de 3 de Julio.

According to the Spanish legislation, ***"Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales",*** all the information obtained from the patient will be confidential and anonymous, being used just for the research. Data will only be accessible for the responsible researchers of the project.

A detailed information sheet ***(Annex 8)*** of the clinical trial will be given to all the participants, then they will be asked to sign the informed consent form ***(Annex 8),*** so they will be enrolled in this trial. In case of patients are unconscious, the information sheet will be given to a close family member, also they will sing the informed consent form. After, the informed consent form will be signed by the patient, once he or she are recovered. In case of minors, the information sheet will be given to her/his parents or legal guardian, they will also sign the informed consent form. Throughout the entire intervention, the principle of autonomy will be respected.

8. WORK PLAN AND CHRONOGRAM

The research team will coordinate, interpret and present the results of the study. To every emergency service team in each hospital, there will be a "main investigator", a coordinator who will meet twice a year with the other coordinators from each hospital.

This study will be **multidisciplinary**, so other professionals will be **co-investigators**: a pharmacist from each hospital, a radiologist from each hospital, doctors and nursing staff from each hospital, one statistician to analyze the results and a project manager.

Stage 0: Study design and preparation of study protocol (September 2019 – December 2019)

- Bibliographic research: large literature research will be done, to define the objectives and the study variables to answer the formulated hypothesis.
- Elaboration of a chronogram will be designed.
- Problem identification, proposal change and protocol development and evaluation.

The investigator will be the main responsible party.

Stage 1: Ethical evaluation of the protocol (January 2020)

- Once the protocol is revised, it will be presented and evaluated by the Clinical Research Ethics Committee (CEIC) of the Hospital Universitari de Girona Doctor Josep Trueta, Girona.
- Presentation of the protocol to AEMPS (Agencia Española del Medicamento y Productos Sanitarios).
- We will not need insurance, because it is a low-level intervention trial and the hospital's civil liability policy will be sufficient.

The investigator will be the main responsible party.

Stage 2: Study coordination (February 2020 – March 2020)

- First meeting of the research team to choose who will be the principal coordinator at each hospital centre included in our study.
- Organize tasks and discuss how training for completing the data information sheet will be included, in the first meeting.

- A project manager will be hired to organize and coordinate the tasks between the medical centres.
- Meetings with multidisciplinary teams and instructions for how to fill in the data collection sheet and sequence of data transference.
- Training: The doctors of Emergency Service who will participate in the study will receive information about the protocol to avoid differences in diagnosis and treatment. Furthermore, the nurses will receive training about the protocol and the treatment, especially how to do the dilution of NAC and its administration. There will be two trainers, who will travel to each hospital to give training about this study and its application.

Principal investigators and co-investigators will take part.

Stage 3: Patient recruitment and data collection (April 2020 – December 2022)

- Database creation: the project manager will perform this activity. The project manager is in charge of collecting all the information from all hospitals through the coordinators, this data will be delivered to a statistician for interpretation.
- The recruitment of the patients will take place in the emergency service of all the participating hospitals. The estimated time of recruitment will be 2 years and 8 months, but it could be prolonged in the case of not achieving the predefined sample size. After assessing whether patients meet all inclusion criteria and none of the exclusion criteria, the responsible doctor will give patients an information sheet and if they agree, the informed consent form will be signed.
- Intervention: the patients will be randomly distributed in group A or B, and they will receive one of the two therapies (Explained in intervention plan section).
- Follow-up: the patients will be followed during his / her length of stay in the emergency service. Once the treatment is finished and the laboratory test is normal, they will be discharged, and the primary attention doctor will take control.
- Data collection: will start in the recruitment phase and will last until the follow up of the last patient. All the information will be collected (Specified in Data collection section) by using the "Data collection sheet" ***(Annex 7).*** This collected data will be periodically evaluated and analyzed by our statistician to control if

the protocol is being followed. Each coordinator will be in charge of collecting the data from his/her hospital sending this information to the project manager.

- Meetings: coordinators from each hospital and the project manager will meet every 5 months to evaluate if the protocol is being well fulfilled. The aim of this is to identify deficiencies in the study design and to correct the methodological defects. The meetings will be performed in the leader hospital, which is "Hospital Universitari Doctor Josep Trueta" in Girona.

Stage 4: Statistical analysis and interpretation of the results (December 2022 – January 2023)

- Statistical analysis: A statistical plan will be given by the investigator to an experienced statistician. The statistician will analyze all the information recorded using different statistical tests according to the variables of the trial.
- Interpretation of the results: Once the statistical analysis has been done, the investigators will draw their conclusions about the results.

Stage 5: Publication of the results (February 2023)

- With all the results, the investigators will write the corresponding articles which will be sent to different medical journals for their publication.

Table 11. Chronogram

Year	2019				2020												2021												2022												2023		
Task / Month	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M
Stage 0: Study design and preparation of study protocol																																											
Bibliographic research																																											
Problem identification, protocol and chronogram development																																											
Stage 1: Ethical evaluation																																											
Evaluation by CEIC and AEMPS																																											
Stage 2: Study coordination																																											
Training																																											
Organize tasks and coordinantion meetings																																											
Stage 3: Patient recruitment and data collection																																											
Data base creation																																											
Recruitment of the patients, data collection, intervention and follow-up																																											
Stage 4: Data analysis																																											
Statistical analysis and interpretation of the results																																											
Stage 5: Publication of the results																																											
Final report elaboration and publication																																											

9.FEASIBILITY

This study will take place between September of 2019 and March of 2023 in 26 hospitals among Spain (Catalonia, Madrid and Andalucía, see hospitals in ***Annex 6***). These centers are equipped medically and technologically to accomplish the objectives of the trial.

Before the starting of the study, we will organize various meetings with one coordinator of each hospital and project manager. In these appointments, we will explain the objectives of the trial, and we will remark the importance of fill all data in the "Data collection sheet" ***(Annex 7).*** The project manager will take charge of creating a database and introducing there the data collected by the nurses and doctors. The study will be carried out by the staff of each hospital (Doctors of Emergency Service, nurses, nursing assistant, personnel of X-Ray and pharmacists). We will hire a statistician specialist to do the statistical analysis.

The hospitals will provide the needed informatic equipment for data collection. Also, it will provide all the necessary material to regarding the assistance of each patient. The material Includes NAC IV which will available in the pharmacy of hospital, X-Ray machine, EKG machine and material for performance a blood extraction.

10.STUDY LIMITATIONS

Paracetamol overdose is a low incidence disease, so the recruitment time would be longer. For this reason, we tried to minimize this circumstance by doing a multicentre trial. As a multicentre study could create variability in the procedures done in each hospital, we have collected some considerations about the suspected of paracetamol overdose (Data Collection Sheet, Annex 7) that are widely accepted to start the diagnosis and treatment process. Furthermore, there will be a very precise training of health personnel on the protocol that will be carried out.

How the paracetamol overdose is a low incidence disease, it is the reason to involve so many hospitals, which helps us to reduce the time of recruitment of patients. Also, we are conscious that the time used in our study is extensive, but we have preferred that it be, and not to involve more hospitals that could not make a correct assessment of the results.

In addition, as our multicentre study include many hospitals and this could mean an erroneous estimate of the data, we will hire a project manager. The designation of a coordinator in each of the hospital centres that participate in the study, together with adequate training of the doctors who will participate in it, this project highly viable in its execution is made.

We do not decide to use a masking technique and we decide to carry put an open-label clinical trial because the main variable dependent (Hepatotoxicity, measured with the parameters of laboratory) is a hard variable which cannot influence by patient or doctor. Thus, it cannot produce a confusion bias.

The fact of being a prospective study has the risk that patients can leave it due to adverse drug effects. We wait not many losses because our study does not require a long follow-up, only during the stance in emergency service. However, an estimated drop-out rate has been taken into account in our study sample, so this should not be a problem.

To avoid confusion bias, we have randomized the sample. Moreover, to avoid confounding variables we will describe the main and secondary variables dependents taking into account the covariates described.

11. BUDGET

Staff and subcontracted professional costs

We can approximate that **50.690 euros** will be needed for staff and subcontracted professionals.

Will be **two trainers** of "Hospital Universitari Doctor Josep Trueta", who will go to different hospitals to make training about protocol, how have to correctly implement it.

Due to in our study, there are many hospitals which participate, a **project manager** will be hired. He / She will be responsible of the data quality control, every five months, during the 43 months of during of study, he will go to each hospital in order to collect the fulfilled data recording sheet of each the patient who was attended in emergency service. The project manager will be responsible of verifying the information introduced in the database and he will make corrections if necessary. Also, the project manager will be in **8 meetings** programmed during study with the coordinators of each hospital.

It will be paid to the **26 coordinators** to will attend during these 8 meetings programmed during all study, necessary to coordinate all hospitals participating. The meetings will be performed in leader hospital, which is "Hospital Universitari Doctor Josep Trueta" in Girona.

Furthermore, we will contract a **statistical** which is in charge of the statistical analysis part once all the data has been collected.

Insurance

Our study is considerate such as “low-level clinical trial” according to “*Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos”*. It is considerate how this because the drug used is authorized and its use based on evidence and without risk or with the minimum risk procedures. For this reason, it is considerate that for the study will **not need contract an insurance**, so, it is covered by **hospital civil liability policy**.

Material and service costs

We can approximate that **1.128 euros** will be needed for materials and service.

The **treatment** with the **NAC** has considered that it is not necessary to pay it, because it is the current treatment that is already being used for paracetamol overdose. The hospital pharmacy already has this drug, our intervention only changes the method of administration.

Furthermore, the **additional tests** to realized (X-Ray, EKG and laboratory test) has considered that it is not necessary to pay it, because are the current tests that is already being when arrives one case of paracetamol overdose. So, it is not considerate an extras tests in our study.

Documents necessary to perform this study include 470 copies of data collection sheet, informed consent form and information sheet for patients, and also will there are 470 copies for representative, familiars or legal guardian. Of each document will be performed 2 copies.

Results publication and dissemination

In case the results are relevant, and we decide to publish them, we can approximate that **7.200 euros** will be needed. Knowing that the costs of publications are around 1.800 euros, the national conference in the next congress will be around 500 euros per inscription and the international conference will be around 600 euros per inscription. We estimate that the cost of accommodation, travel, diet and transport will be 600 euros per person in case of the national conference and 1000 euros per person in case of an international conference. To the conference will go 2 people.

Total cost

The total cost of the study will be **71.412€**, applying the **21% of taxes** to subtotal 59.018€. These taxes are the "canon" that the institution remains in expenses for water, electricity, cleaning, etc.

Budget proposal			
Ítem	**Quantity**	**Cost**	**Total Cost**
Staff			
Statistical specialist	4h/week x 4 weeks	50€/hour	**4.800,00 €**
Data manager	8 hours/day x 1 day/week x 43 months	65€/hour	**22.360,00 €**
Coordination meeting	26 coordinators x 8 meetings		**5.650,00 €**
	From Madrid and Andalucia x person	200€/Travel	2.600,00 €
	From BCN x person	30€/Travel	270,00 €
	From Lleida and Tarragona x person	60€/Travel	180,00 €
	Diet + accomodation x 26 coordinators	100€/Coordinator	2.600,00 €
Formation of trainers	2 trainers, 4h x day	60€/hour	**12.480,00 €**
	To Madrid and Andalucia	Travel: 200€; Accomodation: 80€ x 5 days; Diet: 30€ x 5 days; Transport: 150€	**3.600,00 €**
	To BCN	70€/day (Diet + travel)	**1.260,00 €**
	To Lleida and Tarragona	90€/Day (Diet+ travel)	**540,00 €**
Insurace			
Trial insurance		0€/trial	0,00 €
Material and services			
N-Acetylcysteine	470	0,00 €	0,00 €
X-Ray	470	0,00 €	0,00 €
EKG	470	0,00 €	0,00 €
Laboratory test	470	0,00 €	0,00 €
Data collection sheet	2 sheets x 2 copies/person	0,06€/sheet	**112,80 €**
Information sheet and informed consent	9 sheets x 2 copies/person	0,06€/sheet	**1.015,20 €**
Publication			
Cost of publications	1	1800€/protocol	**1.800 €**
National conference on Toxicology	2 people	500€/inscription x person	**1.000 €**
		600€/person (Diet, accomodation, transport)	**1.200,00 €**
International conference on Toxicology	2 people	600€/inscription x person	**1.200 €**
		1000 €/person (Diet, accomodation, transport)	**2.000,00 €**
		SUBTOTAL	**59.018 €**
		21%	
		TOTAL	**71.412 €**

12. IMPACT INTO THE NATIONAL HEALTH SYSTEM

The main aim of this project is to compare incidence of hepatotoxicity in both therapies, NAC 21 hours protocol (standard) vs. NAC 12 hours protocol (modified). Paracetamol poisoning is more frequent in children by mistake and in some adults as an attempt at autolysis. It is unacceptable the premature hepatic affectation and reduced quality of life in people who are expected to live a much longer life.

Nowadays, in Spain, it is indicated to apply the NAC 21 hours protocol in all patients with paracetamol overdose. Thus, it is extremely important to develop measures to decrease the risk of hepatic affectation in order to severe consequences, such as transplant liver. For this reason, I propose this protocol for implemented the NAC 12 hours protocol in our Spanish hospitals.

The impact on the national health system can be high, since the implementation of the protocol indicated in this research project to treat paracetamol overdose can significantly improve the patient's quality of life by drastically reducing the side effects of at the same time, it can reduce the potential liver transplants that can be derived as a result of paracetamol overdose poisoning. This would lead to a drastic reduction in the socio-health costs of liver transplants in patients with paracetamol overdose.

Besides, we think that the simplified of the terapeutical intervention (administration of NAC to 12 hours) will indirectly entail a decrease of medications errors.

In conclusion, as a whole, it will be a positive change in the way we treat these patients.

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ANNEXES

ANNEX 1: HEPATIC BIOTRANSFORMATION OF DRUGS

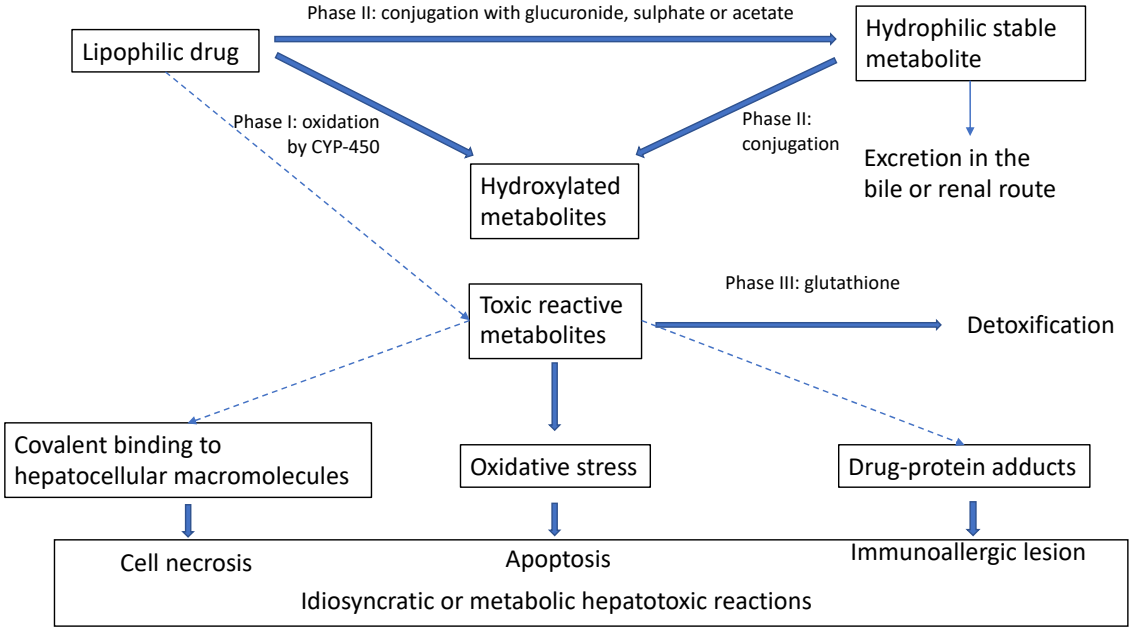

Figure 1. Hepatic biotransformation of drugs in polar compost and hepatotoxicity mechanisms. Adapted from (33)

ANNEX 2: POSOLOGY OF PARACETAMOL

Table 1. Posology of Paracetamol intravenous. Taken from (21)

Posology of intravenous paracetamol				
Weight	Dose/administration	Volume/administration	Volume/administration according the upper limits of weight (mL)*	Maximum dose daily
≤ 10kg	7,5 mg/kg	0,75 mL/kg	7,5 mL	30 mg/kg
>10 kg to ≤ 33 kg	15 mg/kg	1,5 mL/Kg	49,5 mL	60 mg/kg not exceeding 2 grams
>33 kg to ≤ 50 kg	15 mg/kg	1,5 mL/kg	75 mL	60 mg/kg not exceeding 3 grams
> 50 kg with risk factors	1 gram	100 mL	100 mL	3 grams
>50 kg without risk factors	1 gram	100 mL	100 mL	4 grams
* Patients who weigh less, require smaller volume				

ANNEX 3: METABOLISM OF PARACETAMOL

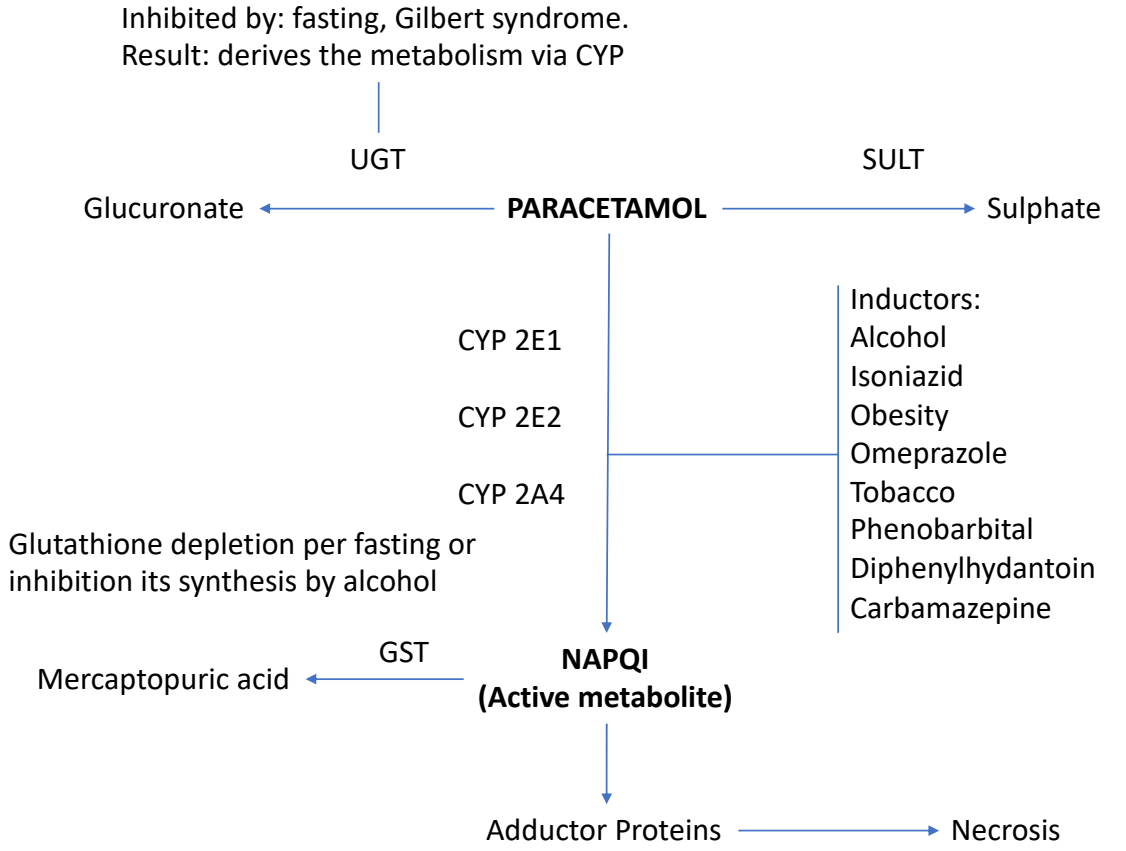

Figure 4. Metabolism of paracetamol and possible mechanisms that increase its toxicity. (30) *CYP: cytochrome P450; NAPQ: Nacethyl-p-benzoquinone-imine; UGT: UDP-glucuronosyltransferases; GST: Glutathione-S-transferases; SULT: Sulfotransferases.*

ANNEX 4: MAIN CAUSES OF LIVER DISEASE

Table 5. Main causes of liver disease to be excluded before considering a diagnosis of hepatotoxicity. (86)

Test	Condition	Commentary
Viral serology IgM anti-HAV IgM anti-HBc Anti-HCV, RNA-HCV (RT-PCR) IgM-CMV IgM-EBV Herpes virus	Viral hepatitis	Less frequent in older patients, especially Hepatitis A, search for epidemiologic risk factors, outcome may be similar to that of DILI following de-challenge.
Bacterial serology: Salmonella, Campylobacter, Listeria, Coxiella	Bacterial hepatitis	If persistent fever and/or diarrhea
Serology for syphilis	Secondary syphilis	Multiple sexual partners. Disproportionately high serum AP levels.
Autoimmunity (ANA, ANCA, AMA, ASMA, anti-LKM-1)	Autoimmune hepatitis, Primary biliary cirrhosis	Women, ambiguous course following de-challenge. Other autoimmunity features.
AST/ALT ratio > 2	Alcoholic hepatitis	Alcohol abuse. Moderate increase in transaminases despite severity at presentation
Ceruloplasmine, urine cooper	Wilson's disease	Patients < 40 yr
Alfa-1 antitrypsin	Deficit of α-1 antitrypsin	Pulmonary disease
Transferrin saturation	Hemochromatosis	In anicteric hepatocellular damage. Middle-aged men and older women.
Brilliant eco texture of the Liver.	Non-alcoholic steatohepatitis	In anicteric hepatocellular damage. Obesity, Metabolic syndrome.
Transaminase levels markedly high	Ischemic hepatitis	Disproportionately high AST levels. Hypotension, shock, recent surgery, heart failure, antecedent vascular disease, elderly
Dilated bile ducts by image procedures (AU, CT, MRCP and ERCP)	Biliary obstruction	Colic abdominal pain, cholestatic/mixed pattern.

ALT: alanine aminotransferase; AP: alkaline phosphatase; AST: aspartate aminotransferase; AU: abdominal ultrasound examination; Anti-HAV: Hepatitis A antibody; Anti-HBc: Hepatitis B core antibody; Anti-HCV: Hepatitis C antibody; anti-LKM-1: Liver-kidney microsomal antibody type 1; AMA: antimitochondrial antibody; ANA: antinuclear antibody; ANCA: perinuclear antineutrophil cytoplasmic antibody; ASMA: antismooth muscle antibody; BPC: Biliary primary cirrhosis; CMV: cytomegalovirus; CT: computed tomography; EBV: Epstein-Barr virus; ERCP: Endoscopic retrograde cholangiography; MRCP: Magnetic resonance cholangiography.

ANNEX 5. RECOMMENDATIONS FOR PERFORMING A SAFE AND EFFECTIVE GASTRIC LAVAGE

Table 6. Recommendations for performing a safe and effective gastric lavage (54):

- An aspiration system should be prepared in case there is gastroesophageal reflux or vomiting.
- In patients in deep coma or with severe swallowing disorders a tracheal intubation should be carried out previously
- Goeddel cannula (optional) in the mouth to avoid bites.
- Place the patient in the left lateral decubitus with semi-flexed legs.
- Use an orogastric tube with the largest possible internal diameter. A nasogastric tube with thick gauge may be used.
- Confirm tube position by aspirating gastric contents and auscultating for insufflated air at the stomach.
- Aspirate all gastric contents before starting the procedure.
- Perform a gastric lavage with warm water (38°C) with saline.
- In adults about 250 mL should be used in each partial wash (10 mL / kg in the child), until the return liquid is repeatedly clear or about 5L of water has been used.
- Perform an epigastric massage while practicing the washing maneuvers.
- After washing, a dose of activated carbon should be administered in general.
- Once the wash is finished, the probe is clamped and removed. If it is a conventional nasogastric tube, it is left in decline. If you have used activated carbon, you should leave the tube clamped for 2 hours.

ANNEX 6. HOSPITALS REFENCE OF CATALONIA, MADRID AND ANDALUCIA

CATALONIA

1. Hospital Universitari Doctor Josep Trueta, Girona (800.000 inhabitants as a reference population).
2. Hospital de Figueres (140.000 inhabitants as a reference population).
3. Hospital Universitari Arnau Vilanota, Lleida (450.000 inhabitants as a reference population).
4. Hospital Universitari Joan XXIII, Tarragona (600.000 inhabitants as a reference population).
5. Hospital Tortosa Verge de la Cinta, Terres de l'Ebre (150.000 inhabitants as a reference population)
6. Hospital Universitari de Bellvitge, Barcelona (1.300.000 inhabitants as a reference population).
7. Hospital Universitari Vall d'Hebron, Barcelona (400.000 inhabitants as a reference population).
8. Hospital Universitari el Clinic de Barcelona (540.000 inhabitants as a reference population).
9. Hospital Germans Trias i Pujol, Barcelona (1.200.000 inhabitants as a reference population).
10. Hospital de la Santa Creu i Sant Pau, Barcelona (408.000 inhabitants as a reference population).
11. Hospital del Mar, Barcelona (344.540 inhabitants as a reference population).
12. Hospital General Hospitalet and Hospital Moises Broggi, Barcelona (500.000 inhabitants as a reference population).
13. Hospital Universitari de Vic (160.000 inhabitants as a reference population).

MADRID

14. Hospital Universitario la Paz (868.138 inhabitants as a refence population)
15. Hospital Universitario 12 de Octubre (439.490 inhabitants as a refence population)
16. Hospital General Universitario Gregorio Marañón (318.830 inhabitants as a refence population)
17. Hospital Universitario Ramón y Cajal (583.400 inhabitants as a refence population)
18. Hospital Universitario Severo Ochoa (314.000 inhabitants as a reference population)
19. Hospital Universitario Principe Asturias (376.274 inhabitants as a reference population)

ANDALUCIA

20. Hospital Universitario Torrecárdenas, Almería (295.871 inhabitants as a reference population)
21. Hospital Universitario Virgen del Rocío, Sevilla (556.065 inhabitants as a reference population)
22. Hospital Universitario Virgen Macarena, Sevilla (481. 296 inhabitants as a reference population)
23. Hospital Universitario Virgen de las Nieves, Granada (442. 500 inhabitants as a reference population)
24. Hospital Universitario Reina Sofia, Córdoba (461.078 inhabitants as a reference population).
25. Hospital Universitario Jerez de la Frontera, Cádiz (400.000 inhabitants as a reference population)
26. Hospital Virgen Victoria, Málaga (467.614 inhabitants as a reference population).

ANNEX 7. DATA COLLECTION SHEET

Hoja de recogida de datos: Intoxicación por paracetamol	**Proyecto**: Study of application of the 12-hour N-Acetylcysteine protocol in the emergency service for paracetamol poisoning

Fecha: ...../...../.....	Nombre del investigador: .....
Hospital	

Datos del paciente

Apellidos		**Nombre**			
Fecha nacimiento	...../...../.....	Día inclusión	...../...../.....	Género	Hombre ☐ Mujer ☐
Identificación numérica del paciente					

Instrucciones:

Para la participación del paciente en este proyecto, es fundamental que cumpla TODOS los criterios de inclusión y NINGÚN criterio de exclusión.

Criterios de inclusión	
≥ 12 años	
Ingesta única de paracetamol: >150mg/kg en niños, >125mg/kg en adultos o >100mg/kg en adultos con factores de riesgo.	
Ingesta repetida de paracetamol durante >24h: >150mg/kg en niños, >125mg/kg en adultos o >100mg/kg en adultos con factores de riesgo.	

Criterios de Exclusión	
< 11 años	
Concentraciones de paracetamol que no tienen indicación de tratamiento según el nomograma 100-150.	
Aquellos que rechacen el consentimiento informado	
Ingesta de paracetamol >36h	
Pacientes en tratamiento con anticoagulantes	
Pacientes con criterios de trasplante urgente: pH<7,3 independientemente del grado de encefalopatía, o los siguientes 3 criterios: - Grado III o IV de encefalopatía - Tiempo de protrombina >100 segundos (INR 6,5) - Creatinina >300mmol/L (3.4 mg/dL)	

Información referente al paciente

Historia clínica

- Alergias
- Medicación habitual
- Antecedentes patológicos
- Antecedentes quirúrgicos

Anamnesis relevante en intoxicaciones por paracetamol

- Tipo de producto de paracetamol y formulación
- Gramos de paracetamol ingeridos. Es posible que el paciente venga con el blíster vacío indicando cuantas pastillas ha ingerido, considerando que cada pastilla es 1 gramo, calcularemos la dosis.
- Tipo de sobredosis por paracetamol (aguda, subaguda, crónica, accidental, autolesiva)
- Otros fármacos y/o drogas de abuso ingerido en los últimos 15 días
- Hábito enólico crónico
- Ingesta aguda de alcohol cuando se tomó la dosis de paracetamol
- Descartar la presencia de factores de riesgo: malnutrición, ayuno prolongado, anorexia/bulimia, caquexia, fibrosis quística, deshidratación, enfermedades hepáticas previas, SIDA, fármacos que estimulan el CYP450, Síndrome Gilbert.
- Síntomas después de la ingesta de paracetamol: dolor abdominal, náuseas, vómitos, irritabilidad, alteración del nivel de conciencia.

Exploración física

- Peso (kg) y talla (cm):
- Constantes vitales
    - Frecuencia cardíaca (lpm):
    - Temperatura (ºC):
    - Frecuencia respiratoria (rpm):
    - Saturación O2 (%):
    - Tensión arterial (mmHg):

Pruebas complementarias que se tienen realizar para establecer el diagnóstico

- Analítica:
    - Hemograma con fórmula leucocitaria
    - Prueba de función hepática, que incluye ALT, AST y GGT (UI/L), bilirrubina total (mg/dL), fosfatasa alcalina (UI/L).
    - Tiempo de protrombina (PT) y relación internacional normalizada (INR)
    - Prueba de función renal, que incluye electrolitos, creatinina y BUN (nitrógeno ureico en sangre)
    - Glucosa y equilibrio ácido-base
- Radiografía de tórax y/o abdomen
- Electrocardiograma

ANNEX 8. INFORMATION SHEET AND INFORMED CONSENT FORM

HOJA DE INFORMACIÓN PARA EL PACIENTE

TÍTULO DEL ESTUDIO: Study of application of the 12-hour N-Acetylcysteine protocol in the emergency service for paracetamol poisoning.

Investigador principal:.....

Hospital asistencial: .....

Introducción

Nos dirigimos a usted para informarle acerca de un estudio de investigación en el cual se invita a su hijo/a o representado/a a participar. Dicho estudio ha sido aprobado por el Comité de Ética de Investigación Clínica de este hospital y por la Agencia Española del Medicamento y Productos Sanitarios, de acuerdo con lo establecido en la legislación vigente, Real Decreto 1090/2015, del 24 de diciembre, por el cual se regulan los ensayos clínicos con medicamentos. Nuestra intención es que usted reciba la información adecuada y suficiente para que pueda evaluar y juzgar por sí mismo si desea o no que su hijo/a o representado/a participe en este estudio. Por ello, le rogamos lea esta hoja informativa con atención y consulte con nosotros cualquier duda que le pueda surgir.

Participación

Debe saber que la participación de su hijo/a o representado/a en este estudio es voluntaria y que puede decidir no participar o cambiar de decisión retirando el consentimiento en cualquier momento, sin que por ello se altere la relación con su médico ni se produzcan prejuicios en su tratamiento.

Descripción del estudio

La intoxicación por paracetamol no es una de las intoxicaciones más prevalentes en nuestro medio, pese a ello el no detectarla y no tratarla adecuadamente y a tiempo puede suponer un riesgo para desarrollar hepatotoxicidad. Ésta en muchos casos es reversible al recibir el tratamiento adecuado. Hay situaciones en las cuales o bien por una ingesta masiva de paracetamol o bien porque no se ha detectado a tiempo (situaciones de sobredosis crónicas), puede evolucionar a un fracaso hepático requiriendo un trasplante hepático, e incluso un fallo multiorgánico derivado de las complicaciones que supone.

Sobretodo serán más vulnerables a una intoxicación por paracetamol aquellas personas que presenten algún factor de riesgo (alcoholismo, enfermedades hepáticas previas, SIDA, Síndrome de Gilbert, etc).

Actualmente se dispone de un protocolo clínico de tratamiento con un antídoto (N-acetilcisteina) del paracetamol, que tiene una duración total de 21 horas. Es un tratamiento efectivo, pero en algunos casos es necesario continuar el tratamiento ya que los parámetros analíticos relacionados con la hepatotoxicidad no se encuentran en los valores normales de referencia. Este tratamiento, además, se acompaña en muchos

casos de efectos secundarios durante la primera hora y una estancia hospitalaria más alargada.

Para poder evitar el riesgo de desarrollo de hepatotoxicidad, efectos secundarios y estancia hospitalaria prolongada, se ha desarrollado este nuevo protocolo de tratamiento que consiste en la modificación del protocolo clínico con una menor duración (total de 12 horas), basado en resultados de estudios recientes.

Objetivo:

El principal objetivo del ensayo es demostrar que hay una reducción en el riesgo de desarrollo de hepatotoxicidad causada por una sobreingesta de paracetamol. Además, demostrar que, con la nueva pauta de tratamiento con el antídoto, los efectos adversos que este produce disminuyen. Con todo esto se vería una disminución de la estancia hospitalaria.

Participación voluntaria del estudio:

Usted es completamente libre de participar o no en el estudio. Su decisión no influirá en su atención médica.

Procedimiento del estudio:

La forma de administración del antídoto en las intoxicaciones producidas por paracetamol no cambiará si usted decide no participar en el estudio. En ese caso, se hará de igual manera el tratamiento estándar que se está llevando a cabo actualmente.

En caso de que quiera participar el ensayo consistirá en:

Se incluirá a todos los pacientes que ha sufrido una intoxicación por paracetamol, una vez han leído esta hoja de información y hayan firmado el consentimiento informado, se procederá a recoger toda la información clínica necesaria para la asistencia médica. Está información será recogida por parte del médico en unos formularios y posteriormente quedará registrado de manera informática en su historia clínica. Según el criterio médico del doctor/a responsable de urgencias, usted podrá ser atendido por otros médicos especialistas. Se le realizarán analíticas a su llegada a urgencias necesarias para determinar el diagnóstico y la decisión terapéutica, así como analíticas de control durante el tratamiento. Además, se le realizaran otras pruebas complementarias, como radiografías y electrocardiogramas, para descartar que no haya intoxicaciones concomitantes.

Los pacientes del estudio se distribuirán de forma aleatoria en dos grupos de tratamiento (A y B). El grupo A recibirá el tratamiento estándar con el antídoto (N-Acetilcisteina) durante un total de 21 horas. El grupo B recibirá el tratamiento estándar con el antídoto (N-Acetilcisteina) durante un total de 12 horas. Una vez haya finalizado el tratamiento se le realizará una analítica para determinar si se le puede dar de alta hospitalaria o usted requiere recibir más dosis con dicho tratamiento. En caso de que sea dado de alta, se realizará un seguimiento por parte del Médico de Atención Primaria.

Debe saber que según el criterio médico o del investigador, usted puede ser excluido del estudio, ya sea por motivos de seguridad, por cualquier acontecimiento adverso que se produzca por la mediación o porque consideren que usted no está cumpliendo con

los procedimientos establecidos. En cualquiera de los casos, usted recibirá una explicación adecuada del motivo por el que se ha decidido su retirada del estudio.

Beneficios y riesgos asociados a la participación del estudio

El fármaco administrado está comercializado, y actualmente ya se utiliza como antídoto para la intoxicación por paracetamol. Dicho fármaco tiene los riesgos de producir efectos secundarios, normalmente entre los 15-60 minutos posteriores a su administración. Entre los efectos adversos más comunes se encuentran los vómitos y náuseas, y pocos casos reacciones anafilácticas. En caso de que apareciera cualquier signo o síntoma indicativo de reacción adversa, el tratamiento con N-acetilcisteina se parará para tratar la aparición de los nuevos síntomas.

Es por eso por lo que en estudios recientes se ha visto que la administración de una pauta con una duración más corta conlleva a reducir de la posible aparición de estos efectos adversos y la estancia hospitalaria.

Se informará en referencia a los posibles signos y síntomas indicativos de empeoramiento de la enfermedad, teniendo en cuenta que se realizarán los estrechos controles sobre la hepatotoxicidad causada por la sobreingesta de paracetamol.

También se ha visto en estudios, que administrar el tratamiento durante las primeras 8 horas reduce el riesgo de desarollar hepatotoxicadad por paracetamol.

Protección de datos

El tratamiento, la comunicación y la cesión de los datos de carácter personal de todos los sujetos participantes se ajustará a la Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales. De acuerdo con esta ley, usted podrá ejercer los derechos de acceso, modificación, oposición y cancelación de estos datos. Los datos recogidos para el estudio estarán identificados mediante un código y solo los investigadores podrán relacionar sus datos. Su nombre, en ningún caso aparecerá en la publicación de los resultados. El acceso a la su información personal quedará restringido a los investigadores, autoridades sanitarias y al Comité de Ética de Investigación Clínica, manteniendo siempre la confidencialidad.

Compensación económica

Los investigadores no obtendrán benefició económico alguno procedente de la realización de este ensayo. Su participación en el mismo no le supondrá ningún gasto. Además, no tendrá que pagar por los medicamentos que le suministren en el estudio.

Información adicional

Si usted decide retirar el consentimiento para participar en este estudio, no se añadirá ningún dato nuevo a la base de datos y, puede exigir la destrucción de todas las muestras identificables previamente obtenidas para evitar la realización de nuevos análisis.

Para hacer cualquier pregunta o aclarar algún tema relacionado con el estudio, o si necesita ayuda por cualquier problema de salud relacionado con este estudio, por favor, no dude en ponerse en contacto con:

Dr. /Dra. ..... Nº Teléfono: .....

HOJA DE CONSENTIMIENTO INFORMADO PARA EL PACIENTE

TÍTULO DEL ESTUDIO: Study of application of the 12-hour N-Acetylcysteine protocol in the emergency service for paracetamol poisoning.

Yo (Nombre y apellidos): .....

con DNI: .....

Declara bajo su responsabilidad que:

- Ha sido informada adecuadamente por el Dr./Dra. _____
- Ha leído detenidamente y he entendido toda la hoja de información que se me han entregado. Entiendo que podré conservar una copia.
- Ha podido realizar preguntas sobre el estudio y todas mis dudas han sido resueltas de manera satisfactoria.
- Ha entendido los posibles beneficios y riesgos que se derivan del estudio
- Ha entendido que todos sus datos serán tratados de forma estrictamente confidencial.
- Ha entendido cuál será su papel como participante del estudio.
- Ha entendido que su participación es voluntaria, y que en cualquier momento del estudio puede cambiar de opinión y revocar el consentimiento previamente firmado, sin tener que dar ninguna explicación y que, independientemente de su decisión, su atención médica y sus derechos legales no se verán afectados.

Por lo tanto, usted acepta voluntariamente participar en este estudio de investigación y da su consentimiento para el acceso y utilización de sus datos siempre en conformidad con la Ley Orgánica de Protección de Datos Personales y garantía de los derechos digitales del 3/2018.

Deseo recibir información vía telefónica o por correo electrónico sobre los futuros resultados del estudio:

☐ SI ☐ NO

Correo electrónico:..... Nº Teléfono:.....

En _____, a _____ de _____ del 20_____

Firma paciente: Firma investigador/a:

DNI: DNI:

REVOCACIÓN DEL CONSENTIMIENTO INFORMADO

Yo, _____, revoco el consentimiento previamente firmado para la participación en el ensayo clínico especificado arriba.

Lugar y fecha: _____, ____ de _____ del 20___

Firma paciente: Firma investigador/a:

HOJA DE INFORMACIÓN PARA EL FAMILIAR O TUTOR LEGAL

TÍTULO DEL ESTUDIO: Study of application of the 12-hour N-Acetylcysteine protocol in the emergency service for paracetamol poisoning.

Investigador principal:.....

Hospital asistencial: .....

Introducción

Nos dirigimos a usted para informarle acerca de un estudio de investigación en el cual se invita a su hijo/a o representado/a a participar. Dicho estudio ha sido aprobado por el Comité de Ética de Investigación Clínica de este hospital y por la Agencia Española del Medicamento y Productos Sanitarios, de acuerdo con lo establecido en la legislación vigente, Real Decreto 1090/2015, del 24 de diciembre, por el cual se regulan los ensayos clínicos con medicamentos. Nuestra intención es que usted reciba la información adecuada y suficiente para que pueda evaluar y juzgar por sí mismo si desea o no que su hijo/a o representado/a participe en este estudio. Por ello, le rogamos lea esta hoja informativa con atención y consulte con nosotros cualquier duda que le pueda surgir.

Participación

Debe saber que la participación de su hijo/a o representado/a en este estudio es voluntaria y que puede decidir no participar o cambiar de decisión retirando el consentimiento en cualquier momento, sin que por ello se altere la relación con su médico ni se produzcan prejuicios en su tratamiento.

Descripción del estudio

La intoxicación por paracetamol no es una de las intoxicaciones más prevalentes en nuestro medio, pese a ello el no detectarla y no tratarla adecuadamente y a tiempo puede suponer un riesgo para desarrollar hepatotoxicidad. Ésta en muchos casos es reversible al recibir el tratamiento adecuado. Hay situaciones en las cuales o bien por una ingesta masiva de paracetamol o bien porque no se ha detectado a tiempo (situaciones de sobredosis crónicas), puede evolucionar a un fracaso hepático requiriendo un trasplante hepático, e incluso un fallo multiorgánico derivado de las complicaciones que supone.

Sobretodo serán más vulnerables a una intoxicación por paracetamol aquellas personas que presenten algún factor de riesgo (alcoholismo, enfermedades hepáticas previas, SIDA, Síndrome de Gilbert, etc).

Actualmente se dispone de un protocolo clínico de tratamiento con un antídoto (N-acetilcisteina) del paracetamol, que tiene una duración total de 21 horas. Es un tratamiento efectivo, pero en algunos casos es necesario continuar el tratamiento ya que los parámetros analíticos relacionados con la hepatotoxicidad no se encuentran en los valores normales de referencia. Este tratamiento, además, se acompaña en muchos casos de efectos secundarios durante la primera hora y una estancia hospitalaria más alargada.

Para poder evitar el riesgo de desarrollo de hepatotoxicidad, efectos secundarios y estancia hospitalaria prolongada, se ha desarrollado este nuevo protocolo de tratamiento que consiste en la modificación del protocolo clínico con una menor duración (total de 12 horas), basado en resultados de estudios recientes.

Objetivo:

El principal objetivo del ensayo es demostrar que hay una reducción en el riesgo de desarrollo de hepatotoxicidad causada por una sobreingesta de paracetamol. Además, demostrar que, con la nueva pauta de tratamiento con el antídoto, los efectos adversos disminuyen. También habría una disminución de la estancia hospitalaria.

Participación voluntaria del estudio:

Usted es completamente libre de participar o no en el estudio. Su decisión no influirá en su atención médica.

Procedimiento del estudio:

La forma de administración del antídoto en las intoxicaciones producidas por paracetamol no cambiará si usted decide no participar en el estudio. En ese caso, se hará de igual manera el tratamiento estándar que se está llevando a cabo actualmente.

En caso de que quiera participar el ensayo consistirá en:

Se incluirá a todos los pacientes que ha sufrido una intoxicación por paracetamol, una vez han leído esta hoja de información y hayan firmado el consentimiento informado, se procederá a recoger toda la información clínica necesaria para la asistencia médica. Está información será recogida por parte del médico en unos formularios y posteriormente quedará registrado de manera informática en su historia clínica. Según el criterio médico del doctor/a responsable de urgencias, usted podrá ser atendido por otros médicos especialistas. Se le realizarán analíticas a su llegada a urgencias necesarias para determinar el diagnóstico y la decisión terapéutica, así como analíticas de control durante el tratamiento. Además, se le realizaran otras pruebas complementarias, como radiografías y electrocardiogramas, para descartar que no haya intoxicaciones concomitantes.

Los pacientes del estudio se distribuirán de forma aleatoria en dos grupos de tratamiento (A y B). El grupo A recibirá el tratamiento estándar con el antídoto (N-Acetilcisteina) durante un total de 21 horas. El grupo B recibirá el tratamiento estándar con el antídoto (N-Acetilcisteina) durante un total de 12 horas. Una vez haya finalizado el tratamiento se le realizará una analítica para determinar si se le puede dar de alta hospitalaria o usted requiere recibir más dosis con dicho tratamiento. En caso de que sea dado de alta, se realizará un seguimiento por parte del Médico de Atención Primaria.

Debe saber que según el criterio médico o del investigador, su representado o hijo/a puede ser excluido del estudio, ya sea por motivos de seguridad, por cualquier acontecimiento adverso que se produzca por la mediación o porque consideren que su representado o hijo/a no está cumpliendo con los procedimientos establecidos. En cualquiera de los casos, usted recibirá una explicación adecuada del motivo por el que se ha decidido su retirada del estudio.

Beneficios y riesgos asociados a la participación del estudio

El fármaco administrado está comercializado, y actualmente ya se utiliza como antídoto para la intoxicación por paracetamol. Dicho fármaco tiene los riesgos de producir efectos secundarios, normalmente entre los 15-60 minutos posteriores a su administración. Entre los efectos adversos más comunes se encuentran los vómitos y náuseas, y pocos casos reacciones anafilácticas. En caso de que apareciera cualquier signo o síntoma indicativo de reacción adversa, el tratamiento con N-acetilcisteina se parará para tratar la aparición de los nuevos síntomas.

Es por eso por lo que en estudios recientes se ha visto que la administración de una pauta con una duración más corta conlleva a reducir de la posible aparición de estos efectos adversos y la estancia hospitalaria.

Se informará en referencia a los posibles signos y síntomas indicativos de empeoramiento de la enfermedad, teniendo en cuenta que se realizarán los estrechos controles sobre la hepatotoxicidad causada por la sobreingesta de paracetamol.

También se ha visto en estudios, que administrar el tratamiento durante las primeras 8 horas reduce el riesgo de desarollar hepatotoxicadad por paracetamol.

Protección de datos

El tratamiento, la comunicación y la cesión de los datos de carácter personal de todos los sujetos participantes se ajustará a la Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales. De acuerdo con esta ley, usted podrá ejercer los derechos de acceso, modificación, oposición y cancelación de estos datos. Los datos recogidos para el estudio estarán identificados mediante un código y solo los investigadores podrán relacionar estos datos con su hijo/a o representado/a. El nombre de su hijo/a o representado/a, en ningún caso aparecerá en la publicación de los resultados. El acceso a la información personal de su hijo/a o representado/a quedará restringido a los investigadores, autoridades sanitarias y al Comité de Ética de Investigación Clínica, manteniendo siempre la confidencialidad.

Compensación económica

Los investigadores no obtendrán benefició económico alguno procedente de la realización de este ensayo. Su participación en el mismo no le supondrá ningún gasto. Además, no tendrá que pagar por los medicamentos que le suministren en el estudio.

Información adicional

Si usted decide retirar el consentimiento para que participe en este estudio su representado o hijo/a, no se añadirá ningún dato nuevo a la base de datos y, puede exigir la destrucción de todas las muestras identificables previamente obtenidas para evitar la realización de nuevos análisis.

Para hacer cualquier pregunta o aclarar algún tema relacionado con el estudio, o si necesita ayuda por cualquier problema de salud relacionado con este estudio, por favor, no dude en ponerse en contacto con:

Dr. /Dra. ..... Nº Teléfono: .....

HOJA DE CONSENTIMIENTO INFORMADO PARA EL FAMILIAR O TUTOR LEGAL

TÍTULO DEL ESTUDIO: Study of application of the 12-hour N-Acetylcysteine protocol in the emergency service for paracetamol poisoning.

Yo (Nombre y apellidos): ..... con DNI ..... en calidad de familiar o tutor legal de Sr/Sra. ..... .

Declara que:

- Ha sido informada adecuadamente por el Dr./Dra. _____
- Ha leído detenidamente y he entendido toda la hoja de información que se me han entregado. Entiendo que podré conservar una copia.
- Ha podido realizar preguntas sobre el estudio y todas mis dudas han sido resueltas de manera satisfactoria.
- Ha entendido los posibles beneficios y riesgos que se derivan del estudio
- Ha entendido que todos sus datos serán tratados de forma estrictamente confidencial.
- Ha entendido cuál será su papel como participante del estudio.
- Ha entendido que su participación es voluntaria, y que en cualquier momento del estudio puede cambiar de opinión y revocar el consentimiento previamente firmado, sin tener que dar ninguna explicación y que, independientemente de su decisión, su atención médica y sus derechos legales no se verán afectados.

Por lo tanto, acepto voluntariamente la participación del Sr/Sra. ..... en este estudio de investigación y doy mi consentimiento para el acceso y utilización de sus datos siempre en conformidad con la Ley Orgánica de Protección de Datos Personales y garantía de los derechos digitales del 3/2018.

Deseo recibir información vía telefónica o por correo electrónico sobre los futuros resultados del estudio:

☐ SI ☐ NO

Correo electrónico:..... Nº Teléfono:.....

En _____, a _____ de _____ del 20_____

Firma del familiar o tutor legal: Firma investigador/a:

DNI: DNI:

REVOCACIÓN DEL CONSENTIMIENTO INFORMADO

Yo (Nombre y apellidos): ..... con DNI ..... en calidad de familiar o tutor legal de Sr/Sra. ...., revoco el consentimiento previamente firmado para la participación del Sr/Sra. ..... en el ensayo clínico especificado arriba.

Lugar y fecha: _____, ____ de _____ del 20___

Firma del familiar o tutor legal: Firma investigador/a: