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Special article

[Translated article] N-acetylcysteine: 50 years since the discovery of an antidote that has changed the prognosis of acetaminophen poisoning

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ABSTRACT

Acetaminophen is one of the most widely used drugs in clinical practice due to its analgesic and antipyretic properties. However, overdose is one of the leading causes of severe acute liver failure. N-acetylcysteine, introduced as an antidote in 1974, has revolutionized the management of this intoxication by reducing hepatotoxicity and mortality associated with acetaminophen toxicity.

At the end of the 19th century, acetaminophen was identified as the main active metabolite of phenacetin and acetanilide. Its therapeutic use began to gain popularity in the 1950s and later became one of the main drugs involved in suicide attempts, particularly among adolescents and young adults. Acetaminophen-induced hepatotoxicity was first described in 1966, establishing that an overdose could lead to fulminant hepatic necrosis. In 1975, Rumack and Matthew published a nomogram that allowed stratification of hepatic toxicity risk based on plasma drug levels.

The mechanism of hepatotoxicity was elucidated in the early 1970s when it was discovered that acetaminophen is metabolized by cytochrome P450 into a highly reactive intermediate, N-acetyl-p-benzoquinoneimine, which is normally neutralized by hepatic glutathione. In overdose situations, glutathione depletion leads to hepatic necrosis. Based on these findings, sulfhydryl-containing agents such as cysteamine and methionine were introduced as antidotes, but N-acetylcysteine ultimately proved to be the most effective treatment.

Since its introduction, N-acetylcysteine administration protocols have evolved to optimize efficacy and minimize adverse effects. Protocols such as the Scottish and Newcastle Acetylcysteine Protocol and the Two Bags regimen have simplified dosing and reduced the incidence of anaphylactoid reactions.

Over the past 50 years, N-acetylcysteine has saved thousands of lives and remains the gold-standard antidotal treatment for acetaminophen poisoning.

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N-acetilcisteína: 50 años del descubrimiento de un antídoto que ha cambiado el pronóstico de la intoxicación por paracetamol

Palabras clave:
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Paracetamol
Acetaminofen
Antídoto
Toxicidad hepática
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R E S U M E N

El paracetamol es uno de los fármacos más utilizados en la práctica clínica por sus propiedades analgésicas y antitérmicas. Sin embargo, su sobredosis representa una de las principales causas de insuficiencia hepática aguda grave. La N-acetilcisteína, introducida como antídoto en 1974, ha revolucionado el manejo de esta intoxicación, reduciendo la hepatotoxicidad y la mortalidad asociada a la intoxicación por paracetamol.

A finales del siglo XIX, el paracetamol fue identificado como el principal metabolito activo de la fenacetina y la acetanilida. Su uso terapéutico se empezó a popularizar en los años 50 del pasado siglo y, posteriormente, se ha convertido en uno de los principales fármacos implicados en los intentos de suicidio, sobre todo en adolescentes y adultos jóvenes. La hepatotoxicidad del paracetamol fue descrita por primera vez en 1966, estableciéndose que una sobredosis podía provocar necrosis hepática fulminante. En 1975, Rumack y Matthew publicaron un nomograma que permitió estratificar el riesgo de toxicidad hepática en función de los niveles plasmáticos del fármaco.

El mecanismo de hepatotoxicidad fue esclarecido a principios de los años 70, cuando se identificó que el paracetamol es metabolizado por el citocromo P450 a un intermediario reactivo, la N-acetil-p-benzoquinoneimina, que es neutralizada por el glutatión hepático. En sobredosis, la depleción de glutatión lleva a la necrosis hepática. Con base en estos hallazgos, se introdujeron como antídotos a agentes sulfhidrilos como la cisteamina y la metionina, siendo finalmente la N-acetilcisteína la que demostró ser el antídoto más eficaz.

Desde su introducción, la pauta de administración de la N-acetilcisteína ha evolucionado para optimizar su eficacia y minimizar los efectos adversos. Pautas como la *Scottish and Newcastle Acetylcysteine Protocol* o la *Two Bags* han simplificado su dosificación y reducido la incidencia de reacciones anafilactoides.

A lo largo de estos 50 años, la N-acetilcisteína ha salvado miles de vidas y se mantiene como el tratamiento antidótico de referencia en la intoxicación por paracetamol.

Introduction

Acetaminophen (paracetamol) is one of the most widely used analgesic and antipyretic medications in adults and children of any age. This over-the-counter drug is commonly found in Spanish households and, at therapeutic doses, is associated with very limited adverse events (AEs). However, acetaminophen overdose entails a very high risk of hepatoxicity, accounting for a leading cause of severe acute liver failure.

Fortunately, this year is the 50th anniversary of the discovery of its antidote, N-acetylcysteine (NAC). The timely administration of this drug in cases of toxic dose intake prevents or reduces hepatotoxicity.

This paper provides an overview of the milestones in the development of this treatment and the diverse NAC regimens suggested by the scientific community.

Establishment of acetaminophen as a medicine and discovery of its hepatotoxicity

At the end of the 19th century, acetanilide and phenacetin were commonly used analgesics. It was not until 1948 that its analgesic effects were found to be mediated by their main metabolite, acetaminophen.[1,2] Acetaminophen was first marketed in the United States in 1950. Five years later, it was available over the counter in a variety of countries. Lacking the gastrointestinal and hematological AEs associated with acetylsalicylic acid, acetaminophen progressively replaced acetylsalicylic acid as an analgesic and antipyretic drug. In addition, unlike acetylsalicylic acid, no evidence was ever found of an association between acetaminophen and Reye syndrome.[3] In Spain, acetaminophen in pure form was first approved in 1955. By March 2025, as many as 339 acetaminophen-containing formulations were marketed in Spain, with acetaminophen being the only component in 12, and used in combination with other drugs in 167.[4]

Soon after acetaminophen gained popularity as a therapeutic agent, it became one of the main drugs used in intentional self-poisoning events, particularly among adolescents. As a result, in a short time, acetaminophen ousted acetylsalicylic acid as the first agent used in suicide attempts, mainly in Anglo-Saxon countries,[5] but also in other regions.[6] In Spain, the incidence of suicide attempts with acetaminophen overdosing climbed from <2% in 1983[7] to over 9% in 2021.[8] Concurrently to the COVID-19 health emergency, an increase in suicide attempts at pediatric ages was observed. Once the pandemic eased, the incidence remained high, with acetaminophen being the first drug involved in these attempts in 2023 (10.6%), surpassing benzodiazepines.[9]

In 1966, the Edinburgh Clinical Toxicology service of the Royal Infirmary of Edinburgh (RIE) reported the first two cases of acetaminophen poisoning as the causative factor of fatal hepatic necrosis.[10] The first large series (41 cases) of paracetamol-induced hepatotoxicity was published in 1970 by the same hospital,[11] whereas the first case in the USA was published in 1971.[12] At that time, acute centrilobular necrosis was known to be the main manifestation of paracetamol-induced hepatotoxicity, which also could cause kidney failure, generally –but not always– in patients with severe liver damage.

In the early 1970s, bromobenzene was a well-known hepatotoxin with the potential to produce centrilobular necrosis, like that observed in patients who died from acetaminophen poisoning. Through animal experimentation, Bernard Brodie discovered that bromobenzene is metabolized by cytochrome P450 into a highly reactive epoxy metabolite that, at low doses, is conjugated with hepatic glutathione and excreted into the urine; however, high doses led to glutathione depletion, thereby resulting in hepatic necrosis. The same author described that hepatotoxicity increased or decreased with treatments that either stimulated or inhibited the activity of this enzyme, respectively.[13] The severity of liver damage increased with the administration of agents that depleted hepatic glutathione and decreased with treatments that promoted glutathione synthesis.[14]

Based on these findings, it was hypothesized that an analog mechanism could explain acetaminophen-induced hepatotoxicity. Evidence was found that acetaminophen was metabolized by cytochrome P450 into a highly reactive product, N-acetyl-p-benzoquinoneimine (NAPQI). This metabolite is rendered inactive when conjugated with

hepatic glutathione; however, overdosing causes glutathione depletion, ultimately leading to hepatic necrosis.[15]

Hence, protection against hepatotoxicity primarily relies on the availability of hepatic glutathione. Glutathione synthesis also depends on the availability of inorganic sulfate to synthesize L-cysteine. This cycle could be maintained through the administration of sulfhydryls such as L-cysteine, methionine or cysteamine.

Rumack-Matthew nomogram

The year 1971 was a milestone in this history, when Laurie Prescott, from the same Scottish hospital, first established a correlation between the elimination half-life of acetaminophen and the risk of developing hepatotoxicity. This finding enabled clinicians attending these cases to establish the prognosis of acetaminophen poisoning in a few hours. Several years later, this finding provided the basis for establishing the indications for antidotal therapy.[16]

In 1975, Barry Rumack and Henry Matthew, based on data from patients attended at the Royal Infirmary and on Prescott's findings, published the so-called "Rumack-Matthew nomogram".[17] In this nomogram, serum acetaminophen concentrations obtained at ≥4 h post-ingestion are plotted against the time since ingestion; then, a treatment line starting at 200 μg/ml at 4 h is plotted, with concentrations decreasing by a half every 4 h. Depending on the concentrations selected for the 4 h-time point, patients are stratified into risk regions.

Cumulative experience with the use of the Rumack-Matthew nomogram led the treatment line to be reduced to an acetaminophen concentration of 150 μg/ml at 4 h. In countries such as the United Kingdom, regulatory agencies reduced the treatment line up to 100 μg/ml.[18]

Cysteamine, the first effective treatment for acetaminophen overdose, and arrival of N-acetylcysteine

In 1973, Prescott et at conducted a pioneer clinical trial to assess the efficacy of cysteamine as an antidote for acetaminophen poisoning. Based on the Rumack-Matthew nomogram, the first patients who received this antidote had a very poor prognosis. Cysteamine was effective in preventing hepatotoxicity when administered no later than 4 h post-ingestion.[19,20]

In 1974, Prescott suggested the use of NAC, a cysteamine form that is soluble in water. In a clinical trial, 15 patients at risk for acetaminophen-induced hepatotoxicity received 150 mg/kg of intravenous NAC over a period of 15 min, plus 50 mg/kg over 4 h, plus 100 mg/kg over 16 h to a total of 300 mg/kg administered over 20 h and 15 min. Hepatotoxicity was prevented in 11 of these patients, who were treated within 10 h post-ingestion. None of the patients died, and no AEs were observed.[21] Over time, Prescott gained cumulative experience with the use of this antidote, leading her to conclusively affirm in 1979 that NAC is the gold-standard antidotal therapy for acetaminophen poisoning.[22] Half a century later, this assertion remains fully valid.

In the USA, it took a long time for the Food and Drug Administration to authorize the NAC formulation for intravenous administration. Until then, the antidote was administered orally at a starting dose of 140 mg/kg, followed by a dose of 70 mg/kg at 4-h intervals repeated 17 times, to a total of 1330 mg/kg of NAC. This oral regimen was proven to be as effective as the intravenous formulation; however, gastrointestinal intolerance in the form of vomiting often hindered the administration of the full dose.[23]

In Spain, NAC was first marketed in 1965 as an injectable 300 mg formulation intended as a mucolytic; however, its use in acetaminophen overdose was impractical due to the low concentration. In 1992, a 5000 mg intravenous formulation became available specifically for acetaminophen poisoning, allowing convenient preparation and administration under the traditional three-bag regimen.

N-acetylcysteine adverse events

The AEs most commonly associated with intravenous NAC are anaphylactoid reactions occurring concurrently to the first bag, which is the one that contains the highest concentration and is administered over the shortest period of time. Hence, the majority of toxicologists recommend the first bag to be administered over 60 min,[24] consistently with the summary of product characteristics of NAC.[25]

Anaphylactoid reactions include nausea, vomiting, facial flush, urticaria and pruritus, manifestations that are probably related to the release of histamine. In severe cases, bronchospasm, angioedema and arterial hypotension have also been described.[26,27]

In the presence of these symptoms, antidote administration is suspended and antihistamine or corticosteroid therapy is initiated; once completed, intravenous infusion is reinitiated until the full dose is achieved.

N-acetylcysteine SNAP regimen

NAC protocols have evolved to simplify NAC dosing, prevent infusion bag preparation errors and minimize AEs. One of these new regimens is the so-called SNAP protocol (*Scottish and Newcastle Acetylcysteine Protocol*) developed by the Royal Infirmary of Edinburgh, which has been proven to preserve its antidotic efficacy while reducing the incidence of AEs.[28]

Since 2020, this regimen has been progressively adopted in a variety of adult and pediatric emergency departments in Spain. Additionally, many toxicologists consider it the gold standard therapy.[29,30] The SNAP regimen involves the administration of the same dose of NAC (300 mg/kg) over 12 h, but at a slower loading dose infusion rate (1st dose: 100 mg/kg in 2 h; 2nd bag:200 mg/kg in 10 h). This regimen recommends the treatment to be continued on the basis of clinical and laboratory parameters.

Studies using this regimen have demonstrated comparable efficacy to the standard protocol, with a lower incidence of adverse reactions and medication errors. Additionally, SNAP enables a more flexible treatment regimen, allowing higher total doses for cases of massive ingestion, and a shorter 12-h course for low-risk patients, thereby reducing hospital stay.[31]

N-acetylcysteine two-bag regimen

Other alternative treatment regimens are available, including the Two Bags Acetylcysteine Protocol, which pursues the same goal as SNAP: reducing the incidence of AEs and guiding clinicians in adjusting the total dose of the antidote based on the risk of hepatotoxicity. This protocol is widely used in countries such as Australia, New Zealand and the USA. The Two-Bags regimen consists of a first bag of 200 mg/kg infused over 4 h followed by a second bag of 100 mg/kg infused over 16 h and, where indicated, a third bag of 100 mg/kg. This protocol of administration was conceived in Australia in 2018.[32]

A recent literature review confirmed that the efficacy of the two-bags regimen is comparable to that of the traditional three-bags regimen, but with an undeniable lower incidence of AEs.[33] Yet, the same authors consider that the dose of the second NAC bag may be insufficient for patients at a high risk for hepatotoxicity and recommend that this dose be doubled. The goal is to produce sufficient glutathione to eliminate the NAPQI resulting from a massive intake of acetaminophen.[34]

Across all protocols, the dosage regimen for pediatric patients is equivalent to that used in adults; however, the volume administered should be adjusted according to the patient's body weight to prevent fluid overload.

Although an international consensus NAC protocol has not yet been established, protocols consistently establish that a laboratory test

should be performed upon treatment completion to determine whether maintaining treatment is or not necessary.

Conclusions

The 50 years elapsed since NAC was established as the gold-standard antidotic treatment for acetaminophen poisoning have proven its undeniable efficacy and limited adverse events.

Along with naloxone, NAC is probably the antidote that has saved the highest number of lives of poisoned patients in the last half-century.

During this time, NAC dosage has undergone a few changes, with the new two-bags regimen –replacing the three-dose regimen– having enhanced patient safety.

However, even 50 years later, there are some areas of uncertainty, including the appropriate NAC dosage in patients ingesting either different or multiple (staggered) doses of acetaminophen, the early identification of patients at risk, or the optimal treatment for patients experiencing acetaminophen poisoning who delay attendance to an emergency department.

Authorship

Santiago Nogué-Xarau: study conception and design, preparation of the first draft of the manuscript, general coordination. **Lidia Martínez-Sánchez:** critical review of the manuscript, contribution of new concepts, inclusion of new references. **Lidia Martínez-Sánchez:** critical review of the manuscript, contribution of new concepts, inclusion of new references. **Lidia Martínez-Sánchez:** critical review of the manuscript, contribution of new concepts, inclusion of new references. **Núria Pi-Sala:** critical review of the manuscript. **Àngels Gispert-Ametller:** critical review of the manuscript. **Emilio Salgado-García:** critical review of the manuscript, inclusion of new references. **Raquel Aguilar-Salmerón:** critical review of the manuscript, contribution of new concepts, inclusion of new references. The three authors approved the final version of the manuscript submitted for publication.

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CRediT authorship statement

Santiago Nogué-Xarau: Writing – original draft, Supervision, Formal analysis, Data curation, Conceptualization. **Lidia Martínez-Sánchez:** Validation, Methodology, Data curation. **Milagros García-Peláez:** Validation, Formal analysis, Data curation. **Edurne Fernández de Gamarra-Martínez:** Validation, Methodology, Formal analysis. **Núria Pi-Sala:** Validation, Formal analysis. **Àngels Gispert-Ametller:** Validation, Methodology, Formal analysis. **Emilio Salgado-García:** Validation, Formal analysis, Data curation. **Raquel Aguilar-Salmerón:** Validation, Methodology, Formal analysis, Data curation.

Conflict of interest

The authors declare no conflict of interest.

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