Modern Health Science; Vol. 8, No. 2; 2025
ISSN 2576-7291 E-ISSN 2576-7305
https://doi.org/10.30560/mhs.v8n2p99

Research Progress on N-Acetyl-4-Aminophenol and Its Toxic Effects

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Received: May 30, 2025; Accepted: June 9, 2025; Published: June 10, 2025

Abstract

N-Acetyl-4-aminophenol (NA4AP) is one of the analgesic and antipyretic drugs found in a large number of over-the-counter medications and is widely used worldwide because of its analgesic and antipyretic effects and because of its rapid and prolonged duration of action. Due to the large amount of use of NA4AP, it has already polluted the environment, such as groundwater, soil, surface water, etc., and it is difficult to be degraded in the natural environment, so the potential threat of NA4AP to human health has aroused people's concern. This paper reviews NA4AP and its physicochemical properties; development process; absorption, metabolism, excretion; toxic effects, etc., to provide a scientific basis for the use and control of NA4AP in China and many countries in the world.

Keywords: N-Acetyl-4-Aminophenol, Physical and Chemical Properties, Toxic Effects

1. Introduction

N-Acetyl-4-Aminophenol (NA4AP) also known as paracetamol, was a widely used antipyretic and analgesic drug. It was first synthesized by Harmon Northrop Morse in 1877 [1]. Although its pharmacological value was not initially recognized, NA4AP was rediscovered in the mid-20th century and became an important over-the-counter medication for relieving headaches, muscle pain, arthritis, and other pain symptoms, while also exhibiting effective antipyretic properties [2]. Due to its rapid onset, prolonged duration, and reliable analgesic and antipyretic effects, it became one of the most commonly used pain-relieving and fever-reducing drugs worldwide [3]. Currently, it is recommended as a first-line treatment for various acute and chronic pain conditions in international guidelines.

Over the past few decades, the sales of analgesics steadily increased, with global annual production exceeding 140,000 tons. China dominated the global production and export of NA4AP. NA4AP was also a major metabolite of aniline, a ubiquitous environmental chemical and one of the most widely produced industrial chemicals worldwide [4]. Due to its extensive use and aniline metabolism, NA4AP contributed to significant environmental pollution. It was detected in groundwater [5] and surface water [6], leading to aquatic contamination and exhibiting varying degrees of toxicity to aquatic organisms [7]. Long-term human exposure to NA4AP may pose potential health risks.

2. Physicochemical Properties and Uses of N-Acetyl-4-Aminophenol

NA4AP (chemical formula C8H9NO2, molecular weight 151.16), was a white crystalline or powdery substance with a slightly bitter taste and no distinct odor. It exhibited good solubility in water, ethanol, and acetone. Its melting point ranged between 168–172°C, and its density was 1.29 g/cm³. NA4AP maintained good chemical stability below 45°C [8]. Notably, its solubility was significantly higher in hot water than in cold water [9]. When exposed to high humidity for extended periods, the amide bond in its molecular structure could hydrolyze, producing p-aminophenol (PAP), which was chemically unstable and prone to noticeable color changes. Therefore, NA4AP required storage under dry conditions to preserve its chemical stability. In addition to being used as an analgesic and antipyretic, acetaminophen was used as an intermediate in pharmaceuticals such as penicillin and as a stabilizing agent for personal toiletries (e.g., shampoos) and cosmetics as well as for peroxides, and was also used as a raw material for photographic chemicals and azo dyes [8]. In addition to this, its widespread use in veterinary medicine, for example, in the treatment of poultry, swine and cattle, where there was no stopping time and no maximum residue limits in the final production [10]. Even some food suppliers unethically used acetaminophen as a food tenderizer, such as meat tenderization [11].

3. N-Acetyl-4-Aminophenol Development Process

In 1878 Morse synthesized NA4AP [1], and the clinical use of this compound began in 1887. But it was soon replaced by finasteride, which was considered less toxic by von Mering. It was not until the 1950s that NA4AP

was rediscovered and marketed as an analgesic alternative to finasteride by Brodie and Axelrod [12]. In their pharmacological analysis of antipyretic ice and finasteride, they found that it was the metabolite NA4AP, rather than the drug itself, that was actually responsible. The nephrotoxicity of finasteride was so significant that there were unfounded concerns about the safety of NA4AP, which led to NA4AP not being widely accepted at the time. Rather, it was only since the 1970s that NA4AP became one of the world's most popular and widely used medications for the treatment of pain and fever. NA4AP held a unique position among analgesics, both in terms of the type of pain relief and side effects.

4. Absorption, Metabolism, Excretion of N-Acetyl-4-Aminophenol

The widespread use of NA4AP resulted in serious contamination of the environment [13] and food [14]. Widespread residues were found in groundwater from drinking water sources [5], surface water [6], food [15], soil [16], and feed [17]. For example, NA4AP was consistently detected in estuarine water samples from six continents, and the weighted average concentration levels ranged from 17.5 ng/L in North America to 3,085.20 ng/L in South America, with high levels of NA4AP contamination in Asian estuaries [18]. Thus, NA4AP could enter organisms through the food chain and drinking water. It was rapidly absorbed in the gastrointestinal tract, and the plasma half-life of NA4AP was about 1.5-2.5 hours [19]. NA4AP was widely distributed in the human body, and its presence was detected in a variety of biological matrices, such as urine [20], blood [21], and breast milk [22]. NA4AP was found to be biopenetrating, not only across the blood-brain barrier but also across the placental barrier. Some studies reported the detection of NA4AP in umbilical cord blood [23] and meconium [24]. NA4AP was metabolized in vivo mainly by the liver and to a lesser extent by the kidneys, generating metabolites via glucuronidation, sulfation, and oxidation pathways, and was excreted mainly in the urine [25].

5. N-Acetyl-4-Aminophenol Toxic Effects

5.1 Hepatotoxicity

The liver carried out the major biotransformation function of NA4AP. The recommended dose of NA4AP in adults and children varied from no more than 4 g/day in adults to up to 60 mg/kg/day in children. Hepatotoxicity could occur at 7.5 g/day to 10 g/day or 140 mg/kg [26]. Cases of hepatic necrosis due to NA4AP were first reported by Davidson and Eastham in 1966. The second most common cause of liver transplantation worldwide was NA4AP toxicity, and more than half of liver failures in the United States originated from NA4AP-induced acute liver injury [27]. At that time, NA4AP abuse existed in some companies worldwide, leading to an increase in the number of cases of liver injury caused by people who had intentionally or unintentionally taken the ingredient [28]. In China, some scholars found that NA4AP induced adverse reactions were associated with single overdose and long-term administration [29]. It was reported that NA4AP metabolism in vivo produced the intermediate metabolite NAPQI [30], which had strong hepatotoxic effects, triggering hepatocellular injury and progressing to liver failure in severe cases. When the metabolism was saturated through the two reaction pathways of glucuronidation and sulfation, excess NA4AP was metabolized by cytochrome P450 to NAPQI, which could be safely reduced to non-toxic mercapturic acid and cysteine compounds by glutathione and then excreted by the kidneys [31]. At the same time, it was found that reduced glutathione utilization or impaired glucuronidation and sulfation capacity increased the risk of NA4AP hepatotoxicity. Patients who had been chronically treated with medications that induced hepatic microsomal enzymes, such as anticonvulsants and isoniazid, and chronic alcohol abusers were at increased risk of NA4AP hepatotoxicity [32]. In addition, when glutathione stores in the liver were depleted to a threshold, once they had been brought to 30% below normal—NAPQI levels increased, and free NAPQI rapidly covalently bound to and arylated cellular proteins, inducing a series of events that could lead to cell death [33]. These events included oxidation of enzymes, DNA fragmentation, and mitochondrial damage, which was not reversible [36].

5.2 Nephrotoxic Effects

NA4AP could affect renal function, and it had caused relatively fewer nephrotoxicity studies than hepatotoxicity. Renal abnormalities were more common after sustained repeated overdose administration [34]. Renal injury could occur after NA4AP overdose, even in the absence of hepatotoxicity [35]. In a case-control study involving 1,077 subjects who regularly took NA4AP, a dose-response relationship between heavy NA4AP use and increased risk of end-stage renal disease was demonstrated [36]. Meanwhile, a study by Türk Özterlemez et al. found that prolonged use of subacute doses of NA4AP during pregnancy in rats resulted in renal damage, causing renal vascular congestion, hemorrhage, and tubular necrosis, which further suggested that NA4AP led to renal dysfunction [37]. A study by Alshahrani et al. also found that NA4AP induced morphological changes and imbalance of oxidative parameters in renal tissues [38]. NA4AP produced PAP in addition to NAPQI during renal metabolism, and the key pathogenetic factor in NA4AP induced renal injury was NAPQI, which led to tubular

necrosis [39].

5.3 Neurotoxic Effects

NA4AP readily crossed the blood-brain barrier and was uniformly distributed throughout the central nervous system, and some studies found the presence of NA4AP in cerebrospinal fluid [40]. Carpenter et al. found that aged mice with a history of NA4AP intoxication exhibited worsening cognitive deficits and persistently elevated astrocyte and microglial cell loads [41]. Meanwhile, Dhakshinamoorthy et al. showed that NA4AP induced neurobehavioral toxic effects in zebrafish [42]. There was an association between prenatal exposure to NA4AP and ADHD, autism, or low intelligence quotient [43, 44] and neurotoxicity in infants and toddlers [43]. Boutis et al. showed that prenatal use of NA4AP was associated with an increased risk of autism with hyperactivity disorder symptoms [45], and a similar association was found in a Spanish study [46]. In addition, postnatal (infancy and early childhood) exposure to NA4AP could result in a much higher risk of autism than prenatal exposure. Schultz et al. found in both studies that NA4AP use in infants and children was associated with an increased likelihood of autism [47]. It was generally accepted that the mechanism of brain changes due to hepatic encephalopathy complicating liver failure from NA4AP poisoning was secondary to the development of liver failure. However, *CYP2E1*, one of the isoforms of *CYPs* involved in the bioactivation of hepatic NA4AP, was also expressed in the brain. *CYP2E1* was found mainly in the olfactory bulb, olfactory cortex, hippocampus, cerebellum, and brainstem, which suggested that NA4AP could be metabolized by brain cells [48]. Only a few studies had described the effects of NA4AP itself on the central nervous system in the absence of liver failure. However, it was found that after oral administration of NA4AP to rats, glutathione levels in different regions of the brain decreased, reactive oxygen species in brain homogenate increased, and mitochondrial membrane potential and related enzyme activities decreased [49].

6. Summary

At present, NA4AP had been widely used all over the world and was the main metabolite of aniline, one of the most productive industrial chemicals in the world, and its use in China was also expanding. Long-term use of or exposure to NA4AP not only caused serious pollution of the ecological environment but also posed a hazard to human health. When long-term exposure and excessive use of NA4AP could produce hepatotoxicity, nephrotoxicity, and neurotoxicity effects on organisms. The toxic effects of NA4AP need to be studied for a longer period of time, more extensive in-depth research, and further experimental validation, and its toxicological safety evaluation needs to be further studied to systematically assess the toxic effects of NA4AP, to provide a solid theoretical basis for the scientific use of NA4AP, and to prevent and mitigate the adverse effects of NA4AP on living organisms.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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