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NITISINONE : AN ENDLESS SUCCESS STORY ?

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Résumé

Nitisinone, chemically known as NTBC (2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione), has emerged over the last two decades as a potent inhibitor of 4-hydroxyphenylpyruvate dioxygenase (HPPD), playing a pivotal role in disrupting tyrosine metabolism. This comprehensive review delves into the intricate biochemical properties of NTBC, elucidating its mechanism of action, clinical applications in the treatment of tyrosinemia, and the potential therapeutic implications in other areas of biochemistry. It aims to provide a holistic understanding of its biochemical significance and future therapeutic potential

Mots clés : Nitisinone, herbicide, history, biochemistry, tyrosinemia,

1. Introduction :

Initially designed as an herbicide, NTBC's unanticipated involvement in tyrosine catabolism has generated interest in its biochemical mechanisms. Through the inhibition of HPPD, NTBC provides a precise method to regulate tyrosine metabolism, introducing innovative possibilities for treating metabolic disorders. The significant influence of NTBC on the tyrosine breakdown pathway highlights its importance in addressing tyrosinemia and potentially expanding to other metabolic disorders [1,2].

This review aims to analyze the chemical structure of NTBC, clarify its precise mechanism of action in inhibiting HPPD, investigate its impact on interconnected metabolic pathways, evaluate its clinical applications in tyrosinemia treatment, explore molecular interactions, and suggest future research directions to enhance the comprehension of NTBC biochemistry.

2. History of Discovery and First Clinical Trials of NTBC

Nitisinone (NTBC) has a fascinating history of discovery and initial clinical trials that have paved the way for its therapeutic use in conditions like Hereditary Tyrosinemia Type 1 (HT1). The drug, also known as 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione, was first evaluated in a pioneering study involving five patients with HT-1 in 1992 [1,2]. This study, published in The Lancet, marked the beginning of NTBC's journey towards becoming a vital treatment option for patients with metabolic disorders [1,3,4].

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NTBC was initially used as a herbicide in the 1980s but was discontinued due to adverse effects in animal studies. Subsequent research identified that the herbicidal effects were associated with increased plasma levels of tyrosine. This discovery prompted the repurposing of NTBC for medical purposes, specifically targeting the enzyme 4-hydroxyphenylpyruvate dioxygenase (HPPD) to inhibit the tyrosine degradation pathway [5].

After the promising outcomes of the initial clinical trial, a global study named the NTBC Study was launched to assess the impact of NTBC treatment on individuals with HT-1. This study, led by the team at Sahlgrenska University Hospital in Sweden, was instrumental in confirming the effectiveness and safety profile of NTBC [1,3]. Over time, NTBC was distributed globally for compassionate use, leading to its approval by regulatory authorities like the FDA in 2002 [4].

The evolution of NTBC since its discovery has been characterized by its transition from a novel therapeutic agent to a cornerstone in the management of metabolic disorders. The discovery and early clinical trials of NTBC not only highlighted its inhibitory effects on key enzymes involved in tyrosine metabolism but also demonstrated its potential to reverse clinical symptoms rapidly. These seminal studies established the basis for subsequent research and the eventual incorporation of NTBC into established treatment regimens for metabolic conditions such as HT-1 [1].

NTBC's evolution is characterized by its expanding applications beyond HT-1. Research has delved into the drug's impact on metabolic pathways involving L-tyrosine, L-tryptophan, and L-phenylalanine, shedding light on its broader therapeutic potential. Studies have investigated the impact of NTBC and its derivatives on different metabolic responses, offering valuable insights into their mechanism of action. This research sets the stage for the advancement of more efficient therapies built upon this drug [6].

The evolution of NTBC usage has been marked by improvements in treatment protocols and patient outcomes. Long-term studies have demonstrated the efficacy of NTBC in improving the prognosis of HT-1 patients, with significant reductions in tyrosine levels and associated clinical symptoms. The drug's role in preventing complications like hepatocellular carcinoma and renal dysfunction has underscored its importance in managing metabolic disorders effectively [7].

The expanding scope of applications and positive clinical results associated with the NTBC highlight its enduring impact in modern medical practice, particularly in the realm of genetic metabolic disorders.

3. Chemical Structure:

Understanding the chemical structure of NTBC is essential for elucidating its mode of action, pharmacokinetics, and potential for therapeutic applications.

The intricate interplay between NTBC's molecular configuration and its interactions with target proteins forms the basis for its efficacy in treating metabolic disorders, especially hereditary tyrosinemia type 1 (HT1)

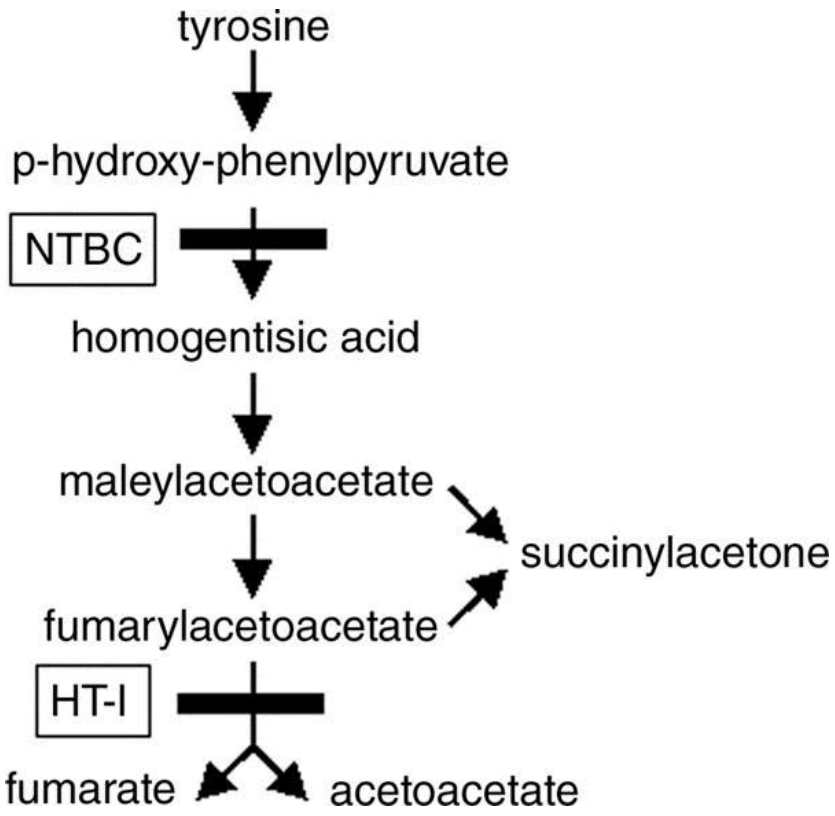

Figure 1 : NTBC level of action in the enzymatic cascade of tyrosine metabolism

The molecular structure of NTBC depicts a benzoyl-cyclohexanedione core with nitro and trifluoromethyl substituents : this unique structure is crucial for its pharmacological activity, particularly its inhibitory effect on HPPD (4-hydroxyphenylpyruvate dioxygenase), a key enzyme in the tyrosine catabolic pathway [8] (Figure 1).

The 3D structure of NTBC, when bound to its target enzyme, provides insights into its mechanism of action : the complex formation of NTBC with HPPD involves precise molecular interactions that interfere with the enzyme's normal function and underlie the potent inhibitory effects of NTBC and ultimately resulting in the intended pharmacological effects in HT-1 [9,10].

4. Clinical Applications for Tyrosinemia Treatment:

Hereditary Tyrosinemia Type 1 is a rare genetic disorder characterized by a deficiency of fumarylacetoacetate hydrolase (FAH), the final enzyme in the tyrosine catabolic pathway. The pathogenesis of HT1 involves the accumulation of toxic metabolites, such as fumarylacetoacetate (FAA), in hepatocytes and renal proximal tubular cells, leading to severe liver disease, renal dysfunction, and rickets in affected children [11,12]. Actually, numerous clinical studies have demonstrated this remarkable efficacy of nitisinone in managing HT-1 [11-13] :

- Patients treated with NTBC show rapid normalization of plasma phosphate levels and improved renal tubular function
- NTBC helps to ameliorate the symptoms associated with tyrosinemia

- The drug's ability to restore metabolic balance and prevent the progression of liver and kidney damage has significantly improved the prognosis for HT1 patients

The NTBC (nitisinone) has emerged as a cornerstone in the management of HT-1 and has really revolutionized the therapeutic landscape for tyrosinemia patients and their families, offering a targeted and efficacious approach to mitigate toxic metabolites, ameliorate symptoms, and improve the prognosis for patients afflicted with this rare metabolic disorder. Current research also aims to optimize nitisinone (NTBC) therapy, explore novel drug combinations, and enhance the understanding of the molecular mechanisms underlying tyrosine metabolism in HT-1 patients.
Moreover, studies are underway to expand the application of nitisinone to other metabolic disorders and investigate its potential use in mitigating systemic complications of hereditary tyrosinemia [14].

Mechanism of Action in HT-1:

NTBC's mechanism of action relies on its high binding affinity to the active site of HPPD, disrupting the enzymatic conversion of 4-hydroxyphenylpyruvate to homogentisate. This interruption halts the progression of tyrosine metabolism at a crucial point. In fact, in patients with HT-1, HPPD inhibition leads to the accumulation of maleylacetoacetate and fumarylacetoacetate, which are subsequently converted to the toxic succinylacetone. This compound inhibits the porphyrin synthesis pathway and can trigger porphyric crises in HT-1 patients [15]. More interestingly, by inhibiting HPPD, an enzyme located upstream in the tyrosine metabolic pathway, before the enzyme fumarylacetoacetate hydrolase, NTBC prevents the buildup of fumarylacetoacetate. This inhibition reduces the load of toxic substances in the liver and kidneys, thereby alleviating cellular damage and enhancing metabolic function in individuals with HT-1 [5].

Administration in HT-1 :
NTBC is typically administered to patients orally in multiple daily doses. The standard regimen for NTBC administration involves two daily doses, but in some cases, patients may require three or four daily doses depending on their individual treatment plan. In conditions like HT-1, precise dosing and adherence to treatment protocols are essential for optimal therapeutic outcomes [1,16-17].

Side effects :
The common side effects of NTBC treatment include elevated tyrosine levels, thrombocytopenia, leukopenia, conjunctivitis, corneal opacity, keratitis, photophobia, eye pain, blepharitis, cataracts, granulocytopenia, epistaxis, pruritus, exfoliative dermatitis, dry skin, maculopapular rash, and alopecia.

Additionally, metabolic side effects such as dehydration and hypoglycemia may occur. It is important for healthcare professionals and patients to be aware of these potential side effects and monitor for any adverse reactions during NTBC treatment [7,18].

Pharmacokinetics :
NTBC is not metabolized by humans but is excreted unchanged in urine, primarily as 4- or 5-hydroxy metabolites, amino acid conjugates, or as 2-nitro-4-trifluoromethylbenzoic acid following hydrolytic cleavage.
In rats, NTBC is excreted in both urine and feces, with urine accounting for approximately 50% of the total excretion.

Following administration, NTBC exhibits a widespread tissue distribution, with detectable levels found in plasma, eyes, liver, kidneys, lungs, and to a lesser extent, the brain [1,18-19].

Biochemical Interaction :

There are few potential drug interactions with NTBC. Nitisinone acts as a moderate CYP2C9 inhibitor, a weak CYP2E1 inducer, and inhibits OAT1/OAT3. These interactions underscore the need for careful monitoring when administering NTBC to patients concurrently taking other medications to prevent potentially serious effects [15].

5. Future Directions

Beyond its established role in tyrosinemia, ongoing investigations are exploring the versatility of NTBC in addressing a spectrum of metabolic disorders and even venturing into uncharted territories such as cancer therapy, underscoring its potential as a versatile therapeutic agent in biochemistry [20]. As research advances and new discoveries emerge, the role of NTBC in medicine is poised to evolve, opening doors to innovative treatments and improved quality of life for patients with diverse genetic conditions [14]. Ongoing research and clinical trials continue to explore the drug's potential applications beyond tyrosinemia, including its use in treating conditions like alkaptonuria and other metabolic disorders [21-22]. Novel approaches, such as the development of binding agents and amino-acid therapies, offer new avenues for expanding the therapeutic utility of NTBC and improving patient outcomes.

Conclusion

This review underscores the pivotal role of NTBC in biochemical disturbances, particularly in the realm of tyrosine metabolism and its clinical applications.

Unraveling the amazing web of NTBC's biochemical properties, mechanisms of action, and therapeutic potential, and proposing innovative strategies to refine NTBC-based therapies or engineer tailored interventions based on a nuanced understanding of its therapeutic mechanisms herald a new era of therapeutic innovation, particularly in the niche of rare diseases and malignant conditions.

Conflicts of interests :

The authors have no conflicts of interest to declare.

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