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Orphan Drug Nitisinone in Dermatology

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ABSTRACT

The structure of Nitisinone is 2-nitro-4-trifluoromethylbenzoyl] cyclohexane1, 3-dione, i.e, 2-NTBC. Discovery of its mechanism of action, with side effects has resulted in clinical use of nitisinone in treating various disorders related tyrosine (Tyr) pathway. Dermatological uses of nitisinone are oculocutaneous albinism, hereditary tyrosinemia, African trypanosomiasis, and alkaptonuria and the nondermatological indication is ocular neuroblastoma. The drug level peaks after 1- 4 h in plasma after ingestion with 95% protein binding. Half-life of the drug is approximately 54 h. Modification of nitisinone in liver and renal dysfunction is yet to be studied. Nitisinone has minimal adverse events with ocular symptoms like irritation, corneal erosions, and photophobia if not on tyrosine restricted diet in HT. It is not known whether nitisinone has direct effects for CNS symptoms such as hypokinesis, seizure, and headache. Transient thrombocytopenia, leucopenia, and minimal GI symptoms such as diarrhea, and enanthem have been reported. Rare dermatological side effects such as alopecia, exfoliative dermatitis, xeroderma, pruritus have been reported. Pregnancy category of the drug and lactational safety yet to be discovered. We want to conclude that even though nitisone is a rarely used drug get familiarize by the drug and its availability. It is the drug that inhibits the tyrosine degradation pathway with minimal side effects. The drug is yet to bed explored further.

Keywords: Nitisinone, Hereditary tyrosinemia, Oculocutaneous albinism, Alkaptonuria, African trypanosmiasis

INTRODUCTION

The structure of Nitisinone is 2-nitro-4-trifluoromethylbenzoyl] cyclohexane1, 3-dione, i.e., 2-NTBC. Discovery of its mechanism of action, with side effects has resulted in clinical use of nitisinone in treating various disorders related tyrosine (Tyr) pathway [1].

The triketone herbicide nitisinone derived from leptospermone, a plant oil compound produced by bottle brush plants. The introduction of nitisinone in 1992 has radically improved the natural course of the disease [2].

Mechanism of action: [3]

USES

- **Oculocutaneous Albinism**

OCA which is characterized by diminished melanin pigmentation in the skin and eyes, as well as vision loss, is brought on by a mutation in the TYR gene. Post-natal visual development is influenced by retinal pigment epithelium. Nitisinone is FDA approved and did not result in an increase in iris melanin content but may increase hair and skin pigmentation in patients with OCA-1 [4].

- **Hereditary Tyrosinemia 1**

HT is an autosomal recessive inborn error of Tyr metabolism brought on by a lack of fumaryl acetoacetate hydrolase which leads to increased maleylacetoacetate precursors which get converted to succinyl acetoacetate. The highly reactive electrophilic toxic metabolites bind to sulfhydryl groups. It clinically presents as photophobia, palmoplantar keratoderma, acute or chronic liver disease, renal dysfunction associated with Fanconi syndrome, hypophosphatemic rickets, polyneuropathy and abdominal pain resembling acute porphyria. Elevated methionine metabolites produce a boiled cabbage odor [5,6]. Nitisone is known to prevent acute life-threatening complications when started in the newborn period started with a dose of 1-2mg/kg/day. Reducing the dose of the drug by determining the level of plasma and urine succinylacetone levels [7,8].

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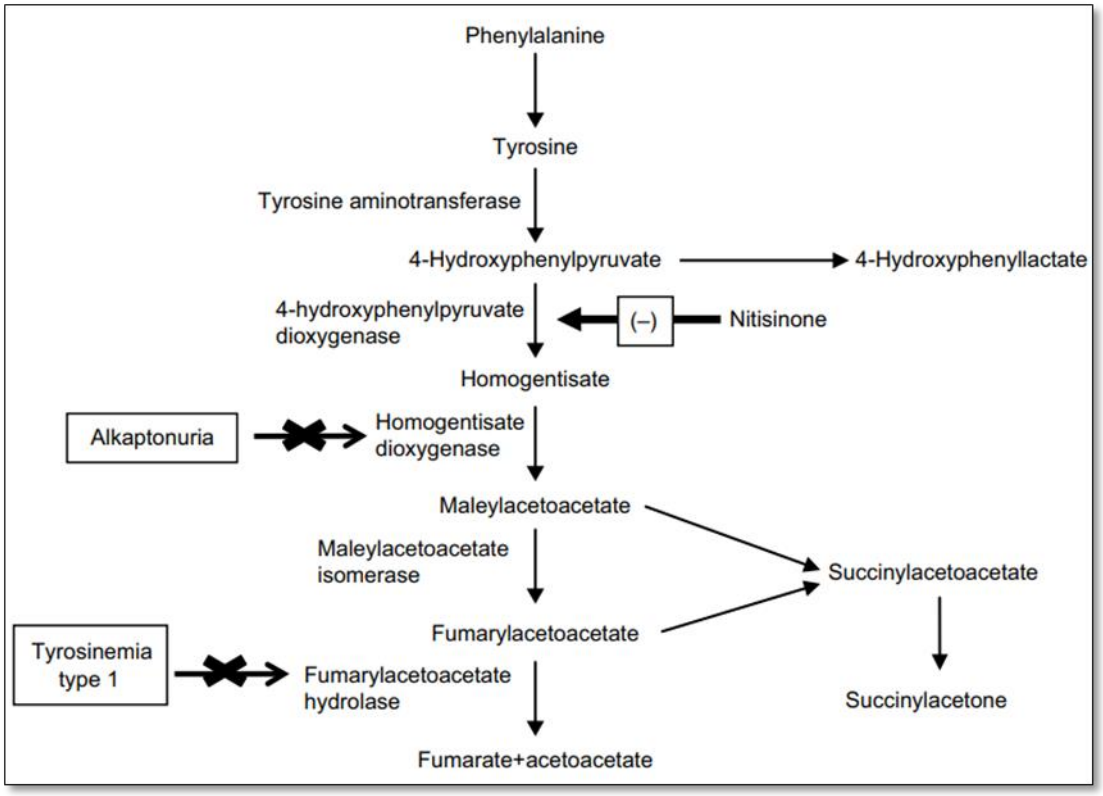

- **Alkaptonuria**

Alkaptonuria (AKU; OMIM 203500) is a rare autosomal recessive disease caused by a deficiency of homogentisate 1, 2-dioxygenase (HGD) that converts intermediate HGA to MAA in the Tyr metabolism pathway [3]. Characteristic dark urine is seen in this disease due to the polymerization of HGA to Benzoquinone acetic acid and deposition and adhering to connective tissue like cartilage forms a pathological pigmentation called ochronosis [9].

- **African trypanosomiasis**

Tsetse fly transmits this fatal disease and no vaccine available to prevent the disease, so control of transmission depends on elimination of tsetse fly population. Neurotoxic pesticides are gold standard for disease control with negative impact on environment. Nitisinone targets tyrosine pathway and RNA interference of either of enzymes in tyrosine degradation pathway was lethal to tsetse fly [10].

Other non-dermatological uses are ocular neuroblastoma [11,12].

PHARMACOKINETICS

The drug level peaks after 1- 4 h in plasma after ingestion with 95% protein binding. Half-life of the drug is approximately 54 h. Modification of nitisinone in liver and renal dysfunction is yet to be studied [11].

The drug is available as capsule (2mg, 5mg, 10mg, and 20 mg), tablet (2mg, 5mg, and 10mg) and oral suspension (4mg/ml) availability in India.

It is administered 1 h prior of 2 h after a meal [11].

SIDE EFFECTS

Nitisinone has minimal adverse events with ocular symptoms like irritation, corneal erosions, photophobia if not on tyrosine restricted diet in HT. It is not known whether nitisinone has direct effects for CNS symptoms such as hypokinesis, seizure, and headache. Transient thrombocytopenia, leucopenia, and minimal GI symptoms such as diarrhea, and enanthem have been reported. Rare dermatological side effects such as alopecia, exfoliative dermatitis, xeroderma, pruritus have been reported [12].

The pregnancy category is not determined all pregnancies were uneventful and there was no evidence of NTBC-induced harm to the developing fetus. It is not known whether nitisinone is present in breast milk while lactating. No contraindications have been labeled till now [12].

CONCLUSION

We want to conclude that even though nitisone is a rarely used drug get familiarize by the drug and its availability. It is the drug that inhibits the tyrosine degradation pathway with minimal side effects. The drug is yet to bed explored further.

CONFLICTS OF INTEREST

None.

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