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Review

The Use of Metyrosine in the Treatment of Pheochromocytoma and Paraganglioma Patients: A Review of the Literature

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ABSTRACT

Metyrosine (α-methyl-parathyrosine) functions as an inhibitor of tyrosine hydroxylase, thereby impeding the conversion of tyrosine to 3,4-dihydroxyphenylalanine. This reaction represents the rate-limiting step in the synthesis of catecholamines. This review examines the mechanisms of metyrosine action and its application for treatment purposes. The published literature was collated from a range of scientific databases, including PubMed, SciFinder, ScienceDirect, Wiley Online Library, Google Scholar and Web of Science. The use of metyrosine has been demonstrated to reduce catecholamine biosynthesis in patients with catecholamine-secreting pheochromocytoma and paraganglioma. The safety and efficacy of metyrosine in the treatment of pheochromocytoma and paraganglioma is substantiated by empirical evidence from studies demonstrating its general tolerability and clinical practice use. Metyrosine has been shown to potentially mitigate the occurrence of surgical complications by enhancing intraoperative hemodynamics. Studies have demonstrated that the administration of metyrosine prior to pheochromocytoma and paraganglioma surgery reduces the risk of hypertensive crisis and severe hypertension, as well as intraoperative haemodynamic variability. It is imperative that further research is conducted to elucidate the pharmacokinetics, intricate molecular mechanisms, and safety profile of methyrone. To this end, the utilization of meticulously designed randomized clinical trials is crucial.

Keywords: Metyrosine, pheochromocytoma, paraganglioma

INTRODUCTION

Mechanism of Action and Uses of Metyrosine

The tyrosine hydroxylase inhibitor metyrosine (α-methyl-parathyrosine) has been shown to inhibit the conversion of tyrosine to 3,4-dihydroxyphenylalanine, which is the rate-limiting step in the synthesis of catecholamines. Methyrosine, a pharmaceutical agent, exerts its biological effects by attenuating the synthesis of catecholamines, a class of hormones, by selectively inhibiting the activity of tyrosine hydroxylase, an enzyme that plays a pivotal role in the aforementioned biosynthetic pathway (Figure 1). In patients with catecholamine secreting diseases such as pheochromocytoma and paraganglioma, daily administration of 1,000-4,000 mg of metyrosine reduces catecholamine biosynthesis by 80%. In catecholamine secreting patients such as pheochromocytoma and paraganglioma, a gradual improvement in urinary catecholamine levels is observed as the metyrosine dose is adjusted up to 1,500 mg daily. Administration of a dose of metyrosine higher than 1,500 mg daily continues to reduce the level of catecholamine, although at a proportionally lower level of urinary catecholamine excretion. The highest level of catecholamine reduction is seen especially within three days. Within four days following the discontinuation of metyrosine

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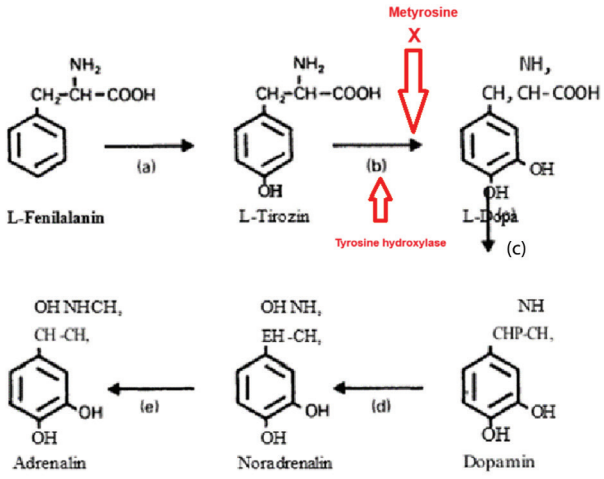

Figure 1. Biosynthetic pathway of catecholamines and enzymes involved.

(a) *L-phenylalanine hydroxylase;* ***(b)*** *L-tyrosine hydroxylase;* ***(c)*** *aromatic L-amino acid decarboxylase;* ***(d)*** *dopamine-β-hydroxylase;* ***(e)*** *phenylethanolamine N-methyl transferase.*

administration, catecholamine and its metabolites in urine concentrations return to pretreatment levels.[1]

The Use of Metyrosine in Pheochromocytoma and Paraganlioma

Pheochromocytomas and paragangliomas are neuroendocrine tumors that derive from chromaffin cells. These cells are located within the adrenal medulla, as well as the paraganglia within the nervous systems that are sympathetic and parasympathetic, respectively.[2] Pheochromocytomas and paragangliomas are tumors that synthesize catecholamines. Symptoms associated with these tumors include paroxysmal hypertension, tachycardia, sweating, episodic headaches, and constipation. Surgical resection has been identified as the primary treatment for these tumors. However, it has been demonstrated that the preoperative administration of medical treatment can effectively prevent intraoperative and postoperative events.[3,4]

Metyrosine, which improves intraoperative hemodynamics, may reduce the incidence of surgical complications.[5,6] Observations have revealed that administration of metyrosine has the potential to mitigate the occurrence of hypertension and hypertensive crises in patients undergoing surgery for pheochromocytoma and paraganglioma. In addition, it was found to reduce intraoperative hemodynamic variability. In a study by Wachtel et al.[4]142 patients with pheochromocytoma and paraganglioma treated with metyrosine and phenoxybenzamine were compared with 32 patients treated with phenoxybenzamine alone. The data from the study showed that intraoperative haemodynamic variability was significantly reduced in patients treated with metyrosine.[5] The incidence of an arrhythmia was significantly lower in those treated with metyrosine than in those treated with phenoxybenzamine.[5]

Steinsapir et al.[6] conducted a comparative analysis of two cohorts of pheochromocytoma patients: one study (n=20) received metyrosine and alpha-adrenergic blockade, while the other (n=6) used phenoxybenzamine. The metyrosine-treated group showed a reduction in the use of intraoperative vasopressors (5% vs. 50%) and a reduction in the need for phentolamine for intraoperative hypertension management (19% vs. 33%) compared with the phenoxybenzamine-only group. In a study comparing outcomes in patients with pheochromocytoma, In the study by Sand et al.[7], 17 patients with pheochromocytoma were treated with metyrosine with phenoxybenzamine (n=14) or metyrosine alone (n=3). The results showed that intraoperative systolic pressure exceeded 180 mmHg in 27% of the group in which metyrosine and phenoxybenzamine were used in treatment, while this rate was higher in 67% of the group in which metyrosine alone was used in treatment.

In supplementary studies, the use of metyrosine has been shown to alleviate symptoms caused by catecholamine excess. Naruse et al.[8] studied 13 patients, including eight patients with metastatic disease, who received chronic medical treatment for pheochromocytoma and paraganglioma. Patients were treated for approximately 125 days using an average dose of 1,028 mg of metyrosine per day. In 25% of the patients, urinary catecholamine levels decreased by more than 50%. The results were favorable with 61.5% of the patients showing a decrease in symptoms related to catecholamine elevation and a tendency to improve.

Effects That can be Observed When Using Metyrosine

Metyrosine is generally well tolerated and no side effects have been observed in patients. Drowsiness and fatigue are the most common side effects observed. The potential for sedation improvement resulting from continued use of metyrosine is a plausible hypothesis; however, it is important to consider that elevated doses of metyrosine have the potential to induce protracted sedation.[9] A variety of adverse effects have been observed, including diarrhea, tremor, anxiety, depression, and weight gain. The metyrosine package insert states that diarrhea and psychiatric effects such as anxiety, depression or hallucinations may occur in up to 10% of patients.[10] Metyrosine is excreted by the kidneys without being metabolized.[11] Caution should be exercised in patients with chronic kidney disease due to renal elimination. At high doses (2 g per day and above), crystal formation in the urine may be observed. If crystal formation is observed, the dose of metyrosine should be reduced in general.[9] Methyrosine may cause extrapyramidal symptoms by causing

MAIN POINTS

- Metyrosine, as a tyrosine hydroxylase inhibitor, effectively reduces catecholamine biosynthesis in pheochromocytoma and paraganglioma patients.
- Clinical evidence demonstrates that metyrosine is generally safe and well tolerated, although adverse effects such as sedation or extrapyramidal symptoms may occur.
- Metyrosine may be considered in patients unresponsive to alpha-adrenergic blockade or at high risk for catecholamine release due to tumor size or location.

a decrease in dopamine levels. The package insert states that up to 10% of patients may experience symptoms ranging from drooling or speech difficulties to overt parkinsonism.[9] The symptoms observed were generally mild. It is usually seen as stiff posture or unsteady gait. Symptoms were severe in three patients, and one patient was treated with intravenous abortive agents because the symptoms did not improve.[12] Extrapyramidal symptoms may worsen in patients taking other drugs that inhibit dopamine activity, such as metoclopramide and antipsychotics.[9] High risk in patients taking serotonin reuptake inhibitors and other antidepressants due to inhibition of dopamine in the central nervous system.[13] Patients using these drugs should be monitored for extrapyramidal side effects and should be informed that these symptoms may occur. The utilization of metyrosine during pregnancy is classified as category C, indicating that its application is permissible only if the anticipated benefits to the mother exceed the potential risks to the fetus.[9] Since it is not known whether metyrosine is excreted in breast milk, it is not recommended for use during breastfeeding.[9]

CONCLUSION

The use of metyrosine is safe in pheochromocytoma and paraganglioma patients before surgical or interventional procedures. In some patients, this procedure has been observed to improve intraoperative hemodynamics and reduce the occurrence of symptoms that are caused by catecholamine elevation. For patients with hypertension who do not respond to alpha-adrenergic blockade, adding metyrosine to their treatment is a viable option. In cases of patient non-compliance with regard to alpha-adrenergic blockade or high risk for catecholamine release due to factors such as tumor size and/or location, and who require intervention that may accelerate catecholamine release, it may be recommended to add metyrosine to treatment.

Author Contributions

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