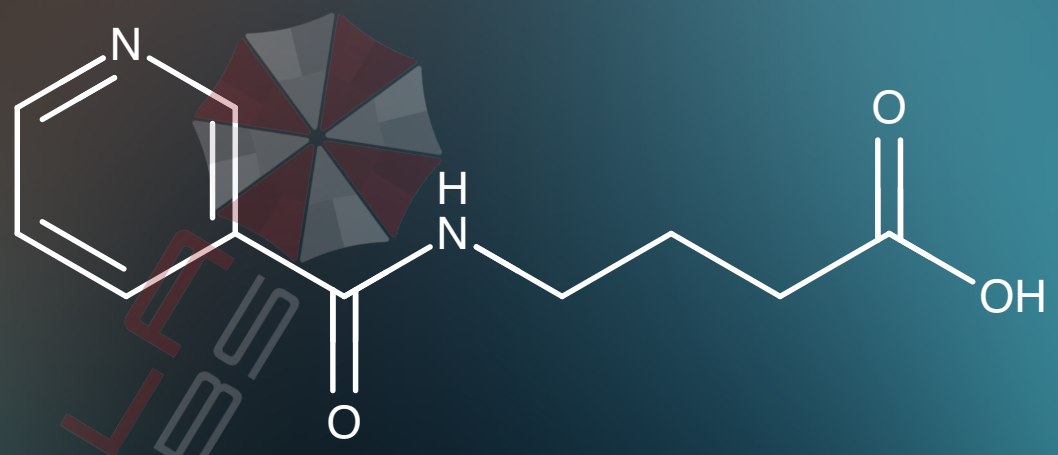

Picamilon - A Comprehensive Review of Its Neuropharmacological Properties

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History

Picamilon (also known as N-nicotinoyl-GABA, pycamilon, pikatropin and pikamilon) was first described in the soviet union in 1969-1970. Chemically, it is a joined form of the neurotransmitter gamma-aminobutyric acid (GABA) and nicotinic acid (niacin/vitamin B3). Subsequent experimental and clinical studies of picamilon showed that its ability to penetrate through the blood-brain barrier (BBB) and accumulate in the brain is about ten times that of GABA. Also, no significant tendency to decompose into its constituents niacin and GABA was observed. This fact and some other observations suggest that picamilon is capable of acting upon GABA receptors. Picamilon has found wide use as a nootropic agent and as tranquilizer. The search for new psychotropic and vasodilative compounds among the derivatives and analogs of picamilon showed that some analogs (N- nicotinoyl-β-phenyl-GABA, N-nicotinoyl-noylglutamic acid, and isonicotinoyl-GABA) are effective tranquilizers, while picolinoyl-GABA exhibits a nootropic activity with pronounced antidepressant and anti-hypertensive effects.[1]

Picamilon can be classified as a drug which increases the activity of GABA in the central and peripheral nervous system. GABA has many functions, but it generally serves as a inhibitory neurotransmitter that regulates neural function and prevents overstimulation. High concentrations of GABA can lead to dizziness and loss of consciousness.

Picamilon is used as a prescription drug in Russia and other countries for a variety of neurological conditions. In the US, it has the status of an unapproved drug. In 2015, the FDA send out warning letters over supplements containing picamilon due to its controversial status in the US. However, picamilon was found as an undeclared additive in several over-the-counter dietary supplements sold in 2021.[2]

Preclinical Data

Picamilon was shown to be rapidly absorbed in the blood (maximum concentration after 15 minutes) to penetrate well through the blood-brain barrier and to be intensively taken up by the animal organs and tissues and to be eliminated mainly in the urine with an estimated blood half-life of 30 mins. The drug bioavailability at oral administration to mice is 21.9%, and to rats between 53 to 78.9%.[3]

Both picamilon and its isomer isopicamilon (IPM) were tested for

their ability to increase tissue GABA levels. It was shown that IPM did have a much higher effect on GABA levels, which also lead to a greater effect in anticonvulsant properties, sleeping time and depressive symptoms, which is consistent with higher GABA concentration in the central nervous system.[4] The finding that blood flow of cerebral blood vessels in rats seems to be increased by picamilon is confirmed by several studies.[5-8]

Experiments with picamilon in rats showed that the cerebrovascular effect of this drug is not affected by receptor blocking with bicucullin (a GABAA receptor antagonist). However, the blocking of chloride channels of the GABAA receptors by picrotoxin significantly decreased the effect of picamilon on the cerebral blood flow.[9] There is also evidence that neuronal activity is directly influenced by picamilon.[10]

The substance picrotoxin can induce seizures in rats at a dose of 0.9 mg/kg. In a study, picamilon and isopicamilon in doses of 20 or 50 mg/kg were injected into animals 30 min prior to injection of Picrotoxin. Both compounds were found to reduce frequency and duration of seizures. However IPM was more effective than Picamilon, as has been reported previously.[11]

Patients with diabetes often suffer from neuropathy, a dysfunction of the nervous system caused by high blood sugar characterized by loss if sensitivity beginning in the feet. Damaged neurons of diabetic rats show an abnormal release of GABA. It was shown that picamilon can normalize GABA release in damaged neurons, but not the release of other abnormally secreted neurotransmitters like serotonin.[12]

In rabbits, picamilon (10 mg/kg, administered intravenously) prevented the development of the vibration-induced intracellular edema and markedly reduced the development of damage to the brain. This is likely due to the effect of picamilon in blood vessels and liquid balance.[13]

There has been an effort to theoretically determine the safety profile of picamilon. 50 important safety related biological targets were screened computationally and in vitro experiments. Picamilon showed no binding to any of those targets, raising no safety concerns for these structures.[14]

Clinical Studies

278 patients over 45 years of age with a diagnosis of chronic cerebral ischemia and cognitive impairment were enrolled in a study to receive either picamilon + ginkgo extract and 139 received monotherapy with only ginkgo extract for 90 days. The combination of both lead to a significantly greater regression of cognitive impairment compared to monotherapy. Significant differences between the groups in the magnitude of cognitive improvement were noted already from the 30th day of treatment. Both picamilon ginkgo and monotherapy with ginkgo biloba extract were safe and were not accompanied by significant adverse events.[15]

In a series of further clinical studies, the efficacy of picamilon in treating eye related neurological conditions. 94 patients at the age of 18-75 years old suffering from glaucoma were divided into 3 groups: 50 patients received combined therapy of mexidol 100 mg and picamilon 150 mg, 22 patients received combined therapy of mexidol 300 mg and picamilon 150 mg, 22 patients received only picamilon 150 mg. All medicine was administered for 14 or 21 days. Results showed that combined therapy with mexidol and mexidol was most effective.[16]

Eighty patients with pigmented retinal abiotrophy (PRA) and 20 controls were examined in a further clinical study. Picamilon therapy in a dose of 2 ml of 10% solution once a day intramuscularly for 10 days led to improvement of the visual function and ocular blood flow in patients with PRA. Treatment efficacy was higher in patients in early disease stages. Picamilon was recommended for the treatment of patients with PRA by the authors of this study.[17]

Picamilon was used in the treatment of 48 patients with central chorioretinal dystrophies. In group 1 the drug was delivered to the eye through an infusion, followed by laser exposure. In group 2 the patients were given picamilon tablets. Subjective and objective parameters improved both in the first and second groups (in 98 and 65%, respectively). Picamilon promoted extension of the peripheral borders of visual field, improved contrast sensitivity, and increased

the velocity of the sensorimotor reaction, which indicated improvement of interactions between neurons and of receptor function.[18]

In 26 children suffering from a neurogenic bladder due to myelodysplastic syndrome, picamilon and atropine were trialed to provide relief from the symptoms. Picamilon was found to potentiate the effects of atropine. The authors concluded that picamilon should be referred to basic drugs for treatment of neurogenic bladder as its combination with atropine possesses a unique efficacy in restoration of the reservoir function of the bladder.[19]

Detection

Some attention has been paid to detect picamilon in dietary supplements and human plasma through HPLC-MS analysis.[20]–[22] Plasma picamilon concentrations are generally in the 500–3000 µg/L range during the first few hours after single oral doses of 50–200 mg. The half-life in human serum is reported with 1–2 hours.

Conclusion

Picamilon has been known for more than 50 years to the scientific literature and has attracted attention in several clinical studies. It has been successfully used to treat cognitive impairment in the elderly and disorders of the eye. The main effects seems to be related to an increase in blood flow to areas with a chronic undersupply, restoring normal function. There is likely also a direct effect on the levels of the neurotransmitter GABA, since some studies claim it is a direct agonist of the GABAA receptor.

The effect strength of picamilon is not sufficiently explored, since there are only few studies for an individual clinical indication. It is also not clear whether picamilon can boost cognitive performance on healthy individuals. In addition, all clinical data stem from russian reports, with limited data disclosed per study.

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