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CHEMISTRY AND PHARMACOLOGY OF CITICOLINE AND PIRACETAM COMBINATION IN BRAIN STROKE

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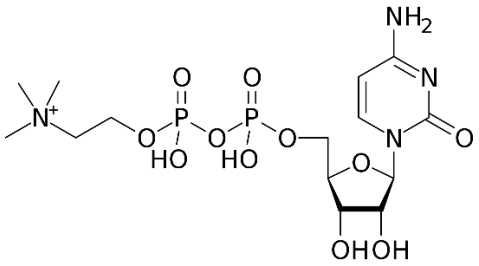
ABSTRACT

Citicoline+Piracetam is used in the treatment of stroke. It is a combination of two medicines: Citicoline and Piracetam. Citicoline is a nerve protecting medicine. It works on the brain by nourishing the nerve cells, protects them from damage and improves their survival. Citicoline and Piracetam is a medication under the branding of CITCOL−P and is used to treat stroke and mental conditions that can lead to the formation of strokes in a person. The class of drugs known as nootropics includes piracetam. This kind of medication increases the brain's cholinergic action. Piracetam is a drug which enhances cognition and memory, slows brain aging, increases oxygen and blood flow to the brain, improves Alzheimer's and aids in stroke recovery and related conditions. Piracetam and citicoline stimulate thought without peripheral nervous system stimulation.

KEYWORDS: Ribonucleotide, ischemic attack, phosphatidylcholine, nootropics, NMDA, blood brain barrier.

INTRODUCTION

Citicoline is a brain chemical that occurs naturally in the body. It's in dietary supplements in the US, but was originally a prescription drug in Japan. Citicoline seems to increase a brain chemical called phosphatidylcholine. Citicoline might also increase the amounts of other chemicals that send messages in the brain. It was originally used as a drug to help improve memory and brain function after a stroke.[1] People use citicoline for age−related decline in memory and thinking, glaucoma, stroke, Alzheimer disease, bipolar disorder, depression, and many other conditions, but there is no good scientific research to support most of these uses.



Figure−1: Citicoline.

Citicoline (Cytidine diphosphate choline): CAS: 987−78−0, IUPAC: 5'−O−[hydroxyl ({hydroxy[2−(trimethylammonio) ethoxy]phosphoryl}oxy) phosphoryl]cytidin is iticoline (INN), also known as cytidine diphosphate−choline (CDP−Choline) or cytidine 5'−diphosphocholine is an intermediate in the generation of phosphatidylcholine from choline, a common biochemical process in cell membranes.[2] This compound belongs to the class of organic compounds known as pyrimidine ribonucleotide diphosphates. These are pyrimidine ribonucleotides with diphosphate group linked to the ribose moiety. It is aromatic heteromonocyclic compound. Citicoline is naturally occurring in the cells of human and animal tissue, in particular the organs. Citicoline is available as a supplement in over 70 countries under a variety of brand names: CereBleu, Cebroton, Ceraxon, Cidilin, Citifar, Cognizin, Difosfocin, Hipercol, NeurAxon, Nicholin,

Sinkron, Somazina, Synapsine, Startonyl, Trausan, Xerenoos, etc. When taken as a supplement, citicoline is hydrolyzed into choline and cytidine in the intestine.[3] Once these cross the blood–brain barrier it is reformed into citicoline by the rate−limiting enzyme in phosphatidylcholine synthesis, CTP−phosphocholine cytidylyltransferase. Memory and cognition studies suggest, but have not confirmed, potential benefits of citicoline for cognitive impairments. Molecular Formula: $C_{14}H_{27}N_4O_{11}P_2^+$, Molar Mass: 489.335 g.mol^{-1}.
Full IUPAC: {2−[({[(2R,3S,4R,5R)−5−(4−amino−2−oxo−1,2−dihydropyrimidin−1−yl)−3,4−dihydroxyoxolan−2−yl] methoxy}(hydroxy) phosphoryl−phosphono)oxy]ethyl}trimethylazanium.

Formulations:

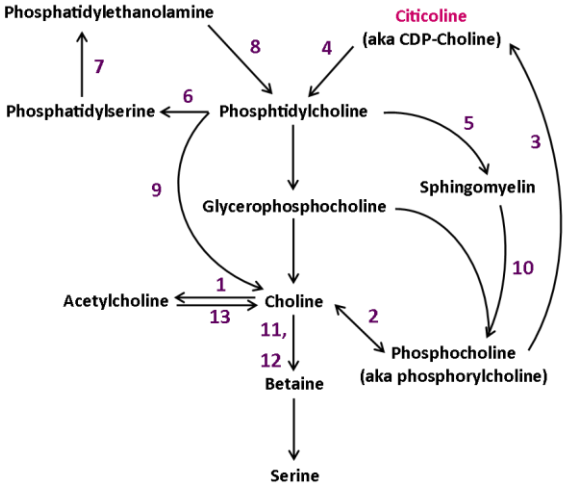
Dosage form	Route	Dose	Dosage form	Route	Dose
Injection	IM, IV	1000 mg/4ml	Injection	IM, IV	125 mg/ml
Injection	IM, IV	500 mg/4ml	Injection, solution	IM, IV	1000 mg/ml
Injection, solution	IM, IV	1045 mg	Injection, solution	IM, IV	0.1 g/2ml
Injection, solution	IM, IV	522.5 mg	Injection, solution	IM, IV	1 g/4ml
Tablet	Oral	522.500 mg	Injection, solution	IM, IV	250 mg/2ml

IM: Intramuscular, IV: Intravenous
Citicoline follows Lipinski's Rule of Five:

Figure−2: Citicoline formulations.

Property:

Water Solubility	**7.99 mg/ml**	**logS**	**−1.8**	**pKa**	**−2.6[basic]**
logP	−1.4, −7.1	pKa	1.84 [acidic]	Charge	−1
Hydrogen Acceptor Count	10	Hydrogen Donor Count	4	Polar Area	213.5 Å^2
Rotatable Bond	10	Refractivity	113.58m^3·mol^{-1}	Polarizibility	42.54 Å^3
Number of Rings	2	Bioavailability	1	Rule of Five	Yes



Figure−3: Mode of action.

Citicoline has been investigated for the treatment of depression, schizophrenia, stroke, Parkinson disease, brain injury, and cognitive deficits (ie, mild to moderate dementia and Alzheimer disease, cerebrovascular disorders), as well as for its ophthalmologic effects. It belongs to the class of other psychostimulants and

nootropics. In summary, citicoline enhances both brain neuroprotective and neurorepair mechanisms following ischemic stroke. Dietary supplementation of citicoline for 12 wk improved overall memory performance, especially episodic memory, in healthy older males and females with AAMI. The findings suggest that regular consumption of citicoline may be safe and potentially beneficial against memory loss due to aging.[4] Choline is an organic, water−soluble compound. It is neither a vitamin nor a mineral. However, it is often grouped with the vitamin B complex due to its similarities. In fact, this nutrient affects a number of vital bodily functions. Several studies have shown that Citicoline supplementation can help enhance attention, focus, and concentration. In one study, healthy adult women took 250−500 mg daily doses of Citicoline for 28 days. The researchers found that the women experienced significant improvements in attentional performance. Citicoline contains equimolar amounts of choline and cytidine. Following citicoline ingestion in rats, the increase in both plasma cytidine and choline occurred quickly, but the molar increase in plasma choline was markedly smaller. The half−life of Citicoline is 56 hours as CO2 and 71 hours in the urine.[5]

Neuroprotective effects: Citicoline may have neuroprotective effects due to its preservation of cardiolipin and sphingomyelin, preservation of arachidonic acid content of phosphatidylcholine and phosphatidylethanolamine, partial restoration of phosphatidylcholine levels, and stimulation of glutathione synthesis and glutathione reductase activity. Citicoline's effects may also be explained by the reduction of phospholipase A2 activity. Citicoline increases phosphatidylcholine synthesis. The mechanism for this may be:

By converting 1, 2−diacylglycerol into phosphatidylcholine

Stimulating the synthesis of SAMe, which aids in membrane stabilization and reduces levels of arachidonic acid. This is especially important after an ischemia when arachidonic acid levels are elevated.[6]

Neuronal membrane: The brain preferentially uses choline to synthesize acetylcholine. This limits the amount of choline available to synthesize phosphatidylcholine. When the availability of choline is low or the need for acetylcholine increases, phospholipids containing choline can be catabolized from neuronal membranes. These phospholipids include sphingomyelin and phosphatidylcholine. Supplementation with citicoline can increase the amount of choline available for acetylcholine synthesis and aid in rebuilding membrane phospholipid stores after depletion. Citicoline decreases phospholipase stimulation. This can lower levels of hydroxyl radicals produced after an ischemia and prevent cardiolipin from being catabolized by phospholipase A2. It can also work to restore cardiolipin levels in the inner mitochondrial membrane.[7]

Cell signalling: Citicoline may enhance cellular communication by increasing levels of neurotransmitters. The choline component of citicoline is used to create acetylcholine, which is a neurotransmitter in the human brain. Clinical trials have found that citicoline supplementation might improve focus and attention.[8]

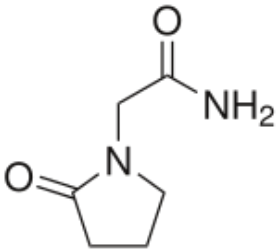
Glutamate transport: Citicoline lowers increased glutamate concentrations and raises decreased ATP concentrations induced by ischemia. Citicoline also increases glutamate uptake by increasing expression of EAAT2, a glutamate transporter, in vitro in rat astrocytes. It is suggested that the neuroprotective effects of citicoline after a stroke are due in part to citicoline's ability to decrease levels of glutamate in the brain.[9]

Pharmacokinetics: Citicoline is water−soluble, with more than 90% oral bioavailability. Plasma levels of citicholine peak one hour after oral ingestion, and a majority of the citicoline is excreted as CO_2 in respiration with the remaining citicoline being excreted through urine. The pharmacokinetic profile of citicholine cannot be described by a single smooth exponential decrease over time. However, the elimination half−life for citicholine has been reported as approximately 50 hours for citicholine removed via respiration and approximately 70 hours for citicholine removed via urine. Plasma levels of choline peak about four hours after ingestion.[10]

Side effects: Citicoline has a very low toxicity profile in animals and humans. Clinically, doses of 2000 mg per day have been observed and approved. Minor transient adverse effects are rare and most commonly include stomach pain and diarrhea. There have been suggestions that chronic citicoline use may have adverse psychiatric effects. However, a meta−analysis of the relevant literature does not support this hypothesis. At most, citicoline may exacerbate psychotic episodes or interact with antipsychotic medication.[11]

Piracetam [CAS: 7491−74−9; IUPAC: 2−(2−Oxopyrrolidin−1−yl)acetamide] is a drug marketed as a treatment for myoclonus. Molecular Formula: $C_6H_{10}N_2O_2$. Molar mass: 142.158 g·mol^{-1}. It is also used as a cognitive enhancer to improve memory, attention, and learning. Evidence to support its use is unclear, with some studies showing modest benefits in specific populations and others showing minimal or no benefit. Piracetam is sold as a medication in many European countries. Sale of piracetam is not illegal in the United States, although it is not regulated nor approved by the FDA so it is legally sold for research use only.[12] Piracetam is in the racetams group, with chemical name 2−oxo−1−pyrrolidine acetamide. It is a cyclic derivative of the neurotransmitter GABA and shares the same 2−oxo−pyrrolidone base structure with pyroglutamic

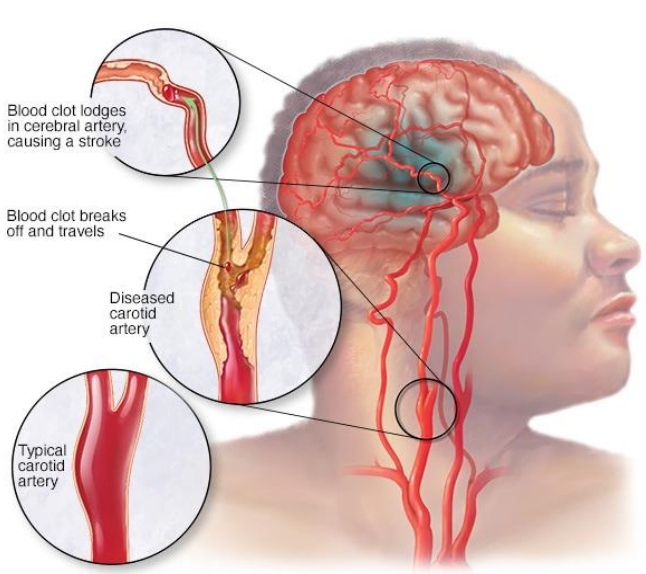
acid. Related drugs include the anticonvulsants levetiracetam and brivaracetam, and the putative nootropics aniracetam and phenylpiracetam.[13] Piracetam is a nootropic cyclic GABA derivative used in myoclonus, sickle cell disease, alcohol dependence, and as a general cognitive enhancer. Piracetam is a nootropic drug in the racetams group, with chemical name 2−oxo−1−pyrrolidine acetamide. It shares the same 2−oxo−pyrrolidone base structure with pyroglutamic acid and is a cyclic derivative of the neurotransmitter γ−aminobutyric acid (GABA). However its mechanism of action differ from that of endogenous GABA. Piracetam has neuroprotective and anticonvulsant properties and is reported to improve neural plasticity. Its efficacy is documented in cognitive disorders and dementia, vertigo, cortical myoclonus, dyslexia, and sickle cell anemia although the clinical application in these conditions is not yet established. Piracetam has effects on the vascular system by reducing erythrocyte adhesion to the vascular endothelium, hindering vasospasms and facilitating microcirculation.[14]

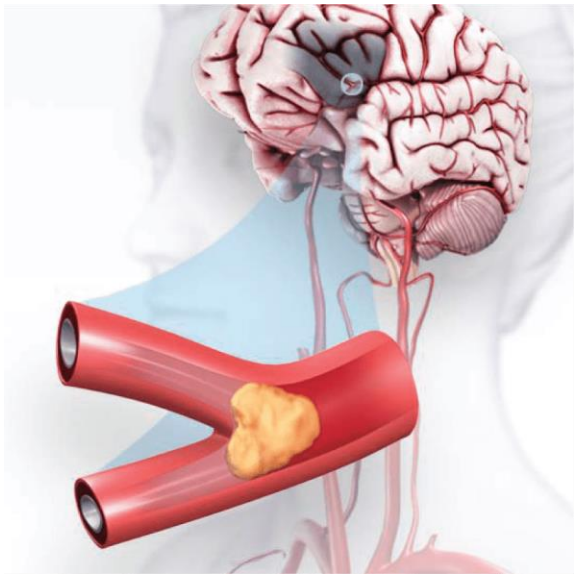


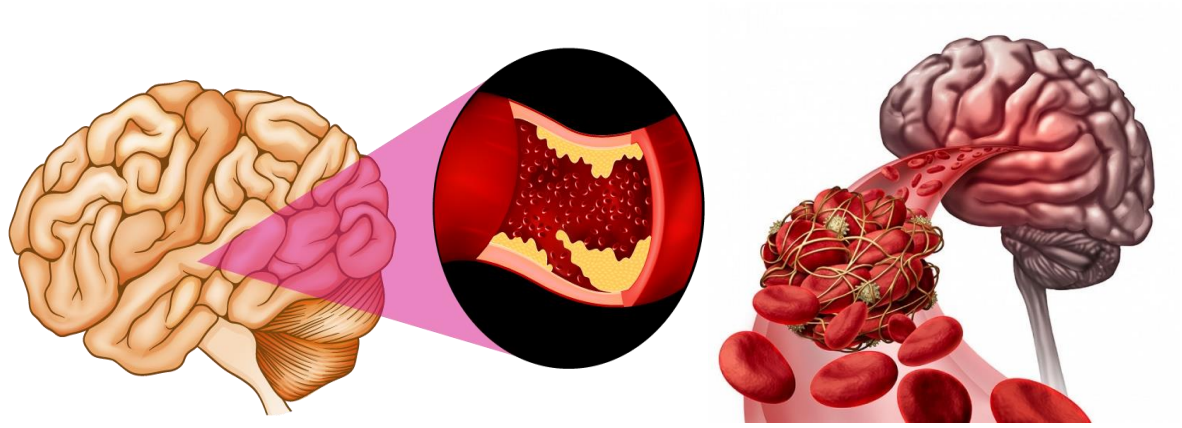
Figure−4: Piracetam.

Pharmacodynamics: Piracetam is known to mediate various pharmacodynamic actions.

Neuronal effects: Piracetam modulates the cholinergic, serotonergic, noradrenergic, and glutamatergic neurotransmission although the drug does not display high affinity to any of the associated receptors (Ki >10μM). Instead, piracetam increases the density of postsynaptic receptors and/or restore the function of these receptors through stabilizing the membrane fluidity 1. In the forebrain of aging mice, the density of NMDA [N−methyl−D−aspartate] receptors was increased by approximately 20% following 14 days of piracetam treatment. The N−methyl−D−aspartate (NMDA) receptor is a receptor of glutamate, the primary excitatory neurotransmitter in the human brain.[15] It plays an integral role in synaptic plasticity, which is a neuronal mechanism believed to be the basis of memory formation. Based on the findings of various animal and human studies, the cognitive processses including learning, memory, attention and consciousness were enhanced from piracetam therapy without inducing sedation and psychostimulant effects. Piracetam mediate neuroprotective effects against hypoxia−induced damage, intoxication, and electroconvulsive therapy.[16] In two studies involving alcohol−treated rats with evidences of withdrawal−related neuronal loss, piracetam was shown to reduce the extent of neuronal loss and increase the numbers of synapses in the hippocampus by up to 20% relative to alcohol−treated or alcohol−withdrawn rats. This suggests that piracetam is capable in promoting neuroplasticity when recoverable neural circuits are present. Although the mechanism of action is not fully understood, administration of piracetam prior to a convulsant stimulus reduces the seizure severity and enhances the anticonvulsant effectiveness of conventional antiepileptics such as carbamazepine and diazepam.[17]







Figure−5: Brain Stroke.

Stroke is a medical condition in which poor blood flow to the brain causes cell death. There are two main types of stroke: ischemic, due to lack of blood flow, and hemorrhagic, due to bleeding. Both cause parts of the brain to stop functioning properly. Signs and symptoms of stroke may include an inability to move or feel on one side of the body, problems understanding or speaking, dizziness, or loss of vision to one side. Signs and symptoms often appear soon after the stroke has occurred. If symptoms last less than one or two hours, the stroke is a transient ischemic attack (TIA), also called a mini−stroke. Hemorrhagic stroke may also be associated with a severe headache. The symptoms of stroke can be permanent. Long−term complications may include pneumonia and loss of bladder control. The biggest risk factor for stroke is high blood pressure. Other risk factors include high blood cholesterol, tobacco smoking, obesity, diabetes mellitus, a previous TIA, end−stage kidney disease, and atrial fibrillation. Ischemic stroke is typically caused by blockage of a blood vessel, though there are also less common causes. Hemorrhagic stroke is caused by either bleeding directly into the brain or into the space between the brain's membranes. Bleeding may occur due to a ruptured brain aneurysm. Diagnosis is typically based on a physical exam and supported by medical imaging such as a CT scan or MRI scan. A CT scan can rule out bleeding, but may not necessarily rule out ischemia, which early on typically does not show up on a CT scan. Other tests such as an electrocardiogram (ECG) and blood tests are done to determine risk factors and rule out other possible causes. Low blood sugar may cause similar symptoms.

Prevention includes decreasing risk factors, surgery to open up the arteries to the brain in those with problematic carotid narrowing, and warfarin in people with atrial fibrillation. Aspirin or statins may be recommended by physicians for prevention. Stroke or TIA often requires emergency care. Ischemic stroke, if detected within three to four−and−a−half hours, may be treatable with a medication that can break down the clot. Some cases of hemorrhagic stroke benefit from surgery. Treatment to attempt recovery of lost function is called stroke rehabilitation, and ideally takes place in a stroke unit; however, these are not available in much of the world.

In 2013, approximately 6.9 million people had ischemic stroke and 3.4 million people had hemorrhagic stroke. In 2015, there were about 42.4 million people who had previously had stroke and were still alive. Between 1990 and 2010 the annual incidence of stroke decreased by approximately 10% in the developed world, but increased by 10% in the developing world. In 2015, stroke was the second most frequent cause of death after coronary artery disease, accounting for 6.3 million deaths (11% of the total). About 3.0 million deaths resulted from ischemic stroke while 3.3 million deaths resulted from hemorrhagic stroke. About half of people who have had stroke live less than one year. Overall, two thirds of cases of stroke occurred in those over 65 years old. There are two main causes of stroke: a blocked artery (ischemic stroke) or leaking or bursting of a blood vessel (hemorrhagic stroke). Some people may have only a temporary disruption of blood flow to the brain, known as a transient ischemic attack (TIA), that doesn't cause lasting symptoms. A stroke, sometimes called a brain attack, occurs when something blocks blood supply to part of the brain or when a blood vessel in the brain bursts. In either case, parts of the brain become damaged or die. A stroke can cause lasting brain damage, long−term disability, or even death. A stroke happens when blood flow to any part of the brain stops. Each person has a different recovery time and need for long−term care. Problems with moving, thinking, and talking often improve in the first weeks or months after a stroke. Some people will keep improving months or years after a stroke. Signs of a TIA or stroke may include:

Sudden confusion, trouble speaking, or trouble understanding speech.
Sudden numbness or weakness, especially on one side of the body.
Sudden severe headache with no known cause.
Sudden trouble seeing from one or both eyes.

Figure−6: Piracetam Formulations.

Vascular effects: Piracetam is shown to increase the deformability of erythrocytes, reduce platelet aggregation in a dose−dependent manner, reduce the adhesion of erythrocytes to vascular endothelium and capillary vasospasm. In healthy volunteers, piracetam mediated a direct stimulant effect on prostacycline synthesis and reduced the plasma levels of fibrinogen and von Willebrand's factors (VIII: C; VIII R: AG; VIII R: vW) by 30 to 40%. Potentiated microcirculation is thought to arise from a combination of effects on erythrocytes, blood vessels and blood coagulation.[18]

Mechanism of action: Half Life: 4−5 hours. Piracetam interacts with the polar heads in the phospholipids membrane and the resulting mobile drug−lipid complexes are thought to reorganize the lipids and influence membrane function and fluidity. Such interaction has been reported in a study that investigated the effects of neuronal outgrowth induced by beta amyloid peptides; while amyloid peptides cause lipid disorganization within the cell membranes leading to neuronal death, piracetam demonstrated to decrease the destabilizing effects of amyloid peptide. The authors suggest that piracetam induces a positive curvature of the membrane by occupying the polar groups in the phospholipids to counteract the negative curvature induced by amyloid peptides, which in turn would decrease the likelihood of membrane fusion. This mechanism of action is thought to improve membrane stability, allowing the membrane and transmembrane proteins to maintain and recover the three−dimensional structure or folding for normal function 4 such as membrane transport, chemical secretion, and receptor binding and stimulation. Through restored membrane fluidity, piracetam promotes restored neurotransmission such as glutamatergic and cholinergic systems, enhances neuroplasticity and mediates neuroprotective and anticonvulsant effects at the neuronal level. It is also demonstrated that piracetam also improves the fluidity of platelet membranes. At the vascular level, piracetam decreases adhesion of erythrocytes to cell wall and reduces vasospasm which in turn improves microcirculation including cerebral and renal blood flow.[19]

Absorption: Piracetam displays a linear and time−dependent pharmacokinetic properties with low intersubject variability over a large range of doses. Piracetam is rapidly and extensively absorbed following oral administration with the peak plasma concentration is reached within 1 hour after dosing in fasted subjects. Following a single oral dose of 3.2 g piracetam, the peak plasma concentration (C_{max}) was 84 µg/mL. Intake of food may decrease the C_{max} by 17% and increase the time to reach C_{max} (T_{max}) from 1 to 1.5 hours. Tmax in the cerebrospinal fluid is achieved approximately 5 hours post−administration. The absolute bioavailability of piracetam oral formulations is close to 100% and the steady state plasma concentrations are achieved within 3 days of dosing.[20]

Volume of distribution: Vd is approximately 0.6L/kg. Piracetam may cross the blood−brain barrier as it was measured in the cerebrospinal fluid following intravenous administration. Piracetam diffuses to all tissues except adipose tissues, crosses placental barrier and penetrates the membranes of isolated red blood cells.

Protein binding: Piracetam is not reported to be bound to plasma proteins.

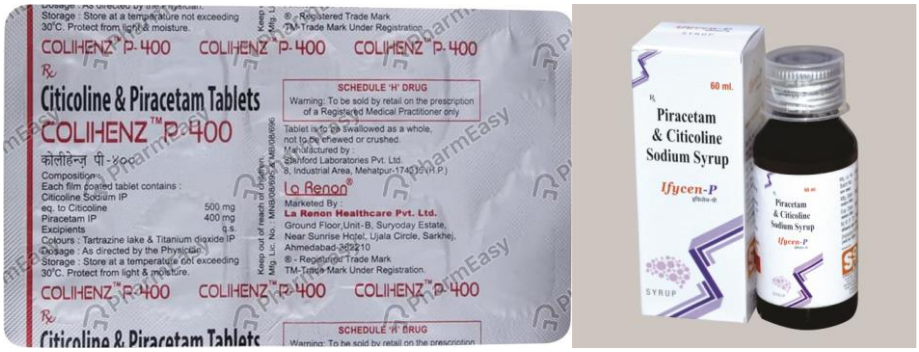
Metabolism: As large proportion of total piracetam administered is excreted as unchanged drug, there is no known major metabolism of piracetam.[21]

Route of elimination: Piracetam is predominantly excreted via renal elimination, where about 80−100% of the total dose is recovered in the urine. Approximately

90% of the dose of piracetam is excreted in the urine as unchanged drug.

Half−life: The plasma half−life of piracetam is approximately 5 hours following oral or intravenous administration. The half life in the cerebrospinal fluid was 8.5 hours. Side effects: Symptoms of general excitability, including anxiety, insomnia, irritability, headache, agitation, nervousness, tremor, and hyperkinesia, are occasionally reported. Other reported side effects include somnolence, weight gain, clinical depression, weakness, increased libido, and hypersexuality. According to a 2005 review, piracetam has been observed to have the following side effects: hyperkinesia, weight gain, nervousness, somnolence, depression and asthenia. Piracetam reduces platelet aggregation as well as fibrinogen concentration, and thus is contraindicated to patients with cerebral haemorrhage.[22]

Clearance: The apparent total body clearance is 80−90 mL/min. Toxicity: The LD50 for oral consumption in humans has not been determined. The LD50 is 5.6 g/kg for rats and 20 g/kg for mice, indicating extremely low acute toxicity. For comparison, in rats the LD50 of vitamin C is 12 g/kg and the LD50 of table salt is 3 g/kg.[23]



Figure−7: Citicoline and Piracetam combination formulation.

Adverse Effects: Improve decision support & research outcomes. With structured adverse effects data, including: blackbox warnings, adverse reactions, warning & precautions, & incidence rates.[24]

Toxicity: The cases of overdose with piracetam is rare. The highest reported overdose with piracetam was oral intake of 75g which was associated with diarrhea and abdominal pain; the signs were most likely related to the extreme high dose of sorbitol contained in the used formulation. In cases of acute, significant over dosage, stomach emptying by gastric lavage or induced emesis is recommended as there are no known antidotes for piracetam. Management for an overdose will most likely be symptomatic treatment and may include hemodialysis, where the extraction efficacy of the dialyser is 50 to 60% for the drug. Oral LD50 in a mouse acute toxicity study was 2000 mg/kg MSDS.[25]

Property

State	**Solid**	**Melting Point**	**152°C**	**Boiling point**	**Decomposes**
Water Solubility	479.0 mg/ml	logS	0.53	pKa	−2 [basic]
logP	−1.6, −1.7	pKa	15.93 [acidic]	Charge	0
Hydrogen Acceptor Count	2	Hydrogen Donor Count	1	Polar Area	63.4 $Å^2$
Rotatable Bond	2	Refractivity	35.06 $m^3 \cdot mol^{-1}$	Polarizibility	13.96 $Å^3$
Number of Rings	1	Bioavailability	1	Rule of Five	Yes

Mechanisms of action: Piracetam's mechanism of action, as with racetams in general, is not fully understood. The drug influences neuronal and vascular functions and influences cognitive function without acting as a sedative or stimulant. Piracetam is a positive allosteric modulator of the AMPA receptor, although this action is very weak and its clinical effects may not necessarily be mediated by this action. It is hypothesized to act on ion channels or ion carriers, thus leading to increased neuron excitability.[26] GABA brain metabolism and GABA receptors are not affected by piracetam. Piracetam improves the function of the neurotransmitter acetylcholine via muscarinic cholinergic (ACh) receptors, which are implicated in memory processes. Furthermore, piracetam may have an effect on NMDA glutamate receptors, which are involved with learning and memory processes. Piracetam is thought to increase cell membrane permeability. Piracetam may exert its global effect on brain neurotransmission via modulation of ion channels (i.e., Na^+, K^+). It has been found to increase oxygen consumption in the brain, apparently in connection to ATP metabolism, and increases the activity of adenylate kinase in rat brains. Piracetam, while in the brain, appears to increase the synthesis of cytochrome b5, which is a part of the electron transport mechanism in mitochondria. But in the brain, it also increases the permeability of some intermediates of the Krebs cycle

through the mitochondrial outer membrane. Piracetam inhibits N−type calcium channels. The concentration of piracetam achieved in central nervous system after a typical dose of 1200 mg (about 100 μM) is much higher than the concentration necessary to inhibit N−type calcium channels (IC50 of piracetam in rat neurons was 3 μM).[27]

CONCLUSION

Memory impairment and enhancement of cognitive function of brain is a part of treatment of various disorders associated with elderly patients or patients with neurological disorders at any age due to stroke and related shocks. Nutraceuticals are effective ways of treating such conditions. Various drugs are identified and established as therapeutic agents for treatment of cognitive disorders. Effective therapy can be set forth if rationale combinations of such agents are being design, characterized for their pharmacological, biochemical and physical compatibility and developed into suitable formulation. Nutraceutical combinations are coming into the market as boost for health care system to prevent early degeneration of neurons, memory loss and brain related aging. Citicoline and piracetam is one of such combination which has been proved pharmacologically, biochemically and physically compatible. It has been developed into tablet formulation which is available into market. This combination has therapeutic applications in alcoholism, clotting, coagulation, vasospastic disorders alzheimer's and senile dementia, depression and anxiety stroke, ischemia and symptoms, dyspraxia and dysgraphia, closed craniocerebral trauma.

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