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REVIEW ARTICLE

Therapeutic Applications of Citicoline and Piracetam as Fixed Dose Combination

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ABSTRACT

Combination of citicoline and piracetam is available in market as fixed dose combination in film coated tablet with dose of citicoline 500 mg and piracetam 800 mg. It has been approved by DCGI in the year 2010. This combination is chemically and pharmalogically safe. The combination is generally prescribed for memory enhancement, neurological and cognitive disorder, Parkinsonism and Alzheimer disorder. These drugs are nutrients and acts as cognition enhancing supplements, and are recommended as part of treatment regimens at some aging clinics. Citicoline has been shown to improve memory and other cognitive functions in patients with chronic cerebrovascular disease or dementia and in old people suffering from memory deficit. 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. Citicoline alone gives a lift and then a depression but not when taken along with piracetam. Whereas piracetam induced headache is reduced when taken along with citicoline. This review highlights need for combination of citicoline and piracetam their pharmacological and therapeutic issues and application.

KEYWORDS: Citicoline, piracetam, nutrients and cognitive functions.

1. INTRODUCTION

Citicoline is first identified in 1955 by Kennedy and colleagues and synthesized in 1956, citicoline has been studied in europe, japan, and the united states for several decades. It is widely available as an approved drug for the treatment of neurological disorders in many countries and is sold as a dietary supplement in the United States. But citicoline is not official in any pharmacopeia. Citicoline which is a form of the B vitamin choline found in all cells. Citicoline has been extensively studied and proven to benefit brain health. It supports brain functions and even ameliorates some of the cumulative damage that has ravaged the brain over a period of time. It plays a vital function in the formation of cell membranes. The brand Citicoline is known for its purity and consistency in quality. They however can be repaired and citicoline plays a vital role in the repair of neurons. Citicoline supports energy production in the neurons. This in turn supports repair and maintenance of cell membranes, synthesis of brain chemicals, and propagation of electrical impulses—all necessary to support the broader functions of the brain such as memory, motor cognitive functions, thought and decision making processes. Supplementing your diet with memory supplements that contain citicoline is an intelligent choice for those who would like to boost their mental energies and preserve memory and cognitive skills.[1]

Piracetam developed in 1967, was the initial compound classified as a nootropic drug. Piracetam is a nootropic drug. It is sold under several names, such as nootropil and pirroxil; there is very little data on piracetam's effect on healthy people, with most studies focusing on people with seizures, dementia, concussions, or other neurological problems. piracetam is a water-soluble pyrrolidone derivative nootropic smart drug. It is chemically similar to pyroglutamate. It is a cyclic derivative of gamma-aminobutyric acid. Its chemical name is 2-oxo-1-pyrrolidine acetamide it shares the same 2-oxo-pyrrolidone base structure with 2-oxo-pyrrolidine carboxylic acid

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(pyroglutamate). Piracetam is a cyclic derivative of gaba. It is one of the groups of racetams. piracetam is prescribed by doctors for some conditions, mainly myoclonus, but is used off-label for a much wider range of applications. Piracetam is an official in British and European pharmacopeia .[2]

STRUCTURE

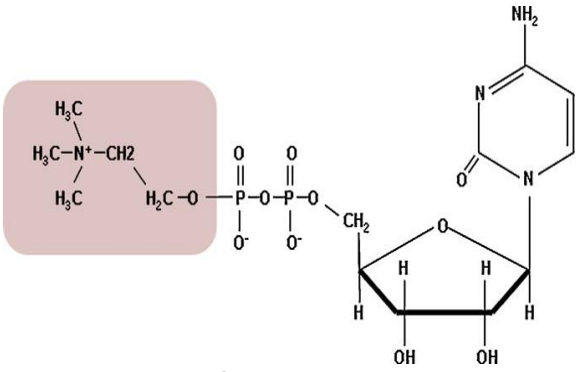

Fig. 1: Structure of Citicoline

Citicoline (CDP-choline, cytidine diphosphate choline, cytidine 5-diphosphocholine,) is a nucleotide composed of ribose, pyrophosphate, cytosine and choline. It is organized in two moieties, cytidine and choline, that are linked by a diphosphate bridge (Fig. 1). It is supplied as a freebase, as a dietary supplement in the United States, and as a sodium salt in Europe (cytidine 5(trihydrogen diphosphate) [2-(trimethylammonio) ethyl] ester inner salt,). It is a water-soluble compound (90-percent bioavailability) which is, after ingestion hydrolyzed in the small intestine and absorbed as choline and cytidine. Following absorption, choline and cytidine are re-phosphorylated and citicoline is synthesized from cytidine triphosphate and choline monophosphate by cytidine triphosphate-phosphocholine cytidylyl transferase. [3, 4, 5]

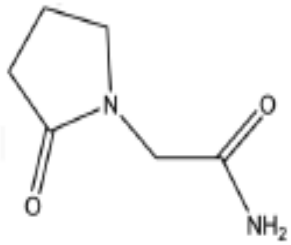

Fig 2: Structure of Piracetam

Piracetam is a class of nootropic drugs that share a pyrrolidone nucleus, molecular Formula is $C_6H_{10}N_2O_2$. It generally shows no affinity for the most important receptors, although modulation of most important central neurotransmitters, including acetylcholine and glutamate has been reported.[6] Like ampakines, the racetams are positive allosteric modulators for the AMPA receptor. Other potent cognitive enhancers in development are also positive allosteric modulators for the AMPA receptor. Racetms are work by activating glutamate receptors that are colocalized with cholinergic receptors, thus increasing the firing of the latter. The racetams consequently increase memory capacity by nearly the same method as the acetyl cholinesterase inhibitors. [7] of the cognitive enhancing members of the racetam family, nootropic potency is increased when taken with choline or acetylcholine precursors.[8]

BIOCHEMISTRY

Grouped with the B vitamins, choline is a trimethylated nitrogenous base that enters three major metabolic pathways (1) phospholipids synthesis via phosphorylcholine (2) acetylcholine synthesis and (3) oxidation to betaine, which serves as a methyl donor. Endogenously, formation of citicoline from choline is the rate-limiting step in the synthesis of phosphatidylcholine, a key membrane phospholipid.[3] Cytidine, a major component of RNA, undergoes cytoplasmic conversion to cytidine triphosphate (CTP). In the citicoline metabolic pathway, choline is phosphorylated by the enzyme choline kinase, the resulting phosphorylcholine combines with CTP to form citicoline.[4] Citicoline then combines with diacylglycerol, forming phosphatidylcholine, with choline phosphotransferase serving as the enzyme catalyst in this reaction. Exogenous citicoline, hydrolyzed in the small intestine and readily absorbed as choline and cytidine, enters the various biosynthetic pathways that utilize citicoline as an intermediate. Citicoline thus has a sparing effect on systemic choline reserves, as well as inhibiting the breakdown of membrane phospholipids .[5]

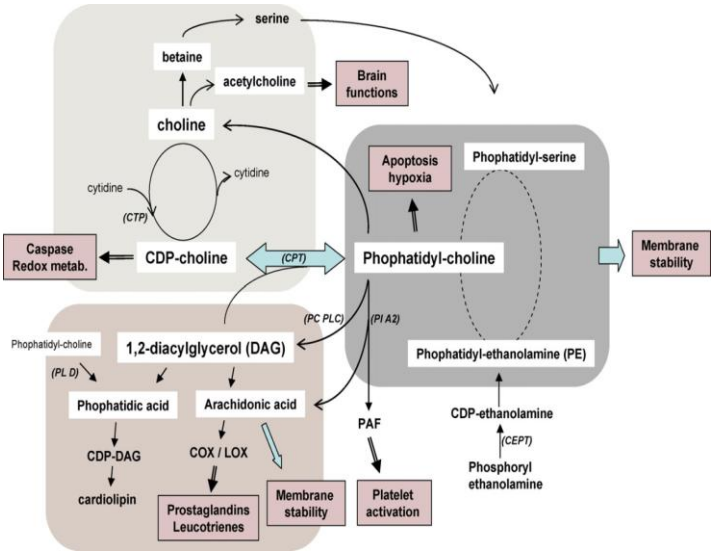

Fig 3: Synthesis of Citicoline

Piracetam is exert their effect on some species of molecule] present in the cell membrane of all excitable cells, i.e. the ion carriers or ion channels and that they somehow accomplish an increase in the excitatory (electrical) response. It would therefore seem that the racetams act as potentiators of an already present activity

(also causing the increase in glucose utilization observed), rather than possessing any [neurotransmitter-like] activity of their own, in keeping with their very low toxicity and lack of serious side effects. The result of their action is therefore an increase in general neuronal sensitivity toward stimulation.[9]

PHARMACOKINETICS

Citicoline is a water-soluble compound with greater than 90-percent bioavailability. Pharmacokinetic studies on healthy adults have shown oral doses of citicoline are rapidly absorbed, with less than one percent excreted in feces. Plasma levels peak in a biphasic manner, at one hour after ingestion followed by a second larger peak at 24 hours post-dosing. Citicoline is metabolized in the gut wall and liver. The byproducts of exogenous citicoline formed by hydrolysis in the intestinal wall are choline and cytidine. Following absorption, choline and cytidine are dispersed throughout the body, enter systemic circulation for utilization in various biosynthetic pathways, and cross the blood-brain barrier for re-synthesis into citicoline in the brain.[6] Pharmacokinetic studies using **C** citicoline show citicoline elimination occurs mainly via respiratory **C** and urinary excretion, in two phases mirroring the biphasic plasma peaks. The initial peak in plasma concentration is followed by a sharp decline, which then slows over the next 4-10 hours. In the second phase, an initially rapid decline after the 24-hour plasma peak is similarly followed by a slower elimination rate. The elimination half-life is 56 hours for **C** and 71 hours for urinary excretion.[10]

Piracetam is rapidly and almost totally (near 100%) absorbed when administered orally. peak blood plasma levels of piracetam occur within 1.5 hours of its oral administration. the blood plasma half-life of piracetam is 5 hours.[11] piracetam effectively crosses the blood-barrier. piracetam does not metabolize within the body to any other substance. in youth, the Cmax of Piracetam (1600mg oral dose, fasted) is 27.6+/-1.3ug/mL with a Tmax of 0.90+/-0.15 hours. In the elderly these numbers are 32.2+/-3.6ug/mL and 0.86+/-0.14 hours in the same study, respectively. A 24-hour AUC of 145 (young) and 188 (elderly) ug/min/ml.The higher AUC in elderly being due to a clinically insignificant lower renal clearance time. Almost all ingested piracetam is excreted from the body via the urine via glomerular filtration.[12]

METABOLISM

Endogenous citicoline serves as an intermediate in the biosynthesis of phospholipids, including phosphatidylcholine, the pmnary phospholipids in cell membranes.[13] Cytidine a major component of RNA, undergoes cytoplasmic conversion to cytidine triphosphate (CTP). In the citicoline metabolic pathway, choline is phosphorylated by the enzyme choline kinase: the resulting phosphorylcholine combines with CTP to form citicoline.[14] Citicoline then combines with diacylglycerol (DAG), forming phosphatidylcholine, with choline phosphotransferase serving as the enzyme catalyst in this reaction.[15]

Piractam has a no affinity for the alpha 1-, alpha 2-, beta-muscarinic, 5-hydroxytryptamine-, dopamine, adenosine-A1-, mu-opiate, gamma-aminobutyric acid (GABA The racetams possess a very low toxicity and lack serious side effects. Increased turnover of different neurotransmitters has been observed as well as other biochemical findings, e.g., inhibition of enzymes such as prolylendopeptidase.[16] the effect of the racetams is due to a potentiation of already present neurotransmission and that much evidence points in the direction of a modulated ion flux by, e.g., potentiated calcium influx through non-L-type voltage-dependent calcium channels, potentiated sodium influx through alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor gated channels or voltage-dependent channels or decreases in potassium efflux. Effects on carrier mediated ion transport are also possible. [17]

MECHANISM OF ACTION

Citicoline acts by various mechanisms as cerebral activator listed below:

a. Phospholipid Precursor*:* Evidence of citicoline role as a phosphatidylcholine precursor has been found in animal studies.[18]

b. Neuronal Membrane Repair*:* Citicoline has been investigated as a therapy for stroke patients. Three mechanisms are postulated (1) repair of the neuronal membrane via increased synthesis of phosphatidylcholine (2) repair of damaged cholinergic neurons via potentiation of acetylcholine production and (3) reduction of free fatty acid buildup at the site of stroke-induced nerve damage.[19]

c. Effect on beta-Amyloid: Evidence has surfaced that citicoline counteracts the deposition of beta-amyloid, a neurotoxic protein believed to play a central role in the pathophysiology of Alzheimer's disease (AD).[20, 21]

d. Effect on Neurotransmitters:

Evidence of citicoline's ability to enhance norepinephrine release in humans was found in a study showing citicoline raised urinary levels of 3-methoxy- 4-hydroxyphenylglycol (MHPG), a norepinephrine metabolite. Norepinephrine increased in the cerebral cortex and hypothalamus, dopamine increased in the corpus striatum, and serotonin increased in the cerebral cortex, striatum, and hypothalamus. [22]

Piracetam 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. it is hypothesized to act on ion

channels or ion carriers, thus leading to non-specific increased neuron excitability, while explaining its lack of agonistic or inhibitory effect on synaptic action and its low toxicity. GABA brain metabolism and GABA receptors are not affected by piracetam. it has been found to increase blood flow and oxygen consumption in parts of the brain but this may be a side effect of increased brain activity rather than a primary effect or mechanism of action for the drug. piracetam improves the function of the neurotransmitter acetylcholine via muscarinic cholinergic 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 appears to increase the synthesis of cytochrome b5 which is a part of the electron transport mechanism in mitochondria. it also increases the permeability of the mitochondria of some intermediaries of the krebs cycle. Piracetam possesses pronounced antihypoxic and antiarrhythmic effect the latter is carried out by decreasing the rhythm rate and increasing the contraction amplitude. Piracetam appears to increase communication between the two hemispheres of the brain, and increases activity of the corpus callosum.[23]

THERAPEUTIC APPLICATIONS OF CITICOLINE AND PIRACETAM COMBINATION

Combination of citicoline and piracetam could be the boon for the management for various cognitive disorders. The combination enters into the cerebrospinal fluid of the brain easily because it can cross the blood-brain barrier. The major indication of the combination could be:

- Memory enhancement
- Neurological and cognitive disorder
- Parkinsonism disorder
- Alzheimer disorder
- Depression and anxiety stroke
- Closed craniocerebral trauma
- Dyspraxia clotting, coagulation
- vasospastic disorders

Nutritional building blocks for healthy brain function. This combination is a physician formulated, science-based brain-health supplement designed to supply the essential antioxidants and nutrients necessary to assist the body in supporting healthy memory, mood and motor functions. It nutritionally supports healthy brain oxygenation, blood flow, immune system defense, and cell membrane structure. In addition, it also nutritionally supports cell-to-cell communication which is crucial to healthy cognitive function.

The brain controls everything we do, see, say, hear, touch, taste, feel and think...all at the same time, Mental clarity, Memory capability, Cell-to-cell communication, Healthy blood flow, Brain oxygenation, Cell membrane structure and Immune system function etc.

The brain is the command center of the body. The brain has about 100 billion neurons that fire messages across trillions of microscopic gaps each moment of your life. It has more than 10 billion interlinked cells. It sends messages to, and receives stimulation from, all parts of the body and the brain operates while you're sleeping or awake. So, it's no wonder the brain is probably the most nutritionally demanding organ in the body. [24]

Memory loss is not inevitable. Many people believe that poor memory is a natural consequence of aging. However, if that were true, then why do we all know senior citizens who can still think as clearly as many younger people? And why are there senior citizens that are totally capable of living happy, healthy, independent lives? The answer is simple...significant memory loss is not necessarily a fundamental part of aging.

It keeps your brain functioning at its optimum level. Strong evidence suggests that those who take the most proactive stance on healthy nutrition typically enjoy greater physical and mental wellness. And therefore, many complementary alternative medical practitioners believe that supplement intervention with memory-specific nutrients; plus a healthy lifestyle, annual check-ups and regular physical and mental activities may support mental sharpness, speed, and flexibility well into the senior years.

Whereas, Citicoline is a naturally occurring nontoxic and well-tolerated drug that is an essential intermediate for the synthesis of phosphatidylcholine, a major constituent of the gray matter of brain tissue. Citicoline promotes brain metabolism by enhancing the synthesis of acetylcholine and restoring phospholipids content in the brain. Citicoline is a used in pharmacotherapy of brain insufficiency and some other neurological disorders, such as stroke, brain trauma, and Parkinson's disease. It can also cross blood-brain barrier and treats brain related disorders. It improves memory loss, concentration, learning ability, alertness, brain injury, Alzheimer's disease, headache, dizziness, and tinnitus, improves cognitive functions, glaucoma, Parkinson's disease, Vascular Dementia. 500 mg per day might be the optimum citicoline dose and it can go up to 2,000 mg. It was concluded that citicoline modestly improves memory and behavioral outcomes. Both the salts separately prescribed by physicians, cardiologists, dialectologists, neurologists and general physicians.

Piracetam influences neuronal and vascular functions and influences cognitive function without acting as a sedative or stimulant. it is therapeutically used for the treatment of nerve degeneration and to treat alcoholism , clotting, coagulation, vasospastic disorders alzheimer's and senile dementia ,depression and anxiety stroke, ischemia and symptoms ,dyspraxia and dysgraphia ,closed craniocerebral trauma Usual dose starts dose of 4.8 to 9.6 grams divided into three daily doses at 8 hours.[25]

MARKETED FORMULATION;

Following are the marketed formulations for citicoline and piracetam combination in fixed dose of Citicoline-500 mg + Piracetam-800 mg

Tablet Formulation	Manufacturer
Cicolin P	RPG Life Sciences Ltd
Strolin P	Torrent Pharmaceuticals Ltd.
Citico Plus	Cadila Pharmaceuticals Ltd.
Citistar PM	Lupin Laboratories Ltd.
Clinaxon P	Abbott Health Care (P) Ltd.
Somazina Plus	Elder Pharmaceuticals Pvt Ltd

Table 1: Marketed formulations of citicoline and piracetam combination in fixed dose of Citicoline-500 mg + Piracetam-800 mg

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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Conflict of Interest: None Declared

