

CDP CHOLINE (CITICOLINE = NICHOLIN) THERAPY ON SOME CASES OF CHILDREN WITH ORGANIC BRAIN SYNDROME

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ABSTRACT

CDP choline (citicoline) indicates a clear consciousness recovery, which is followed by a great improvement on EEG scheme, general behavior and the decrease of brain edema. These effects are particularly caused by the reformation of phospholipid metabolism disturbance as a result of brain dysfunction. We will be reporting the results of CDP choline therapy in four syndromes caused by head trauma, brain ischemia, encephalitis and autistic syndrome.

Keywords: CDP choline, children, organic brain syndrome

INTRODUCTION

Neuroscience is progressively discovering the secrets of how the brain operates and what it requires to function optimally. (Sadock BJ and Sadock VA, 2003) One of the principal areas of the scientific study has been the research on the membrane that surrounds the neuronal cell and the function of this membrane is to protect the cell, but it also entails the coordination of a high level of communication (Sadock BJ and Sadock VA, 2003).

It has become increasingly clear that phospholipids, the various fatty acid mineral molecules that comprise a significant portion of the membrane which plays key roles in maintaining brain cell efficiency. Phospholipids are the attendants at the entry gates into our neural cells helping to transport "substrates as fuel needed for healthy and efficient operation. Phospholipids help maintain and regulate cell membrane integrity, strength, permeability, elasticity and resistance to stress, among other function. Without sufficient nutrient to properly maintain phospholipids, we would not be able to think very well. (Getova D and Petkov V, 1990; Secades JJ and Frontera, 1995).

Since a clinical therapy has been introduced for the first time in 1963 up to now, hardly do we find any studies describing the effects of citidine diphosphate choline (CDP choline) or citicoline which is intramuscularly injected to children or teenagers with organic brain syndrome (Shimamoto K and Azamaki J, 1975).

More than 30 years of brain research has resulted in a convergen of knowledge about citicoline (cytidine-5-diphosphocholine = CDP choline), a naturally occurring precursor to one of the most important phospholipids, phosphatidylcholine. (Weiss GB, 1995). Phosphatidylcholine is thought to play a major role in neuron membrane structural function and in lipid turnover (utilization of fatty acids) and communication signaling. It also acts a neuroprotector Citicoline donates the components choline and cytidine, both of which are precursors to the synthesis of phosphatidylcholine, required to form, repair and even restore function to nerve cell membranes. Cytidine is involved in the synthesis of other phospholipids. Choline promotes the synthesis of acetylcholine, a neurotransmitter intimately associated with cognition (Weiss GB, 1995). As an information transmitting molecule, acetylcholine is necessary for proper memory function. (Alvarez XA et al, 1997).

CDP choline is an unique form of choline that readily passes through the blood brain barrier directly into brain tissue CDP choline has been found to be of value in studies on animals and humans (Levin HS, 1991; Shimamoto K and Azamaki J, 1975). CDP choline (citicoline) is approved as a drug in Europe and Japan for use in stroke, head trauma and other neurological disorders. (Calatayud Maldonado V et al, 1991; Djoenaidi, W et al, 1981; D'Orlando KJ and B W Sandage Jr, 1995, Levin H S, 1991; Sinforiani E et al, 1986), and it is presently being evaluated in phase II/III stroke trials in the United States. CDP choline may reduce central nervous system ischemic injury by stabilizing cell membranes and reducing free radical generation (Petkov VD et al, 1990). Citicoline has been found to support membrane integrity, enhance acetylcholine formation, and to contribute to such critical metabolic functions as nucleic acids (e.g RNA and DNA) and protein synthesis. In the brain, in addition to promoting phospholipid synthesis, citicoline

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also inhibits phospholipid degradation (Alvarez X A et al, 1997). Citicoline demonstrated a long lasting effect on cognition and behavior with improved activation levels and attention responsiveness. Citicoline enhances vascular function in the brain resulting in strengthened immune function which improves bioelectrical activity, all of which translated into cognitive benefits. (Calatayud Maldonado V et al, 1991). Schematically, citicoline's effect are vascular enfranchement, immune enhancement, bioelectrical enhancement, cognitive enhancement (Franco Maside A et al, 1994; Kuroda K et al, 1978; Petkov VD et al, 1990).

In amnesia induction protection citicoline was found to increase memory retention but piracetam did not do it (Alvarez X A et al, 1997; Mosharrof AH and Petkov VD, 1990). Citicoline induces bioelectrical changes in the brain (measured using a spectral electroencephalogram) showing increased alpha activity. (Franco Maside A et al, 1994). Researchers who have studied the effects of citicoline on electal activity, specifically regarding mapping and mental performance, have observed that it lights up certain maps of the brain: Areas of the brain found to be affected by citicoline include the cortex, hypothalamus and the purkinje cells of the cerebellum. (Kuroda K et al, 1978; Petkov VD et al, 1990).

Several clinical facts revealed some effective benefits of cytidine diphosphate choline (CDP choline) either injected intravenously or injected into the subarachnoid area on the spinal cord to recover the brain activity for the sufferers of head trauma, "apoplectic", and other brain dysfunction. Functioning clinically as to recover mental and somatic dysfunction, CDP choline has indicated a clear consciousness recovery, which is then followed by a great improvement as seen on EEG scheme, general behavior, and the decrease of brain edema. Therefore, such a therapy had reflected a very rapid recovery from the clinical symptoms (Chandra B, 1982; Shimamoto K and Azamaki J, 1975; Warsiki E, 1993). The effects of this therapy was particularly caused by the reformation of "phospholipid metabolism" disturbance as a result of brain defect or brain dysfunction.

Phospholipid is the most important substance of all lipid and one of their elements is lecithin. Lecithin is a very significant element of cell membrane composition, such as, plasma membrane, mitochondria, reticule endoplasm, and nuclear membrane that is particularly found in the myelin membrane of the nerve. (Getova D and Petkov V, 1990; Carcassonne M, 1997; Secades A and Frontera G, 1995; Shimamoto K and Azamaki J, 1975) Some lecithin defects can cause an extensive

decrease of cell metabolism. (Clark WM et al, 1997; Shimamoto K and Azamaki J, 1975)

Ozawa, Ischie et al. revealed that a brain defect, which is experimentally made, produces much less amount of phospholipid in the brain. It especially decreases the lecithin level. (Djoenaidi W et al, 1981; Shimamoto K and Azamaki J, 1975) CDP choline is yielded from the reaction between choline triphosphate (CTP) and phosphoryl choline. CDP choline constitutes a very important element to produce alpha lecithin, while "cytidine pathway" is very necessary for the process of lecithin biosynthesis in the brain. In other words, the choline source in the brain is very important to help a person suffering from endogenous synthesis deficiency in her or his brain by giving CDP choline to the brain defect. (D'Orlando KJ and B W Sandage Jr, 1995)

Studies on CDP choline have already been carried out by several writes, such as:

- "CVA" by Djoenaidi W and Hazama T.
- "Nontraumatic coma" by B. Chandra.
- "Children neurotraumatology" by Carcassonne.
- "Kontusio serebri" by Levin HS, Maldonado.

All the studies above revealed that there was a significant difference between the patients to whom CDP choline is given and those to whom placebo is given. That is to say, the therapy reflected different result after giving CDP choline and placebo to the patients. (Carcassonne M, 1997; Chandra B, 1982; Clark WM et al, 1997; Djoenaidi W et al, 1981; Levin HS, 1991).

In addition to that, Hazama T and Djoenaidi W reported the result of their study about "CVA" suffers. However, they recited that they did not find any significant different effects after they gave the patient intravenous injection of CDP choline either with a high dosage (1,000 milligram of citicoline) or with a low dosage (250 or 500 milligram of citicoline). (Clark WM et al, 1997; Weiss GB, 1995). According to Shimamoto B, B. Chandra and Djoenaidi W, CDP choline injection can cause several effects for the brain such as (Chandra B, 1982; Clark WM et al, 1997; Shimamoto K and Azamaki J, 1975; Weiss GB, 1995):

- increasing dopamine synthesis
- increasing lecithin synthesis in the brain
- decreasing serotonin level in hypothalamus and in the brain stem
- increasing glucose metabolism in the brain
- accelerating blood circulation in the brain.

After accomplishing our research on the effects of CDP choline injection given to the children with organic brain syndrome caused by infection, including measles, varicella, influenza, hemorrhagic fever, gastroenteritis and so forth (Weiss GB, 1995)., we next explored to

give CDP choline therapy to the children or teenagers with organic brain syndrome caused by head trauma, brain ischemia, autistic and the like.

We will be reporting the results of CDP choline therapy towards four children's cases as follows:

- 1 (one) child case with organic brain syndrome caused by head trauma.
- 1 (one) child case of brain ischemia caused by "cardiac arrest" during anesthetization before undergoing a tumor surgery underneath the tongue.
- 1 (one) child case of post-encephalitis caused by measles.
- 1 (one) child case with autistic syndrome.

CASE REPORTS

- I. A nine-year-old boy, third grader, a very polite and obedient student in his school, leader of the class, and having a good performance during the class, got an accident. When he was riding his bicycle on the street, a motorbike hit him. He was falling down. As a consequence, he got a brain concussion and was unconscious for three days. He had to stay in the hospital, in this case, in a surgery room for medical treatment for about one month. Then, the following month (a month after he returned home from hospital), his mother took him to an outpatient clinic of psychiatric department because he became easily to get angry, liked to throw away all the things he saw at home, whenever he found mistakes, even a small mistake. When he was in the outpatient clinic, he put his feet on the doctor's table and threw away everything on that table. Again, without any sensible reasons, the patient became easily hurt and liked to throw away all the things around him.

Then we decided to give him citicoline injection with the dosage of 250 milligram once a day which is intramuscularly injected for fifteen times. The mother was asked to take him back to the outpatient clinic for his routine checkup after finishing the fifteen times nicholin injection. During his first checkup in the outpatient clinic, (after finishing fifteen times nicholin injection), the mother explained that her child's condition was getting normal again. He was no more bad tempered nor shy after he got fifteen times nicholin injection. The patient also warned his mother not to tell anyone about his impolite behavior, just like putting his feet on the doctor's table. Moreover, he was able to answer all of the questions given by the doctor very fluently. In spite of his mental condition improvement, we decided to continue giving him

nicholin injection up to thirty times with the same way and dosage like before. During his second checkup in the outpatient clinic, the mother reported that the patient's behavior and intelligence as well as he had already been totally normal just like before he got sick. Therefore, the nicholin injection was no more given. So, it was given only fifteen times.

Patient diagnosis : organic brain syndrome (organic personality syndrome) caused by brain concussion.

- II. A five-year-old girl, Kindergarten student having a good performance at school, was hospitalized in a surgery room in order to get medical treatment before undergoing her tumor surgery underneath the tongue. Because of certain reasons, "cardiac arrest" happened during the anesthetization. As a consequence, the surgery was canceled. As soon as the patient got conscious, the patient behaved like a baby. She did not even recognize her mother. She was not able to sit nor to speak. Her senses of vision and hearing got worse. She was hospitalized in the anesthetic room and was given intravenous nicholin injection with the dosage of 250 milligram i.v. once per day for thirty times. After giving thirty times intravenous nicholin injection with the dosage of 250 milligram once per day, the team did not notice a satisfactory result of the therapy yet.

The patient's physical and mental conditions were still not getting better. In fact, the child still could not stand up although she already could sit and see as well. In spite of her ability to see, the patient still could not recognize her parents. Therefore, we decided to form a team of medical specialists including a pediatrician, an ophthalmologist, a specialist of ear, nose and throat, a neurologist, a psychiatrist, a medical rehabilitation specialist, a surgeon and an anesthetist. From the physical examination, the team found a very serious problem with her senses of vision and hearing, extremities paralysis, a problem with her expressive and receptive languages, EEG examination: an severe diffuse disorder. Since the examination result of her mental development phase was reflecting just like the mental development of a nine-month baby, the team decided to continue giving her intravenous nicholin injection with the dosage of 250 milligram i.v. once per day for sixty times. As a result, the child got a very satisfactory mental and physical progress.

She finally could see and hear very well. She could walk, run and speak very well too. She could even sing all the songs she ever learned before when she was in the Kindergarten, although she did not have any teachers or nurses to teach her in the hospital. At this moment, her mental development phase has already been about five years. During the therapy, the child was being treated in the Anesthetic Department of Dr. Soetomo Hospital.

Diagnosis : Organic mental disorder caused by brain ischemia (cardiac arrest)

Main Therapy: 250 milligram of intravenous nicholin injection once a day for ninety times.

Now : She was in third grade of Elementary School.

- III. A nine-year-old girl, third grader of Elementary School, suffering from measles living out of Surabaya, was taken to the hospital in Surabaya by her parents for she lost her unconsciousness (soporocomateous). She was hospitalized in the pediatric room of Dr. Soetomo Hospital in order to get an intensive medical treatment. According to the encephalitis diagnosis, the patient's condition was acute. The patient is our colleague's daughter, so we decided to form a team of medical specialists, including a neurologist, a medical rehabilitation specialist, a child psychiatrist, and a pediatrician. When the patient was said that she had recovered from the brain inflammation, she was still being unconscious.

Therefore, the team of medical specialists attempted to give her intravenous citicoline injection with the dosage of 250 i.v. milligram once a day for thirty times. Before citicoline was injected, EEG examination was previously done and it was severe diffuse disorder. After the citicoline was injected, the patient's consciousness became much better and after the citicoline was entirely injected (thirty times), the patient already gained her normal condition again.

Psychological Test : IQ = 87

EEG examination : normal

According to her mother, the patient is an adopted child, showing not so good performance in her school. Having recovered from her illness, she performed much better and became as intelligent as before.

Diagnosis : Encephalitis caused by measles.

Now she was in second grade of Senior High School.

- IV. A three-year-old boy was taken to the psychiatry department by his mother because he liked being alone, sitting in a dark places, and frequently walking around and around in the same way and direction. At his age of one and a half year, the patient could speak only four words (*becak* = pedicab, *bapak* = father, *cecak* = small house lizard and *tindak* = to go). At his age of two and a half, the mother once stopped breast-feeding him suddenly, he became really mad and hit his own head to the wall. It happened for about three months. Since then, the patient could speak only two words, that is ("*bapak*" = father and "*enggak*" = no) until he was three years old.

EEG examination : not very serious diffuse disorder that tends to be "Generalized epileptic pattern"

Diagnosis : Autistic syndrome

Methods of therapy:

* Speech therapy

* Drug : - Pimozide 1 X 0,5 milligram per day
- Intramuscular citicoline injection 100 milligram once per day for sixty times

The patient could speak fluently after he got sixty times citicoline injection but we continue giving him the injection up to eighty times. In 1998 he was eleven years old, in the fifth grade of Elementary School, with 7.5 point average in his report card.

Repeated EEG examination : normal

In 2003, he was in third grade of Senior High School.

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