

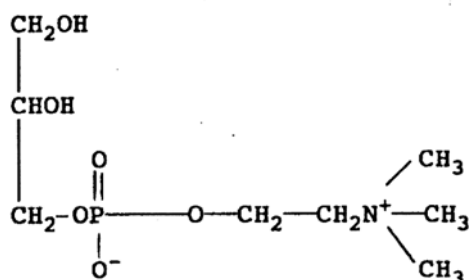
CLINICAL TRIAL SUMMARIES

GPC Injectable

GlyceroPhosphoCholine (GPC), Orthomolecular Nutrient

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Glycerophosphocholine or GPC (technically, glycerol[3]phosphocholine) is an orthomolecular nutrient present in all our cells and other life forms. This deceptively simple molecule has myriad functions in the body. Some of these are described below:

Osmotic protectant and metabolic stress regulator, reaching very high concentrations in the kidneys.

Unique water-phase phospholipid, energy-favored precursor to lipid-phase phospholipids that are cell membrane building blocks.

Structure-function synergy with DHA, a favored substrate for combination with this omega-3 fatty acid (docosahexaenoic acid) to make omega-3 phosphatidylcholine (PC-DHA) that helps build highly fluid cell

membranes. Such molecules are especially utilized by the most metabolically active tissues such as brain gray matter, retina, skeletal muscle, and spermatozoa.

Highly bioavailable by mouth, readily metabolized to the essential nutrient choline. Readily crosses the blood-brain barrier.

Ready precursor to acetylcholine (ACh). ACh is a key chemical transmitter both for the CNS and for the autonomic nervous system (sympathetic and parasympathetic systems). ACh is required to drive the neuromuscular junctions that regulate the skeletal (“twitch”) muscles as well as the smooth muscles and the myocardium.

Essential for male fertility. Prevalent in the mature semen. Maturing mammalian spermatozoa draw on GPC to make PC-DHA that fluidizes their cell membranes to enable adequate motility. Low semen GPC correlates with poor sperm motility. GPC may also be a source of energy for sperm capacitation effectuated in the female reproductive tract.

Important precursor for skeletal muscle sarcoplasmic reticulum. This membrane system is highly fluid and transports calcium at very high speed. Deficiency of GPC in skeletal myofibers may contribute to muscle dysfunction and clinical dystrophy, especially Duchenne Muscular Dystrophy.

Indications for GPC Injectable

- Stroke recovery
- Post-surgical encephalopathy
- Memory loss and other cognitive difficulties
- Personality deterioration, social withdrawal
- Growth hormone/anterior pituitary revitalization
- Craniocerebral injury (hematomas, contusions, concussions)

Product Form

GPC Injectable is supplied in a 20 cc multidose vial that delivers 500 mg ultrapure GPC per cc. The typical injection dose is 1000 mg given once

daily, preferably in the morning, and is extremely well tolerated. GPC Injectable is available exclusively from College Pharmacy in Colorado Springs, Colorado.

Human Trials with Injected GPC

A total of 15 published clinical trials and other human studies with injected GPC are reviewed herein. Whatever the route of administration, GPC acts rapidly and with no major adverse effects.

PHARMACOKINETICS IN HEALTHY SUBJECTS

De Moliner et al, 1993¹

This was a pharmacokinetic study of i.m., i.v., and oral dosing with GPC. Four healthy volunteer subjects aged 19-24 years received GPC 1000 mg by i.v., then subsequently by i.m., then by mouth, then received a placebo by mouth, in four separate sessions separated by one-week washouts. During each session blood was sampled periodically over 10 hours.

With i.v. administration of GPC, plasma total choline peaked at 5 minutes and returned to baseline by 4 hours. With i.m. administration, plasma total choline peaked at 0.5 hours and returned to baseline by 6 hours. With oral GPC, plasma total choline peaked at 3 hours, at a concentration slightly less than half that reached by i.m. administration. But with oral GPC the plasma total choline remained above baseline at 10 hours. The investigators concluded that i.v. and i.m. GPC both delivered virtually identical total plasma doses (AUC, Area Under the Curve), and that oral administration delivered about half this amount.

STROKE TRIALS

Stroke initiates localized and spreading cell destruction that involves cell membrane breakdown, phospholipid catabolism, and metabolic dysregulation. GPC is known to protect against all these adverse processes. Five trials were conducted with GPC, altogether involving a total 2,972 stroke victims. All the patients were started on GPC 10 days after their

stroke. The usual regimen was 1 month of intramuscular GPC (1,000 mg, once per day) followed by 5 months of oral intake (1,200 mg, taken between meals). GPC markedly improved the pace and extent of recovery. All aspects of memory, cognition, mood, word fluency, sociability, and overall clinical status were subject to improvement by this 6-month GPC regimen.

Consoli et al, 1993²

This study involved 172 patients aged 45-85 years, recruited from 20 centers distributed throughout Italy. All the patients had suffered cerebral ischemic attacks (stroke or TIA) within the previous 10 days. This could not be a placebo-controlled trial because the patients were too severely afflicted. After clinical examination was completed, the patients were evaluated by the Modified Mathew Scale for focal neurological deficits. Those with dementia, chronic neurological pathologies, or disabling psychiatric disorders, were excluded.

The Mathew Scale was developed by Mathew and collaborators in 1972 (Lancet ii, 1327-29) to more objectively assess the functional state of patients after stroke. The scoring is based on neurological examination (speech, cranial nerves, motor power, reflexes and sensation); and mental examination (levels of consciousness and orientation, performance), and scored from 0 (worst) to 100 (best).

In this trial, treatment proceeded in two phases. First, starting by day 10 following the event, GPC was given by injection to stem the deficits. After a month, GPC treatment was switched to oral supplementation for better patient compliance. In the first phase, the patients received GPC 1000 mg i.m. daily for 28 days. The second treatment phase was GPC 1200 mg by mouth (400 mg 3 times per day; 2 capsules at 8 am then 1 cap at 4 pm), for 5 more months. By completion of the first phase (week 4 of GPC i.m.), on the Modified Mathew Scale the percentage of patients who scored normal or had only mildly impaired performance-disability moved from 34% to 68%, with improvements in level of consciousness, space-time orientation, speech, facial paralysis, and motor capacity.

During the second phase of this trial (GPC oral, for 5 months), three assessment scales were used. On the MMSE (Mini Mental State Examination), which judges cognitive functions, there was significant improvement ($p < 0.01$). On the SCAG Scale (Sandoz Clinical Assessment Geriatric), there were significant improvements in cognitive dysfunction, interpersonal relations, affective disturbances (mood), apathy and isolation, and somatic disturbances ($p < 0.01$ in all cases). On the GDS (Global Deterioration Scale), only about 100 patients were assessed but there was a clear pattern of improvement. GPC was judged excellent or good by 79% of the patients, while 71% of the patients were judged similarly improved by their physicians. Tolerability was judged excellent or good by 98% of the patients, and at 99% by the clinicians. One patient dropped out due to persistent insomnia.

Aguglia et al, 1993³

This also was an Italian multicenter trial, and involved 425 patients aged 45-85 years, recruited from 44 centers distributed throughout the country. All the patients had suffered cerebral ischemic attacks (stroke, TIA or acute cerebral ischemia) within the previous 10 days. It was another open trial, since the patients were too severely afflicted to be subjected to placebo treatment. Patients who scored 35 or below on the Mathew Scale were eligible for the trial, but not comatose patients or others not expected to live or judged unable to comply over the 6-month tenure of the trial.

As per the typical GPC stroke protocol, treatment proceeded in two phases, first giving GPC 1000 mg i.m. in-hospital daily for 28 days then switching to GPC 1200 mg by mouth for 5 more months (400 mg 3 times per day). Upon completion of the GPC i.m. phase, on the Mathew Scale there was an average improvement of 18.56% (11.5 points, from 62.02 to 73.53). This was statistically highly significant over baseline. A 20% or greater improvement was seen in 168 (39.5%) of the patients. By this measure the more impaired, older patients (65-85 years) were more likely to benefit than were the younger patients 45-64 years).

During the second phase, after discharge (GPC oral, for 5 months), evaluation was based on clinical interviews and three assessment scales were

used. On the MMSE for cognitive functions, there was a 12.3% improvement (from 21.53 at week 5 to 24.19 at 6 months). A 20% or greater improvement was seen in 126 patients (29.7%). On the Global Deterioration Scale, there was an average 20.2% improvement. A 20% or greater improvement was seen in 180 patients (42.3%). On the Crichton Geriatric Rating Scale, which assesses mainly behavioral functioning, there was an average 19.5% improvement. A 20% or greater improvement was seen in 166 patients (39.1%).

The researchers judged GPC to be effective and well tolerated both parenterally and orally. They noted that despite the many drugs with which GPC was co-administered, no single GPC-drug interaction was observed clinically or in laboratory tests. GPC's benefits were consistent, and spanned functional state as well as performance and social behavior. With the possible exception of the MMSE (at 12.3%), the degrees of improvement from GPC on the various scales were well above that expected from a placebo, namely 12% in at least 20% of such patients.

Barbagallo Sangiorgi et al, 1994⁴

This study involved 2,044 patients aged 45-85 years, recruited from 176 centers in Italy. All had suffered cerebral ischemic attacks (stroke or TIA) within the previous 10 days. Most patients (87.1%) had concurrent diseases, mostly cardiovascular. Once again, this could not be a placebo-controlled trial because the patients were too severely afflicted. A minimal 35% degree of consciousness (35 on the Mathew Scale) was necessary for inclusion in the study. Patients were further classified into “more deteriorated” (Mathew 35-65) and “less deteriorated” (Mathew >65).

The usual neurological assessments and blood chemistries were done, and the patients received conventional treatment for stroke. As per the prevailing protocol, treatment was in two phases, the first phase being GPC 1000 mg i.m. daily for 28 days then the second phase being 1200 mg by mouth for 5 more months. After the first phase a high percentage (47%) of the patients moved from being more deteriorated to less deteriorated ($p < 0.001$). During the second phase, on the MMSE (cognitive functions) there was an average 15.7% increase as the 60% of patients with “abnormal

deterioration” at day 28 fell to 35% at 6 months. Using the Crichton Geriatric Rating Scale (behavioral), there was an average 25.8% improvement. The count of patients with severe deterioration fell from 9.8% at day 28 to 2 percent at 6 months; those with moderate deterioration, from 30.4% to 14.3%; and those with mild deterioration jumped from 59.8% to 83.7 percent. On the Global Deterioration Scale there was an average 25.9% improvement during the second phase.

At the end of the first phase of this trial (28 days) the investigators judged that 94% of the patients showed very good to moderate improvement. At 6 months, the end of the second phase, this fraction was still 95%, with clinically significant improvements in cognition, behavior, and overall condition. Of an original 2,056 treated patients, 14 (0.68%) withdrew due to adverse effects, their problems being mostly heartburn, nausea, or overexcitation

Gambi and Onofrj, 1994⁵

This was another open trial, conducted similarly to the foregoing trials. A total of 320 patients aged 40-85 years were recruited from 34 centers in Italy; all were suffering from mental deficits following cerebral ischemic attack. Again, there were the two phases: GPC 1000 mg i.m. once daily for 28 days, then 1200 mg by mouth for another 5 months. In the first phase, GPC significantly improved patients on the Mathew scale of consciousness by week 2 ($p<0.0001$). By the end of the second phase, at 6 months, there was highly significantly improvement of the patient population on the MMSE, on the SCAG, and on the Global Deterioration Scale (GDS).

The MMSE scores showed marked recovery of cognitive-memory functions by 6 months ($p<0.0001$). Similarly on the SCAG, the total scale and all the subscales—cognitive dysfunction, interpersonal relationships, affective disturbances, apathy/isolation, and somatic disturbances—were highly significantly improved between week 5 and 6 months ($p<0.0001$). The GDS scores on confusion and other dementia-like symptoms also markedly improved over the second phase, indicating an overall lessening of the severity of the mental decline ($p<0.0001$).

These physicians concurred that about 70% of the patients were “excellent” or “good” by the 6-month mark. GPC's tolerability was judged excellent or good in more than 90% of the patients, the main problem in the first phase being dizziness and in the second, stomach upset. They concluded that altogether, the cognitive and global clinical assessment scales showed a “large improvement” of the mental status of the patients. They praised “a considerable contraction” in the normal recovery times for stroke during the first 2 weeks of the first phase, also stating:

The marked resolution in 4 weeks of focal neurological deficits, particularly regarding space-time orientation, degree of consciousness, language, motor capacity and degree of invalidity...leads us to think that GPC is an optimum therapeutic choice...The changes recorded over the 5 months (of the second phase),,,represents an attainment of an acceptable quality of life for the patients. [Discussion]⁵

Tomasina et al, 1991⁶

This was a small open trial that followed the usual GPC stroke protocol. Eleven patients of average age 74 years received GPC 1000 mg i.m. once daily for 28 days, then 1200 mg by mouth daily for at least another 20 weeks. On various rating scales (Mathew, MMSE, SCAG, the Psychic Evaluation Scale) GPC significantly improved memory, anxiety, emotional lability, sociability, spatial orientation, and aspects of language; eye deviation; confusion, vigilance, and general mental sharpness. Two patients complained of a slight, transitory heartburn but did not withdraw from the trial. At 6 months the physicians judged 10/11 of the patients as excellent to fairly good, while 10/10 patients judged themselves as excellent to fairly good.

Thus, in 5 open trials completed by 2,972 patients variously afflicted by stroke, a regimen of 1 month of intramuscular GPC followed by 5 months of oral intake produced clinically remarkable improvement. Given that the patients were generally too ill to be given placebos, the degrees of clinical improvement over the 6-month trial durations were well above those predictable as placebo effects. Many patients showed accelerated

improvement within the first 2-4 weeks then continued to improve over the remaining 5 months. The physicians as well as the patients uniformly judged GPC to be very well tolerated.

COGNITIVE DECLINE

Cognitive decline resulting from vascular or Alzheimer's dementia, to “senile organic brain syndrome,” or from injury, involves neural circuit breakdown linked to oxidative and/or inflammatory processes and perhaps also to excitotoxic damage. Similar to stroke, the cell-level degeneration features cell membrane breakdown, phospholipid catabolism, and metabolic dysregulation. In 5 trials that involved a total of 388 patients, GPC given i.m. improved memory and other cognitive functions, interpersonal relationships, and word fluency. The regimen was 1 gram of intramuscular GPC (1,000 mg), once per day, for 3 months.

Vascular dementia patients were recruited into a series of 3 randomized, controlled trials, very similarly designed but carried out by 3 different groups in Italy. GPC i.m. was compared against citicoline (CDP-choline) i.m. GPC proved superior in all three trials.

Muratorio et al, 1992⁷

Multi-infarct (vascular) dementia, mild to moderate. Ninety-seven (97) patients were randomized to receive GPC 1000 mg i.m. or citicoline 1000 mg i.m., once daily for 90 days/3 months. Seventy-three (73) patients completed the 90- day follow-up period. CDP-choline significantly improved only word fluency, which benefit persisted into followup. GPC significantly improved ALL the measures of dementia, including memory (by 30 days) and other cognition measures, behavior, and disability. GPC's benefits all persisted into followup.

Frattola et al, 1991⁸

Multi-infarct (vascular) dementia, mild to moderate. A total 117 patients were randomized to receive GPC 1000 mg i.m. or citicoline 1000 mg i.m., once daily for 90 days/3 months. Both agents significantly improved memory, other cognition, and behavior, but GPC had earlier onset and was significantly more beneficial for memory, other cognitive functions, interpersonal relationships, and word fluency.

DiPerri et al, 1991⁹

Multi-infarct (vascular) dementia, mild to moderate. A total 115 patients were randomized to receive GPC 1000 mg i.m. or citicoline 1000 mg i.m. once daily in the morning for 90 days/3 months. Both nutrients significantly improved memory, mood, and behavior, but GPC proved significantly more beneficial over citicoline.

Schettini et al, 1993¹⁰

Probable Alzheimer's patients, double-blind trial. Nineteen (19) patients older than 60 years received GPC 1000 mg i.m. or a placebo once daily for 3 months (12 weeks). In addition to neuropsychological assessment, blood hormone levels—cortisol, ACTH, prolactin, growth hormone (GH)—were measured, at baseline and at 3 months.

The SCAG total score was significantly improved by GPC over the placebo, at 3 months; the subscales for cognitive disturbances and apathy/isolation also showed significant improvement. Interestingly, GPC significantly reduced plasma cortisol and ACTH levels over the placebo, but not prolactin. Growth hormone levels were significantly increased over baseline at 12 weeks; the placebo group had fallen below baseline.

Brain SPECT scanning (single-photon emission computed tomography) was conducted on 9 of the GPC and 9 of the placebo patients, also at baseline and at the 3-month mark. None of those on placebo showed an increase; rather, on average there was a decrease. Of the GPC patients 4/9 showed a $\geq 7\%$ increase in cerebral blood flow, over the entire cerebrum including the temporal-parietal zones.

The investigators that GPC could be useful for down-regulating HPA (hypothalamic pituitary adrenal axis) over-activation, which can contribute to neurodegenerative progression. The increase in GH was clinically meaningful.

Abbati et al, 1991¹¹

Forty (40) patients with “senile organic brain syndrome” were randomized to receive GPC 1000 mg i.m. or oxiracetam 1000 mg i.m., once daily at 8

am for 12 weeks/3 months. Both agents improved cognition, behavior, and reaction time. GPC showed significant improvement after 6 weeks, with further improvement at weeks 8 and 12. GPC lagged behind oxiracetam for the first 8 weeks, then caught up with oxiracetam and maintained its benefits significantly longer, 8 weeks after treatment was discontinued.

The encouraging outcomes of these trials with intramuscular GPC are reminiscent of others conducted on cognitive decline patients with GPC given by mouth. However, increase of serum growth hormone levels after giving only GPC by mouth has not yet been unequivocally demonstrated.

GROWTH HORMONE POTENTIATION

It is well established that blood growth hormone levels undergo dramatic decline as humans enter middle age, and that such decline is linked to aging. Attempts to revitalize fading functions by injecting GH itself tend to generate undesirable effects. An orthomolecular - metabolic intervention that successfully elevates GH via endogenous release would have great value for healthy aging. Intravenous GPC is such an intervention.

Several papers were published on this subject by one research group. Three protocols were followed, each utilizing intravenous GPC to potentiate GHRH stimulation of GH release.

Ceda et al, 1994¹²

This paper was the last published, and conveniently includes all 3 protocols. The subjects for each protocol were drawn from a pool of healthy young (n=8) and elderly (n=17) volunteers. Blood GH was measured following an i.v. injection of 1 microgram per kilogram of GHRH (Growth Hormone Releasing Hormone) that was preceded by injection of GPC or placebo.

In one protocol, GPC at either 2000 mg or 1000 mg was injected i.v., followed immediately by GHRH injection, into young and old subjects. GPC significantly enhanced GH release into the blood, with the 1000 mg dose seemingly as effective as the 2000 mg dose.

In a second protocol, GHRH was injected i.v. twice into elderly subjects, with a 120 minute interval between the 2 GHRH injections. Fifteen (15) minutes before the second GHRH bolus was given, GPC 2000 mg was injected i.v. This GPC shot significantly potentiated GH responsiveness to the second GHRH stimulation, as compared against GHRH given twice by itself.

The third protocol was a subacute one, and used elderly subjects. Every day for 15 days, first GPC 2000 mg was injected i.v., then came the standard GHRH injection. Normally these repeated daily injections of GHRH would blunt the GH secretory response. In this experiment, GPC blocked the blunting effect of repeated GHRH.

These protocols establish the efficacy of intravenous GPC to potentiate GH release. They also gibe with the above-described double-blind study by Schettini et al, in which 3 months of daily i.m. GPC injections raised blood GH levels. Altogether, these findings indicate GPC acutely potentiates GHRH, the physiologic GH releaser from the hypothalamus; and that GPC might prove useful to facilitate endogenous GH availability on an ongoing daily basis.

BRAIN INJURY

In this category three studies were located. One involved heart surgery survivors. Two reported on patients with subdural hematomas, cerebral contusions, or concussions. Of these latter, one successfully employed GPC i.v. in very high doses for comatose patients.

Auteri et al, 1993¹³

Some 50-60% of cardiac bypass and other open heart surgery survivors emerge from the anesthesia with amnesic or other cognitive difficulties. Some recover within days or weeks, others suffer permanent disablement. In addition to memory difficulties, mental fatigue is common and also changes in affect and personality, rather resembling a diffuse post-surgical encephalopathy. This small trial was conducted double-blind, and successfully utilized GPC both i.v AND i.m.

Post-cardiac bypass patients were studied. Twenty (20) patients aged 45-65 years were randomized into two groups. Cognitive functions were tested using the Wechsler Memory Scale, the Benton Visual Retention Test, and the Wechsler Adult Intelligence Scale. One group received GPC, 1000 mg i.v. once daily for 4 weeks, then 1000 mg i.m. once daily for another 5 months, to total 6 months of treatment. The other group received a placebo.

Significant changes were found on the Wechsler Memory Scale. Already by the 4 week timepoint, GPC had benefited memory significantly over the placebo. By the 24 week/6 month final timepoint, there was a striking superiority of GPC compared to the placebo. While the patients on placebo continued to exhibit decline throughout the trial, at 6 months the GPC patients had reversed their decline and returned almost to baseline.

Mandat et al, 2003¹⁴

The trauma of craniocerebral injury (CCI) produces metabolic disturbances that are likely to include mixed ischemic-hypoxic, oxidative, inflammatory, and excitotoxic cascades. This study evaluated the risk and efficacy of GPC (“choline alfoscerate,” CA) in 23 CCI patients. Of these, 8 had acute hematoma with multiple hemorrhagic foci, of which 7 were operated on with extreme urgency and one later. Another 6 had cerebral contusion with multiple hemorrhagic foci, and 9 patients had concussions. At admission, 11 patients were assessed at 8 points on the ATS (Adult Trauma Scale); 4 scored at 9 on the ATS; and 8 scored at 11 on the ATS.

The approach was 2-phase, similar to the protocol for stroke management. Patients were evaluated on the ATS or the Karnofsky Scale at admission, then at days 1, 2, 5, and 14 following the injury, and at 2 and 3 months following the injury. GPC was administered at 1000 mg per day i.m. for 14 days, then at 800 mg per day by mouth for 28 days.

After 3 months, 96% of the patients had improved. Fourteen patients (61%, including ATS admission scores of 9 and 11) were independent and professionally active, at 90-100% on the Karnofsky Scale. Five (22%) were independent but did not work (70-80% Karnofsky); three (13%) required

permanent care (40-60% Karnofsky). No complications from GPC were observed.

This paper is notable both for the degree of difficulty of the cases treated, and for the low oral GPC intake that was used: 800 mg per day, one-third lower than the oral doses used in the other trials. That 96% (22 of 23) of these seriously injured patients could respond over the 3-month period to only 2 weeks of i.m. GPC and such a low oral intake, suggests the simple GPC molecule may be very strong medicine.

Madorskyi S and Amcheslavskiy V, 1994 (abstract report only)¹⁵

These clinicians, working at the famed Burdenko Neurosurgical Institute in Moscow, studied the effects of GPC on the dynamics of consciousness recovery and brain bioelectrical activity in comatose patients with head injury (HI). Investigation was carried out in 25 comatose patients on day 3-14 after HI. GPC was given intravenously at 150 mg/kg (equivalent to 10.5 grams of GPC per 154-lb patient), and the results compared against a control group. Judging from the Glasgow Coma Scale, GPC effected earlier emergence from the Coma State (on the 3rd day on average), less speech impairment, and more effective regress of focal neurological symptoms than for controls. Using EEG spectral power mapping and coherence analyses, the researchers concluded GPC tended to normalize cerebral blood flow, decrease vascular resistance, and improve spontaneous brain bioelectrical activity along with restoration of circuits. This trial, unfortunately available only in abstract form, seems to suggest that very high doses of GPC are safe for injection, and that GPC can be effective even for patients who are comatose following head injury.

Closing Remarks

In all the 15 trials reviewed above, injected GPC proved effective and safe to take, with minor adverse effects that rarely forced withdrawal from the studies, even with fragile patient populations. The most common regimen was daily intramuscular injection of 1,000 mg GPC, usually in the morning, for 30 days; then oral supplementation with 1200 mg GPC daily for another

5 months. GPC as a dietary supplement is best taken in a single dose before breakfast, and/or between breakfast and lunch in 2 divided doses.

GPC is compatible with drugs in common use by the elderly,¹³ but being a cholinergic agent may not be fully compatible with high doses of cholinergic drugs. As an injectable, GPC has remarkable potential for stroke management and for accelerating recovery from virtually any brain injury as well as for the other indications listed in a foregoing section.

Injectable GPC as provided is highly stable and easily buffered in the syringe. The multidose vials provided by College Pharmacy supply GPC 500 mg/cc, total 20 cc. For i.m. administration, simply draw 2 cc (1000 mg GPC) and administer as is. For i.v. use, mix 2 cc (1000 mg GPC) into 50-100 ml normal saline, lactated Ringer, or dextrose 5% in water, then run it in over 15-30 minutes.

GPC has been safely used by i.m. injection in the many clinical studies just described. GPC was administered by i.v. injection into the postsurgical, elderly heart patients at 1000 mg per day for 4 weeks; into young and old healthy subjects for the growth hormone studies, at up to 2000 mg per day for 15 days; and supposedly into comatose, brain-injured patients at 150 mg per kilogram body weight for at least 3 days.

Although GPC is relatively stable to oxidation, no information is available on giving GPC by injection along with oxidants like ozone and peroxide. Also, since GPC raises blood choline it is relatively contraindicated with anticholinergic drugs. Still, for patients being maintained on such protocols additional benefits from GPC could be anticipated. Here I suggest titrating the GPC orally (high-quality 300-mg hardgel capsules are available from College Pharmacy), increasing the dose from 300 mg per day to 600 mg per day then 1200 mg per day over 3-4 weeks.

GPC's very high degree of safety is undoubtedly related to its being an orthomolecule, and additionally a major physiological antitoxin for the kidney, liver, brain and probably all the organs.

GPC's diverse applications for cognitive decline and stroke were earlier reviewed in 2001 by the veteran researcher Lucilla Parnetti.¹⁶ This review covers additional trials that were not yet available at that time. GPC's diverse applications as a dietary supplement are further documented in my more extensive review article that accompanies this one.^{17,18} This latter review more specifically explores GPC's clinical applications as a dietary supplement, the putative mechanisms by which the GPC orthomolecule can have such remarkable efficacy and safety, and other aspects of GPC's uniqueness for active living and healthy aging.¹⁸

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