Insulin Potentiation Therapy: Reckless Human Experimentation or Bona Fide Medicine?

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Insulin potentiation therapy (IPT) is an unproven adjunct to cancer chemotherapy that uses insulin followed by sub-therapeutic doses of chemotherapy or other medications well below their proven efficacy. Theoretically, IPT boosts the pharmacologic efficacy of medications by increasing uptake into the cells of the body. During IPT enough insulin is given to induce hypoglycemic shock (perspiration, tachycardia, and coma). Ironically, IPT is touted as a gentle cancer treatment without the side effects of traditional chemotherapy (alopecia, mucositis) because lower doses are used yet clinical evidence is lacking to support this claim. Consequently, due to the lack of literature support, IPT lies in the realm of dangerous human experimentation and should not be considered as an “off-label use” of insulin in chemotherapy.

Dr. Donato Perez Garcia, Sr. is credited with the discovery of IPT in 1926, which he practiced for 43 years until his death in 1971.1 Dr. Garcia, who suffered from a gastrointestinal problem which rendered him rather malnourished, first became interested in insulin for nutritional purposes. Eventually, Dr. Garcia decided to inject himself intravenously with insulin before meals to stimulate the appetite. From his experiences with self-administration of insulin, he hypothesized that insulin enhanced transport of nutrients across the walls of the digestive system and into the tissues and cells of the body and that it would enhance the permeability of cells to drugs as well.

To test his hypothesis, Dr. Garcia decided to experiment with dogs to see if insulin would enhance the absorption of syphilis treatments into the central nervous system (CNS). He formed two groups of dogs and injected them with mercury and arsenic salts (the current treatment for neurosyphilis at the time), after one of the groups had received insulin. Upon an autopsy of the canines he concluded that the concentration of the mercury and arsenic salts was significantly increased in the CNS of the dogs who received insulin concurrently, compared to dogs who did not receive insulin, from this he surmised that,

“It is quite possible that a particular activity of the cells for glucose sets in at that very same time, so that if any substance is added to the glucose which is injected into the blood, such a substance can penetrate more readily than when the hormonal disequilibrium created by the insulin does not exist.”2

The results of his experiment later inspired him to use IPT to treat syphilis, ulcers, polio and cancer in humans.

One of the few American physicians to integrate IPT into their practice was Dr. Steven G. Ayre, a Chicago based family doctor who first learned of IPT in 1975. Fascinated by the unique approach of IPT, he eventually contacted the son of the founder of IPT, Dr. Donato Perez Garcia y Bellon. Ultimately, Dr. Ayre did not begin to use IPT until 1997 which is when he felt that there was enough evidence to support its use in clinical practice. However even Dr. Ayre comments on IPT’s lack of validity, “while individual anecdotal case reports over forty years suggest that this treatment may be
effective, there is at present no collection of scientific data to validate Insulin Potentiation Therapy as a treatment for malignant neoplastic diseases, or cancer.\(^3\)

Lately IPT has become more popular after a famous actress, Suzanne Somers, developed breast cancer to which she opted to receive alternative and traditional treatment therapies including IPT. Instead of receiving traditional chemotherapy IPT was used in addition to an adjunctive medication derived from mistletoe called Iscador. Despite, her use of alternative treatments, she did compromise by receiving traditional radiation treatments and urged viewers on Larry King that these alternative treatments may not be for everyone.\(^4\)

Considering breast cancer ranks second to lung cancer as the cause of cancer death in American women, it is not surprising that afflicted patients may be willing to forego traditional chemotherapy for alternative unproven therapies such as IPT. Perhaps equally as disheartening is the fact that 1 in 33 women will die from breast cancer, primarily women greater than 40 years of age. However, the prognosis of a breast cancer diagnosis is based on multiple factors, namely, tumor size, lymph node involvement and metastasis to distant organs. Small tumor size, no lymph node involvement or metastasis suggests a better prognosis and higher 5-year relative survival rate than a larger tumor with nodal involvement and active metastasis.

The treatment of breast cancer is based on many factors including disease stage, menopausal status, steroid receptor status (estrogen or progesterone receptor positive), performance status and co-morbid conditions. More specifically, a woman that has a small breast tumor with no lymph node involvement or metastasis may benefit from surgery or radiation or the anti-estrogen drug tamoxifen. On the other hand, as the size of the tumor increases, the need for surgery becomes more urgent in addition to chemotherapy including neo-adjuvant medications such as anti-estrogens and aromatase inhibitors (inhibit conversion of testosterone to estrogen).

Tamoxifen is classified as a selective estrogen receptor modulator (SERM). What this means is that tamoxifen is able to antagonize estrogen receptors present in breast tissue, inhibiting growth of breast tissue, but conversely may act as an agonist at other bodily organs including bone. Yet adverse effects of the drug may preclude its use in certain patient populations, for example, uterine malignancies, stroke and pulmonary embolism are all possible following administration of tamoxifen. Further, a selective estrogen receptor modulator may not be indicated in breast tumors that lack estrogen receptors.

Traditional chemotherapeutic regimens for breast cancer may involve anthracyclines (adriamycin), taxanes (paclitaxel), vinca alkaloids (vinorelbine) or a phosphoramide mustard such as cyclophosphamide. Despite their efficacy and clinical experience against breast tumors these agents are usually associated with poor tolerability and a high degree of toxicity. For example, adriamycin, an anthracycline which is usually first line in the treatment of breast cancer, is a potent vesicant meaning that it cause can damage to soft tissues including necrosis, infection, severe pain and loss of mobility upon extravasation. In addition, the anthracyclines are associated with dose-related cardiotoxicity which limits the total amount of drug a patient may receive. In
general, chemotherapy may induce allergies and hypersensitivity which require additional pharmacologic treatment.

Cyclophosphamide, a phosphoramidate mustard, can be used to treat acute lymphocytic leukemia, Burkitt’s lymphoma, and breast cancer, among others. The drug was discovered based on similar principles to IPT, for example, it was observed that cancer cells contain much more phosphamidases than non-malignant cells. Similarly, cancer cells also contain a greater number of insulin receptors as well. Therefore, it was believed that cyclophosphamide would act as a substrate to these phosphamidases which would ultimately lead to demise of cancer cells due to the destruction of cellular DNA from a toxic intermediate, a mechanism similar to that of mustard gas which is why cyclophosphamide is classified as a mustard. However, the actual mechanism was totally different than predicted, instead liver enzymes initiated the metabolic process that lead to formation of the active component of the drug. The bioactivation of cyclophosphamide to its active moiety, also results in the formation of acrolein which can produce hemorrhagic cystitis, a potentially fatal condition that is characterized by excessive bleeding from the bladder. With regards to IPT, the actual mechanism in cancer may be completely different than previously proposed so additional research is warranted.

On the other hand, the procedure for a patient receiving IPT is relatively simple, yet it is not standardized or published in any clinical journals. Prior to receiving IPT the patient is to fast overnight to achieve a fasting blood glucose upon initiation of therapy. An enema or cathartic may be used to “detoxify” the body. Following “detoxification” of the body an intravenous continuous infusion of insulin is established at a dosage range of 0.1-0.4 Units per kilogram of body weight. The insulin most commonly used and preferred in this procedure is Humalog because of its rapid onset of action and predictable pharmacokinetics, although Humulin (regular insulin) may be given as well. Within minutes of insulin administration, any oral or intramuscular medications may be given as needed.

Shortly after insulin administration, symptoms of hypoglycemia may occur and it is believed that more profound results can be attained with deeper and more long lasting hypoglycemia. Symptoms of hypoglycemia may be recognized by tachycardia, diaphoresis (profuse sweating) and decreased cognition. During the hypoglycemic phase, blood sugar drops to 55-60 mg/dL, well below the normal range of 80-100 mg/dL. How long the patient remains in the hypoglycemic phase is primarily left to the discretion of the clinician as the patient approaches the “therapeutic moment” where intravenous medications are absorbed most effectively.

Following the intravenous administration of the patients’ treatment medications, an intravenous hypertonic glucose solution is given along with a sweet beverage such as Gatorade or fruit juice to restore the patient’s blood sugar to normal values. After the procedure patients may be prescribed oral medications to take until the next treatment. Additional IPT treatments if needed may be given anytime from two days to two months.

The influence of patient co-morbid conditions must be taken into account in IPT therapy. For example, hypertensive patient’s medications are suspended on the day of IPT and they receive a cathartic at a lower dosage. Insulin is given as a fixed dose (10 Units) via the intramuscular route instead of weight based dosing as in normotensive
individuals. Signs and symptoms of headache are also closely monitored in the hypertensive patient during IPT to avoid hypertensive urgency or emergency. Patients who present with chronic renal insufficiency also receive a fixed dose of insulin and a dose reduction by 5 Units upon subsequent IPT treatments if signs and symptoms of hypoglycemia are excessive.

Perhaps the most disturbing aspect of IPT is the fact that many of the proposed mechanisms of action lack supportive evidence and are unlikely to be studied due to the risks involved. For example, increased serum levels of insulin in addition to leptin, triglycerides and a reduced level of HDL-C (“good cholesterol”) may actually increase the risk of breast cancer. In a study by Matheiu et al, the insulin receptor content was measured in relation to the clinical outcome in 584 tumor specimens from patients with node-negative breast cancer. It was found that the greater the number of insulin receptors on the tissue biopsy correlated with a greater 5-year disease-free survival rate. The results from this study would appear to suggest that insulin receptor content is a major predictor of disease-free survival.

Apparently, the central tenet of IPT is that insulin interacts with insulin receptors to potentiate chemotherapy. Insulin receptors are present in every cell in the human body and even more so in malignant cells. Other mechanisms of action of insulin, in addition to promoting cellular uptake of glucose, involve gene regulation and tissue growth.

Insulin potentiation therapy is purported to increase the permeability of the malignant tissues and cells. The rationale for this mechanism in IPT is that lower doses of chemotherapy may be utilized to effectively eliminate malignant cells. Because of the lower doses of chemotherapy used, side effects associated with traditional chemotherapy such as mucositis, alopecia and nausea may be mitigated or eliminated. Evidence for this mechanism is inferred from a phenomenon called “receptor-mediated endocytosis” where cells can be stimulated via a receptor to engulf an extracellular substance.

Because insulin causes cellular uptake of glucose, an osmotic gradient theory is proposed. Osmosis is diffusion of a substance that occurs across a selectively permeable biological membrane. In terms of IPT, increased uptake of glucose would create an osmotic gradient, diffusion of glucose across a selectively permeable membrane from an area of higher concentration (extracellular space) to an area of lower concentration (intracellular space) enhancing the absorption of chemotherapeutic medications.

Detoxification of the body is also postulated mechanism. The rationale is that because of the proposed enhanced absorption of exogenous substances, toxins would be mobilized better and eliminated from the body more effectively. Because the liver has a role in clearing the body of toxins it was hypothesized by Dr. Garcia that patients with poor liver function will not do well with IPT.

An immunomodulatory effect is also attributed to IPT. The rationale for this mechanism is that since insulin and insulin like growth factor receptors are present on cells of the immune system and the subjective observations that patients who receive treatment with IPT experience rapid healing of wounds and infections. Therefore it is deduced that IPT stimulates the components of the immune system and converts these components into a healthier less reactive one.
Nevertheless, a placebo effect cannot be ruled out. The doctor-patient relationship in relation to the placebo effect is well established and may lead to observable physiological changes such as increased blood pressure, attributable to the “white coat phenomenon”. In fact, Dr. Garcia has noted that IPT appears to work better in patients with a positive attitude. Further, Dr. Garcia is reluctant to treat patients with IPT if they don’t have a positive attitude.

One of the most obvious flaws to IPT is that it does not work as well in diabetic patients. The mechanism for this is thought to be from down-regulation of insulin receptors. The protocol for the initiation of IPT involves administration of regular and NPH or intermediate-acting insulin to diabetic patients to stabilize glucose levels prior to treatment. Dosing of insulin is performed according to ideal body weight and oral anti-hyperglycemics are withheld during treatment with IPT.

It is also believed that IPT allows for increased transport of medications across the blood-brain barrier. The rationale for this mechanism in IPT is that CNS diseases that may involve chronic infections such as neurosyphilis may be eliminated more effectively with IPT due to enhanced penetration of the blood-brain barrier by antibiotic medications given concurrently with insulin. Dr. Perez Garcia experimented with IPT in humans and animals suffering from neurosyphilis, however recent clinical data demonstrating this effect is lacking.

Another proposed mechanism for IPT is that it induces metabolic changes in tumor cells. More specifically, metabolism induced by IPT would allow the tumor cells to become more sensitive to the cytotoxic effects of the chemotherapeutic regimen. For example, it is reported that IPT increases the toxicity of methotrexate by a factor of 10,000 in a laboratory setting, yet clinical evidence is equivocal regarding this matter.

In addition, while evidence seems to show that malignant cells may contain elevated insulin receptor content, this is a favorable prognosis. For instance, insulin may interact with other receptors such as the insulin like growth factor receptor, which is also over-expressed in malignant conditions. Papa et al. evaluated the significance of insulin like growth factor receptor content in breast cancer specimens by dividing them into high-risk and low-risk specimens. Specimens were considered high-risk if they were positive for estrogen and progesterone receptors among other factors, low-risk specimens were negative for estrogen and progesterone receptors. The study showed that the concentrations of insulin like growth factor receptors in malignant breast tumors are nearly 10-fold higher compared to healthy breast tissue and that the concentration of the receptors in low-risk specimens was significantly higher than those in the high-risk specimens.

Insulin may also have a regulatory role in breast cancer cell growth. Milazzo et al. utilized three human breast cancer cell lines and one nonmalignant cell line to compare insulin receptor content and functionality in response to insulin and a monoclonal antibody to the insulin like growth factor receptor. Insulin receptors were found to be more concentrated in the breast cancer cell lines and the action of insulin had a more pronounced effect in breast cancer cell lines causing incorporation of the nucleic acid thymidine, a component of DNA, into the malignant cells.
Another mechanism of action of IPT is increased formation of blood vessels (angiogenesis). The angiogenic property of insulin was recently observed in a recent study by Lee et al. in which human umbilical vein endothelial cells exposed to insulin like growth factor stimulated migration and differentiation of the cells leading to neovascularization. The authors conclude that insulin like growth factor may have a role in tumor cell growth.

An increase in angiogenesis would seem to be detrimental in cancer survival. An actively growing tumor needs nutrients supplied from blood vessels in order to grow, therefore angiogenesis plays a key role in survival of the tumor. In fact, inhibition of angiogenesis has become the new target of pharmaceutical companies wishing to create more innovative medications in the treatment of cancer. Bevacizumab (Avastin) is one example of an inhibitor of angiogenesis. Bevacizumab is an antibody that is highly specific inhibitor of vascular endothelial growth factor (VEGF). Clinical studies appear to be very promising regarding the use of this drug in cancer.

Based on clinical data it appears that exogenous administration of insulin may actually increase the risk of breast cancer because higher insulin serum levels have been correlated with an increased risk of breast cancer. Also, because an over-expression of insulin receptors may suggest a better prognosis, response to IPT implies a favorable prognosis due to overactive insulin receptors and the ability of insulin to regulate tumor cell growth. Therefore the women most likely to respond to IPT may have a greater chance of survival prior to IPT. Conversely, exogenous insulin administration may promote increased tumor cell growth from increased formation of blood vessels that may assist in “feeding the tumor”.

Until recently there has never been a clinical trials assessing the efficacy of IPT in malignant conditions, in fact the only clinical trial to date was a small prospective, randomized clinical trial performed in Uruguay. The purpose of the study was to evaluate the use of insulin as a potentiator of methotrexate in 30 women with metastatic breast cancer resistant to Adriamycin, fluorouracil and cyclophosphamide. Patients were randomized to three groups of 10 patients and received two 21-day courses of insulin and methotrexate, methotrexate alone, and insulin alone with the size of the tumor being measured before and after treatment. Patients in the methotrexate + insulin group or the insulin alone group received insulin intravenously at a dose of 0.3 Units per kilogram every other day. Methotrexate was given twenty minutes after the insulin in a 15-minute intravenous infusion at a sub-therapeutic dose (2.5 mg/m² in 50 ml of 30% glucose). However, in the event that hypoglycemia occurred after insulin administration, the methotrexate/glucose infusion was given immediately in addition to an oral glucose supplement, although the mean blood glucose level for all patients who received insulin was 456 mg/dL (range 376-520 mg/dL).

There are many issues with this study that negatively impact its external validity. Although the study was randomized and prospective in design, the low number of patients enrolled (n=30) would dramatically decrease the power of the study to determine statistical significance. In addition, the lack of blinding and choice of study medications was not optimal. Methotrexate, Adriamycin, fluorouracil, or cyclophosphamide as monotherapy is not recommended by any evidence-based treatment guidelines. Further, no staging of breast tumors or definition of treatment resistance was given. Due to the
lack of tumor staging and blinding it is difficult to assess the patients’ likelihood of survival or whether the observed treatment effect of the insulin + methotrexate is due to the hawthorne effect where the expectations of the patients may cause them to show improvement on a treatment regimen that is not optimal.

Due to its lack of mainstream acceptance training for a clinician wishing to practice IPT is not standardized. Nurses may attend an IPT training session if they desire to do so. The IPT training workshops are two days in length and have several requirements. First, the student must present two letters of recommendation from physicians who have been previously trained in IPT and practice in good standing, second the student must be approved by the president of the ethics committee. Third, the student has to present copies of their medical diploma, license and curriculum vitae and fill out a registration form. Finally, after completion of IPT training the physician should get a free listing on GetIPT.com, which is free for the first three months and requires an annual fee thereafter.\(^1\)

Regarding the role of IPT in practice today, it is often described as an “off label” use of insulin. The FDA requirements for off label use of a pharmaceutical product are as follows:

“Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgment. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects. Use of a marketed product in this manner when the intent is the "practice of medicine" does not require the submission of an Investigational New Drug Application (IND), Investigational Device Exemption (IDE) or review by an Institutional Review Board (IRB). However, the institution at which the product will be used may, under its own authority, require IRB review or other institutional oversight.”\(^1\)

Due to the lack of literature support for IPT, use of insulin for the potentiation of chemotherapeutic regimens is arguable, yet because the FDA regulates interstate commerce, regulation of IPT in the clinical setting will most likely be managed by institutional review boards. Therefore, while regulation by institutional review boards may keep IPT out of mainstream practice it is unlikely to ban the practice altogether.

The ethical issue here involves the fact that two different treatment approaches may be utilized, traditional chemotherapy or unproven IPT. Practitioners’ moral values may play a role in deciding which treatment route to take when deciding which ethical issue is most important. Beneficence may be the primary issue for physicians who decide to use either treatment approach. Using traditional proven chemotherapeutic regimens is the most commonly accepted practice, however using IPT or other alternative approaches to cancer chemotherapy has been touted as “real medicine”. For example, websites of physicians who practice IPT may try to rationalize the lack of FDA approval by making the claim that IPT would not be profitable to pharmaceutical companies because it would cure patients of their cancer, using lower less expensive doses and precluding additional
pharmacological treatment. Patients with refractory end stage cancer may be persuaded on the basis of desperation as opposed to sound evidence-based practices to undergo IPT. Conversely, evidence for beneficence on behalf of mainstream society for end stage conditions such as cancer can be seen in the drug approval process. Cancer chemotherapeutic medications may be put on the “fast-track” for drug approval so that patients may receive the life-saving benefits of the drugs in a timely fashion.

Two different perspectives may guide the decision to undergo IPT. From a deontological perspective, practitioners have a moral obligation to do what is right. In this case, traditional chemotherapy would be the way to go because there is more evidence supporting its use. Arguably, using an unproven treatment such as IPT is intrinsically wrong in this scenario and if physicians hold fast to their moral obligations of using traditional approaches then the consequences of such actions should not matter. However, from a utilitarianistic approach, the physician should look at the consequences of their actions in choosing which therapeutic alternative to consider and ascribe to the one that is most pleasing to both parties.

Despite the practitioner’s moral obligations and values, the patient’s autonomy must also be taken into account. If a patient is diagnosed with advanced end stage cancer and given a poor prognosis they may not be as rational in their decision making regarding the safest most efficacious treatment as their illness progresses. With IPT this becomes evident as physicians who practice it will admit that there are no statistics to give patients regarding long-term benefits with IPT yet patients may still continue to seek treatment despite the risks. After all, increased insulin levels has been associated with an increased risk of breast cancer, not to mention IPT may not be as efficacious in patients whose tumors do not contain that many insulin receptors (decreased 5-year survival rate) compared to those with a preponderance of insulin receptors (increased 5-year survival rate).

Another caveat to the use of IPT is the ability of insulin to induce angiogenesis, or the formation of new blood vessels, a mechanism that could be detrimental in malignant conditions. Therefore, it is difficult to classify IPT as an “off label” use of insulin because, such a use should be based on sound clinical evidence. Yet with evidence lacking regarding the long term safety and efficacy of IPT it becomes challenging for the physician to be well informed regarding the use of insulin in this setting. Nevertheless, patient autonomy should take precedence over all other ethical issues since their condition may be severe in many cases with a poor prognosis, well and informed decisions may not mean as much to the patient. Therefore, if IPT is to become a commonly accepted practice outside of the realm of reckless human experimentation it is imperative that well controlled clinical trials be performed. Anecdotal evidence from personal observations and case reports are not enough to support the proposed mechanisms for IPT, since additional research is needed from well designed, prospective, randomized, double-blind trials. Once these trials have been performed clinical guidelines may be established and the level of evidence rated accordingly to justify IPT as bona fide medicine.
References

1. http://www.iptq.com