Malshe et al., J Clin Exp Oncol 2016, 5:1
http://dx.doi.org/10.4172/2324-9110.1000150

Journal of Clinical & Experimental Oncology

Research Article

A SCITECHNOL JOURNAL

Hydrogen ion/Proton Dynamics: A Possible Therapeutic Approach in Malignancy Treatment

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Abstract

Background: Current research is towards proton dynamics across the cell membrane with a view to make intra-cellular space acidic. Different proton migration inhibitors are being tried, need for developing appropriate transporter with lesser side effects is being felt. These efforts have ignored realising acid-base variations and variant pH leading to impaired glycolysis rate.

Aim: Use of proton rich chemical like hydrochloric acid would rebalance acid-base proportion and bring pH back into accepted range avoiding malignant cell formation. Normalising glycolysis rate would obviate need of developing anti-porter inhibitor compounds.

Design: Hypothesizing; malignancy developed following imbalance between acid-base proportions of intra and extra cellular environment. Proton dynamics via use of proton rich chemical like hydrochloric acid rebalances and bring pH back in the prescribed range, avoiding formation of a cancerous cell.

Method: Hypothesis based on available published work.

Results: Hydrochloric acid restores acid-base proportions, increases oxygen contents of RBCs, CTLs besides acidifying cytosolic environment thus bringing about apoptosis of a malignant cell.

Conclusion: Malignancy is pH dependent. Increasing intracellular alkalinity is the beginning of cancerous development. Adequate availability of proton rich chemical like HCl is essential in maintaining acid-base balance and alkaline pH throughout in the prescribed range, thus avoiding formation of malignancy.

Keywords

Anti-porter inhibitor; Proton dynamics; Extra cellular environment

Introduction

Cancer cases have been increasing the world over in spite of efforts of several research organisations. The rampant growth of this deadly disease could be attributed to life style changes. Several scientists in large number of research organisations are engaged in discovering a suitable anticancer molecule that can arrest the spread of this deadly disease. In this regard, any new approach, even if unusual, should be made known to research fraternity. In this respect, a rather unconventional but seemingly acceptable aetiology and the suitable treatment is presented. Two physicians namely Dr Fergusson and Dr Guy practicing in America in early 20th century came out with very thought provoking findings. Fergusson [1] experimented with various drugs and chemicals like bismuth, mercury, arsenic, quinine, insulin. He also experimented method like cupping, bleeding, hot and cold water, diathermy etc. to see their effect on phagocytosis. Though they have immediate effect on cellular system, however, such reaction depends on everybody's response. Fergusson was anxious to find out such a chemical which would produce cellular response but would not develop toxicity. Once he was treating patients wounded by shrapnel, when he observed that after giving injection of salicylate, the recovery was found to be quick but it was accompanied by toxicity. However after listening to a lecture of Dr. Granvile Hanes ('Introduction by Henry Pleasants, Reprints of Medical World's Three Years of HCl Therapy' available at Books and Pamphlets tab in www.arthritistrust.org) in 1927, he became curious to experiment this technique of using hydrochloric acid. In this regard he injected hydrochloric acid to himself and found increase in poly-nuclear leucocytes but without developing any toxicity. He attributed this effect to hydrochloric acid which is a naturally secreting inorganic acid. In this regard, a paper by Dr S.M. Alter [1] demonstrated that "diabetes, cancer and many other infections are accompanied by acid-base variations on the alkaline side. He stressed that it is necessary to look for such a chemical which will both stimulate glandular and cellular forces and modify excess alkalinity. Such a chemical which would satisfy all requirements is hydrochloric acid". Dr. Guy [2] another contemporary physician concluded that growth and productivity of soil depends on influence of both potassium and hydrochloric acid. He contemplated that same principles must be operating also in nourishment in human beings. Further he stated that lymph is the most important fluid in circulation in the body. Any stasis developed in its flow would have serious and deep seated effects on every cell. Dr. Guy referred to Prof. Keen's letter, addressed to Dr Sampson Handley [2] of Middlesex Hospital pertaining to cancerous development. In which Handley stated that "lymph stasis is the greatest physiological factor that lays foundation of cancer. Papilloma or papillary adenoma is the characteristic product of lymphatic obstruction then we are getting nearer to conclusion that all cancers are the result of lymphatic obstruction". In the same context and during the same period another physician Dr Wiley Meye [2] of New York expressed that "exact pH measurement revealed that malignancy is always associated with high degree of alkalosis and alkalosis precedes malignancy. There can be alkalosis without malignancy but there cannot be malignancy without alkalosis. More virulent the malignancy stronger must be the alkalosis". Guy further quoted that deficiency or excess of certain minerals is bound to have effect on pH, while chemical imbalance is found in cancerous conditions. During same period, some research Foundations were working under Dr Ellice MacDonald, University of Pennsylvania on the thinking that cancer has definite relationship with pH of blood plasma. Guy [2] concluded that anaemia, metabolic disturbances and formation of malignant cell occur due to changes in hydrogen concentration of lymph. Such changes develop blockages in lymph flow tending to diseases. On studying the lymph of large number of carcinoma patients he found higher hydrogen concentrations in lymph than in normal ones. However giving potassium salts along

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Received: October 24, 2015 **Accepted:** January 11, 2016 **Published:** January 18, 2016

doi:http://dx.doi.org/10.4172/2324-9110.1000150

with hydrochloric acid, patients made remarkable improvement and their hydrogen concentration became normal. This salt is essential for nourishment, while its shortage creates pathological disturbances. It is also necessary for secretion of hydrochloric acid whose adequacy helps digestion. Guy further formulated combinations[1]of acid solution and prescribed to patients. It was noticed during their study that use of hydrochloric acid was found to be toxicity free. Its use did not diminish its clinical potency which remained same throughout the treatment. Oxygen content of RBC was increased while combining power of CO_2 decreased and Leucocytes and phagocytes were increased. These and few more physicians from other States and other countries tried this HCl therapy on number of cancer patients with good results. Another contribution came from an Australian surgeon, Dr. Smalpage [3] practising in Melbourne in the middle of 20th century. While analysing urine and blood samples of cancer patients, he observed complete absence of chlorides and phosphates with excess of carbonates in urine specimen. He also observed that deficiency of both chlorides and phosphates but appreciable presence of carbonates and deficient red cell oxy-haemoglobin in blood samples of proven cancer patients. He propounded a theory as to how a cancer cell originates. Subsequently he prescribed both hydrochloric acid and phosphoric acid to such patients. Contributions of these physician-researchers remained ignored, unnoticed and unattended. Even at present also it appears un-recognised. Though this work was carried out quite long time back, still its approach and the school of thinking deserve a second look.

Present situation

Presently, attention is being drawn to the concept of 'proton dynamics', where efforts are concentrated on developing of proton inhibitors. Such an inhibitor would prevent proton from migrating into extracellular space. This migration makes intracellular environment alkaline. In this respect an "International Society for Proton Dynamics" has been formed in 2010. The objective of this society is to focus on aspects of pH and Dynamics of proton. Such efforts would lay emphasis on acidity and proton dynamics in cancer patients. And exactly for this purpose such a substance is required which would provide ample of protons in the extracellular space and create proton gradient. This would prevent proton migration into extracellular space. Such a situation would make intracellular environment acidic leading to apoptosis. In this regard it is hypothesized that a nontoxic chemical like hydrochloric acid providing enough protons is required. There are some incidences when hydrochloric acid [4-7] was used for therapeutic purpose. At present, efforts are being continued to develop anticancer molecules for destroying cancerous cells without developing toxicity.

Hypothesis

It is hypothesized that acid-base i.e. pH variations, thus developing alkalosis is the root cause of developing malignancy. A chemical such as hydrochloric acid for normalising and bringing back pH within accepted range is necessary. Such a measure appears as an appropriate means of making a patient free of malignancy. Making up of chloride and potassium deficiency is essential for secretion of adequate amount of hydrochloric acid. Thus maintenance of pH in the normal range by using hydrochloric acid is hypothesized to be the proper measure in remaining free of malignancy. This indicates that malignancy is a function of pH.

Basis for hypothesis

Dr. Smalpage [3] observed absence of chlorides in urine, while its noticeable decrease in blood samples. He further noticed excessive presence of carbonates in urine and blood samples of cancer patients. Such an anomaly makes one to look back into causes as to why such abnormality has developed. Adequate availability of hydrochloric acid is essential for digestion of food. While its inadequacy results in indigestion of food. This situation leads to formation of unwanted acids like lactic acid, carbonic acid and uric acid etc. Yamagata [8] has indicated that though lactic acid is produced in higher amount due to glycolysis, it is not the only source of acidity. This group hypothesized that carbonic acid, produced from CO_2 plays a major role in making tumour environment acidic. It has also been concluded by Gabriel Helmilinger [9] and others that CO_2 production may significantly acidify the interstitial environment of solid tumours. Presence of such undesirable acids leads to development of diseases. Since all the chemical reactions do take place at exact pH, deficiency in HCl production and its inadequate availability disturbs the acid-base balance. It affects the glycolysis process which results in higher formation of lactic acid. This situation develops into un-real acidity i.e., developing 'Pseudo-acidosis'. Use of bicarbonate as reported in research papers does not seem to be an appropriate measure. Such a measure adds to the sodium and carbon dioxide load. Rather, employment of hydrochloric acid balances the disturbed pH, while proper digestion takes place. This situation does not allow formation of undesired acids. Thus non availability of chloride and potassium ions in the oxyntic cell leads to non or lesser secretion of hydrochloric acid. This appears to be the origin and the cause of developing malignancy.

Discussion

Cardone et al. [10] have mentioned in their paper ' that 'Both in vitro cell-culture studies and in situ tumour, spectroscopic studies utilising the 31P isotope have reported that tumour cells have alkaline intracellular pH (pHi) value (7.12-7.65 compared with 6.99-7.20 in normal tissues and acidic interstitial extracellular pH (pHe) values (6.2-6.9 compared with 7.3-7.4)' [11-13]. This shows that extracellular atmosphere of the tumour is more acidic than that in intracellular environment. As and when tumour produces H^+ ions then for its survival the anti-porter system in the cell membrane comes into action. This time cell membrane accepts Na^+ in exchange of H^+ ion thus making intracellular atmosphere alkaline. Presently efforts are directed to develop a molecule for inhibiting this migration of H^+ ions. As the migration of H^+ is prohibited then intracellular atmosphere remains acidic. In such a situation apoptosis would occur. Ferdia Gallaghar et al. [14] demonstrated the use of Nuclear Polarisation Technique in mouse tumour model for finding pH. Such imaging technique can be used in clinics for diagnosis and prognosis and for treatment. However clinical data is not available. Tumour possesses property of higher [11] formation of lactic acid due to increased glycolysis as indicated by Karin Fischer. As noticed by Erecinska [12] any increase in hydrogen ions reduces lactic-acid formation while its decrease enhances lactate formation. This indicates and supports that formation of hydrochloric acid has an impact on lactic acid formation. This situation leads to conclude that higher the formation of hydrochloric acid, lower would be the glycolysis and lower would be the formation of lactic acid. In other words, it can be concluded that higher the pH, lower is the formation hydrochloric acid when glycolysis rate is increased and higher formation of lactic acid takes place. Eventually higher lactate is formed. This situation results in greater possibility of developing malignancy. Any change in pH affects the availability of H^+ ions and

doi:http://dx.doi.org/10.4172/2324-9110.1000150

also formation of lactic acid. This helps to conclude that both glycolysis rate and formation of lactic acid are pH dependent and a function of pH. Regulation of pH is very crucial for tumour survival which produces higher amount H^+ ions. Such tumours should have higher [13] activity for H transportation than normal cells. With the knowledge of accurate pH as shown by Gallaghar [14] it is possible to predict prognosis and advise treatment. Ferdia Gallaghar and others has shown that Nuclear Polarisation Technique can be utilised in clinics for pH estimation. Tumour cells have acidic environment due to higher formation of lactic acid. However cells have to drive H^+ ion out in the extra-cellular space in exchange of Na^+ ion in the intra-cellular space. This situation maintains alkaline intra-cellular environment which is necessary for cell's survival. Intra-cellular alkalinity continues to increase. Such increase is due to continuous incoming of sodium ions in exchange of H^+ ions. Such exchange continues to widen the gap of pH between intra and extracellular environment. This forms the early step in neoplastic progression [15]. Stephan J Ruskin [16] confirmed that activation of NHE-1 and resulting in thereby cellular alkalinisation is a key mechanism in oncogenic transformation. He further reported that this is necessary for development and maintenance of transformed phenotype. Tendency of the tumour cell of maintaining alkalinity by driving H^+ ion out in the extracellular environment needs to be curbed. It amounts to curbing the operation of anti-porter mechanism present in the cell membrane. Under such a situation, H^+ ion would remain back in the intracellular space and that apoptosis would take place. This situation helps in avoiding malignancy. In this regard inhibition of proton movement or proton dynamics [17] is significant in prevention, development and transformation of normal cell into malignant cell. Non availability of adequate amount of hydrochloric acid results in increasing the glycolysis rate. Karin and Hoffmann reported that as tumour formation increases, glycolysis mechanism also increases leading to higher and higher formation of lactic acid. This process leads to reduction in formation of human cytotoxic T lymphocytes even up to 95%. Cytotoxic activity also simultaneously reduces by 50%. The reducing number of T lymphocytes affects their cytotoxic ability. Lactic acid being a weak acid does not provide enough hydrogen ions on dissociation which hydrochloric acid does. This concludes that lactic acid production helps the formation of tumour. However providing abundant protons through addition of hydrochloric acid would help increase apoptosis mechanism. Fergusson reported considerable increase in leucocyte count with definite increase in polynuclear percentage after injecting hydrochloric acid to himself, as reported earlier. It is necessary that acidity due to availability of hydrochloric acid needs to be increased. While acidity due to formation of undesired acid like lactic acid etc. and becoming pseudo-acidic should be curbed. Such situation would also prevent from being malignant. It is therefore essential to normalise the glycolysis mechanism by employing a suitable chemical so that intra and extra cellular alkalinity status would be achieved and that there would be no necessity for developing anti-porter inhibitor. Otto Warburg (Wikipedia) [18] stated that prime cause of cancer is the replacement of respiration of oxygen by fermentation of sugar. Normal body cells meet their energy needs by respiration of oxygen while cancer cells do so by fermentation. Naturally higher oxygen intake would prevent cells from becoming malignant. An intravenous injection of hydrochloric acid of proper dilution within short time increases oxygen content of red blood cells and decreases combining power of carbon dioxide, as reported by Dr. Roth. This school of thinking satisfies Otto Warburg hypothesis. Electrolyte particularly potassium [19] and acid-base deficiencies are noticed in leukemic patients. Potassium deficiency affects hydrochloric acid secretion. These deficiencies form stasis in normal blood and lymph flow. This is probably the hidden cause of developing leukemia as explained under. Supplementing potassium externally in the form of mineral salts along with hydrochloric acid is hypothesized to correct the so far interrupted hydrochloric acid secretion, and thereby leukemic conditions. Severe alkalosis followed by malignancy is almost certain in cancer patients. Smalpage explained as under as to how and why such condition arises. Various sodium compounds besides sodium chloride are consumed in food or medicine. These include sodium benzoate, sodium glutamate; sodium bi carbonate, sodium alginate; sodium iodide, sodium ascorbate and many more are consumed. These compounds are further hydrolysed in stomach forming soda. This soda formed needs be neutralised. In this effort, it gets combined initially with easily available chloride or phosphate. However due to excessive consumption of various sodium compounds other than sodium chloride, ions like chloride and phosphate in course of time are not available adequately. This situation affects neutralisation of soda formed. In the absence of these two acidic radicals, soda has to combines with CO_2 and forms carbonate. That is why Smalpage found excess carbonate in both urine and blood of cancer patients while chlorides and phosphates were either absent or deficiently present. Presence of excess carbonate in blood may be treated as a precancerous condition. As and when obstruction or stasis takes place, this carbonate gets hydrolysed thus forming soda but without having any protective radicals such as chloride, phosphate or carbonate for neutralisation. This being an exothermic reaction, heat liberated starts destroying tissues by burning, or ulceration or fibrosis or inflammation. This again develops stasis and continues to destruct tissues till body endeavours by certain means to prevent burning and destruction. In this attempt soda combines with lactic acid formed due to increased glycolysis as explained earlier and forms lactate. This process continues over and over again as increased glycolysis rate produces more lactic acid continuously thus forming cancerous cells. It may be inferred that higher formation of lactate should be viewed as an indication of malignancy. Normally one is not likely to be easily exposed to X-rays as well as energetic gamma radiations very often. Therefore more probable cause of developing malignancy could be pH variations and the heat liberated in the cell due to chemical reaction. Intracellular alkalinity continues to increase as long as increasing glycolysis mechanism is in force. Formation of sodium lactate in increasing amount may be treated as sign of developing malignancy. Lactate on hydrolysis forms soda. This soda formed being a strong base changes the pH of cytoplasm and nucleoplasm on the alkaline side. Purschke et al. [20] reported that protein degradation and DNA damage occur due to heat exposure of cells. In the present paper, heat is shown liberated due to chemical reaction taking place within both cell and nucleus. Heat thus liberated in the reaction is diffused to both the medium like cytoplasm and nucleoplasm. This heat is expected to shrink both cytoplasm and nucleoplasm. It amounts to shrinking of both cell and nucleus. Cell volume shrinkage has been reported by Bortner and Cidlowski [21].

The heat liberated damages the nucleus and eventually nucleolus and the species within such as chromosomes and DNA i.e. genes as also damages RNA and affects protein synthesis. The shrunken cell and the nucleus in the situation distorts DNA molecule. In the situation, environment in the cell and the nucleus is alkaline. This alkalinity is expected to reduce the solubility of solutes present in cytoplasm and nuleoplasm. Under this situation colloidal dispersion is formed wherein particles of solute assume larger size. Possibly

such bigger particles are unable to pass through nuclear and cell membrane. Under such situation presumably their passage clogs the nuclear and cell membrane. This situation causes another hindrance. Now the situation in the cell is as follows:- Contains damaged and distorted DNA, degraded proteins, alkaline environment of both nucleoplasm and cytoplasm, increased temperature of cell and nucleus, solute particles with larger size and possibly nuclear and cell membrane clogged. In this whole disrupted situation as the genetic code is damaged, the distorted signalling system bypasses the information transfer mechanism. Genes expresses differently and in the situation cells forget to die and continue to grow and proliferate, forming tumour. The principle factor which possibly affects the cell and the nucleoplasm is variation in acid-base i.e. pH on the alkaline side. However as and when such anomaly occurs in hematopoietic cell, then, it results in developing leukemic conditions. There are three major buffer systems operating in the body fluids such as bicarbonate, phosphate and protein buffer system in addition to few more [22]. In bicarbonate system concentration of CO_2 and HCO_3 is not much. In phosphate buffer system, even its operating at maximum capacity; concentration of phosphate in extracellular fluid is only $1/12^{th}$ as compared to bicarbonate buffer system. This results in reducing buffering capacity of phosphate buffer system as compared to bicarbonate buffer system. While bicarbonate and hydrogen ions take several hours to diffuse through membrane. This slowness delays the buffering capacity of protein to buffer acid-base variations in extracellular environment for a long time. This system is not therefore effective in view of time taken by hydrogen ions to buffer extracellular fluids. In the present paper soda formation has been shown to form and liberate heat also. Soda is a strong alkali, which dissociate to a greater extent. Additionally soda formation is continuous. In view of the short comings of buffer systems as mentioned here, existing buffer systems do not operate effectively to maintain pH within range. While continuous soda formation tilts the pH balance on alkaline side. Destruction of cancer cells by inhibiting proton migration and thereby acidifying intracellular environment is an interesting mechanism for initiation of apoptosis. However maintaining acid-base balance in the prescribed range throughout appears preferable, easier and simpler to avoid malignancy. In this regard, knowing pH accurately and then employing proper chemical treatment as introduced here is desirable. Providing protons through the use of hydrochloric acid and/ or combinations of mineral chlorides with hydrochloric acid appears to be inexpensive and definite way of restoring pH back to normal and avoid being malignant. This indicates the anti-proliferative [23] property of hydrochloric acid. Summing up, it is concluded that malignancy is pH dependent. Variation in pH beyond the accepted range on the alkaline side is the beginning of mal-functioning of body's mechanism. This situation leads to diseases like malignancy. Use of hydrochloric acid would restore pH and would correct the body mechanism back to normal state thus avoiding being malignant. In this regard it is hypothesized that use of hydrochloric acid would be an additional weapon in the armoury to fight this deadly disease.

Conclusion

It is hypothesized that malignancy occurs as a result of insufficient availability of hydrochloric acid due to inadequate availability of chloride and potassium ions in the oxyntic cell. This situation results in reduced secretion of hydrochloric acid. It further leads to formation of higher pH and thereby increasing glycolysis rate, producing higher amount of lactic acid. In such circumstances anti-porter mechanism present in cell membrane initiates its operation when intracellular hydrogen ion is driven out in to extracellular space in exchange of sodium ion. This makes the intracellular environment alkaline and extracellular one acidic. This situation is congenial for developing malignancy. Briefly speaking, acid-base imbalance leading to increasing intracellular alkalinity widens the pH difference between intra and extra cellular environmental pH. This results in pH variation and increasing higher glycolysis rate. Thus, this situation forms higher lactic acid, which is hypothesized as a cause of developing malignancy. This indicates that malignancy is a function of pH. Higher levels of lactic acid may be viewed as a beginning of cancerous development. Heat developed due to exothermic reactions shrinks both the cell and nucleus volume thus distorting the nucleolus and the DNA structure. It is also possible that solubility of nucleolus contents decreases. In this situation colloidal particles are formed which clog the nuclear membrane. This situation again put forth another obstruction. Distorted DNA sends distorted messages. Such differently expressed messages bypass the apoptosis mechanism which results in abnormal growth of cells. However pH variation in of hematopoietic cell on the alkaline side is believed to develop leukemic condition. Injecting hydrochloric acid and making up its deficiency, balances the pH, normalises the glycolysis rate and prevent over-formation of lactic acid. As such pH in both intra and extracellular space would be made alkaline. Such a condition would prevent cell from becoming malignant. Hydrochloric acid acts as a leucocyte stimulant and increase poly-nuclear proportion besides itself being non- toxic. It increases immune response and cytotoxic activity of T lymphocytes. It is therefore concluded that intra and extra-cellular pH needs be alkaline. However higher pH i.e. higher intracellular alkalinity should be regarded as possibility of developing malignancy. Maintenance of acid-base balance and subsequently pH in the prescribed range is hypothesized as one of the ways to avoid cancerous development. In this regard use of hydrochloric acid appears necessary in remaining away from developing malignancy. In view of this proposed hypothesis and explanation thereof, it is necessary that more work like finding pH through use of imaging technique, clinical trials, dosage, side effects etc. be carried out with an intention of bringing results in the use of therapeutics without any delay.

Dosages as prescribed by Dr. Guy are given below. Besides this, figures of dosages and any other additional information is not available.

Liq. Potass. Arsenitis (Fowler's)…πλ xv, Tr. Ferri chloride...f3iss, Sol. Potass. Chloride (10 %)...f3iij

Sol. Acid hydrochlor (3 %) ……adf3j

Combination 2:- Sol. Potass arsen (Fowler's)……f3j, Tr.ferr chloride ...f3V, Sol potass chloride (10 %), Sol potass sulphads (10 %)….aaf3j, Sol acidi HCl (2 %)……adf3iIv

Combination 3 Revised:- Liq potas. Arsenitis……I/00, Sol potas. chloridi ($i0^0$J)…8/00, Sol potas sulphates (i0 %)…16/00, Sol acidi hydrochlorici dil ……q.s.ad30/00. And few more combinations used.

These quantities of dosages cannot be interpreted further.

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