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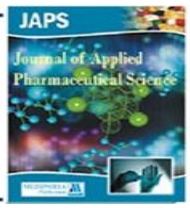

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Phenytoin-Folate Interactions: How Far is Safe Folate Supplementation in Phenytoin Treated Epileptic Patients?

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ABSTRACT

Chronic administration of phenytoin has been associated to have a number of adverse effects. Falling serum folate levels is one such most often reported adverse drug sequelae of long term phenytoin usage. Folates administered at pharmacological doses, on the other hand, have been blamed for a decrease in the serum concentration of phenytoin, severe enough to precipitate seizures. This review substantiated with references from various studies focuses on the folic acid-phenytoin interaction and discusses the feasibility of using folate supplements to avoid such inadvertent drug sequelae in epileptic patients kept on chronic treatment with phenytoin.

Keywords: Phenytoin, anti-convulsant, folate metabolism, seizures.

INTRODUCTION

Epilepsy is described as a chronic neurological disorder characterized by recurrent seizures of cerebral origin, presenting with episodes of sensory, motor or autonomic phenomenon with or without loss of consciousness (Sridharan, 2002). A recent meta-analysis of published and unpublished studies puts an overall prevalence rate of epilepsy in India at 5.59 per 1,000 populations (Sridharan, 1999). Despite the tremendous advances in the management of epilepsy, phenytoin still remains the drug of choice (Scheinfeld, 2003; Hassessian, 2003) however; the long term administration of phenytoin has been seen to lead to a number of adverse effects (Hassell, 2000, Ciancio, 1972). Falling serum folic acid levels is one such most commonly reported adverse drug sequela of long term usage of phenytoin (Brunet, 1996). While the details of these interactions remain obscure, several potential mechanisms have been proposed as explanations. One of the first hypotheses suggested that phenytoin increased the pH of the small intestine inhibiting the intestinal conjugase activity impairing the intestinal absorption of folates by the anti-convulsant drugs. Other hypotheses include direct competition between folate and phenytoin for uptake sites, inhibition of folate inter-converting enzymes by phenytoin, increased catabolism of folates by phenytoin induction of folate catabolic enzymes and inhibition of central appetite centers by phenytoin decreasing food intake and thereby leading to decreased tissue folate concentrations.

Folates administered at pharmacological doses, on the other hand, have been blamed for a decrease in the serum concentration of phenytoin, possibly due to direct competition between folate and phenytoin for uptake sites, severe enough to precipitate seizures. Numerous studies conducted in the past have proposed different reasons for falling serum folate levels on long term administration of phenytoin (Majola, 2000; Reynolds, 1971, Sener, 2006; Linnebank, 2011). This review focuses on a concise overview of the mechanisms that have been proposed in the literature regarding the deficiency of folic acid seen and also, discusses the feasibility of using folate supplements to avoid such inadvertent drug sequelae in epileptic patients kept on chronic treatment with phenytoin while simultaneously preventing the precipitation of seizures.

Phenytoin Use and Folate Deficiency: A Brief Overview of the proposed Hypotheses

Phenytoin administered at therapeutic dosages has been shown to deplete plasma folate concentrations in humans (Pisciotta, 1982). This has been later confirmed in other studies as well. While the details of these interactions remain obscure, several potential mechanisms have been proposed as explanations. One of the first hypotheses suggested that phenytoin increased the pH of the small intestine inhibiting the intestinal conjugase activity (Hoffbrand, 1968) impairing the intestinal absorption of folates by the anti-convulsant drugs (Meynell, 1966, Dahlke, 1967). Eighty percent of the folates are present in the diet in the form of non-absorbable polyglutamates (Butterworth, 1963) which are deconjugated by the intestinal enzyme conjugase into absorbable monoglutamates during absorption (Rosenberg, 1967). The phenytoin-generated increase in gut pH was hypothesized to decrease the driving force of the proton pump which supplied the energy for at least one folate transporter in the gut (Schron, 1991). Other hypotheses that have been stated in the literature in this regard include direct competition between folate and phenytoin for uptake sites (Rosenberg, 1979), inhibition of folate inter-converting enzymes by phenytoin (Carl, 1983), increased catabolism of folates by phenytoin induction of folate catabolic enzymes (Chanarin, 1979) and inhibition of central appetite centers by phenytoin decreasing food intake and thereby leading to decreased tissue folate concentrations (Hoppner, 1989). The fact that anti-convulsant drugs are known to induce hepatic enzymes led to a further series of hypotheses. Richens and Waters suggested that folate deficiency in long term phenytoin users might arise due to induction of enzymes involved in folate metabolism. Maxwell et al proposed that folate deficiency in phenytoin users might be a result of an increase in the demand for the folate co-enzymes required either for the anti-convulsant drug hydroxylations or, for other hepatic enzymes induced by these drugs.

Phenytoin and Folate Interaction: A Review of Different Studies

In a study published in 1966 in the British Medical Journal by Malpas JS, Spray GH and Witts LJ (Malpas, 1966) on serum folic acid and vitamin B_{12} levels in anti-convulsant therapy, the results substantiated the earlier work of the association of megaloblastic anemia with anti-convulsant therapy as reported first by Mannheimer, Pakesch, Reimer and Vetter (1952). The finding of normal levels of vitamin B_{12} and the correction of anemia following folic acid therapy suggested the role of anti-convulsants on folic acid metabolism. Further evidence for this had been the demonstration of macrocytosis or low serum folic acid levels in about half the patients who had been on anti-convlsant drugs (Hawkins, 1958; Klipstein, 1964).

In another original report published in the British Medical Journal in 1967 by Wells DG and Casey HJ (Wells, 1967), low CSF folate levels were observed in treated epileptic patients which was found to be significantly different from that of a control group irrespective of whether the results were analyzed using a log-normal or a Gaussian distribution.

In another study detailed in the British Pharmacological Society conducted by Richens A and Waters AH (Richens, 1971) based on the acute effects of phenytoin on serum folate concentration, in the results, five of the six subjects showed a gradual fall in the concentration of serum folate during the 4 days of treatment and four subjects had developed a subnormal value by day 3. Six days after stopping the drug, serum folate returned almost to control levels, however, red cell folate concentrations were seen to fall only slightly .These findings suggested that the acute fall in the serum folate concentration was due largely to a disturbance in the folate metabolism caused by the administration of phenytoin, the exact mechanism, however, for this remained unexplained. It was proposed; however, that phenytoin might inhibit intestinal conjugase and thereby impair the absorption of polyglutamates.

In a study published in 1971 in the Journal of Neurology, Neurosurgery and Psychiatry based on folate metabolism in epileptic and psychiatric patients by Reynolds EH, Preece J and Johnson AL (Reynolds, 1971), significant lowering of serum folate and red cell folate levels was observed in epileptic patients with psychiatric illness, and a less significant fall in red cell folate levels was found in non-epileptic psychiatric patients. A significant correlation was found between serum and red cell folate values in control, epileptic, and non-epileptic patients. In the epileptic patients there was a significant association between low serum and red cell folate levels and the presence of psychiatric illness.

In a study published in 1972 in the British Medical Journal by Maxwell JD, Hunter John, Stewart DA, Ardeman Simon and Williams Roger (Maxwell, 1972) to find out the role of hepatic enzyme induction behind folate deficiency after anti-convulsant drugs, serum and red cell folate levels were found to be reduced in children with epilepsy attending a residential school. Also, the degree of folate deficiency was significantly related to increased hepatic microsomal enzyme activity as assessed from increased urinary excretion of D-glucaric acid and also, correlated with the daily dose of anti-convulsant taken. Anti-convulsant drugs have long been known to have enzyme inducing properties and decreased levels of folate suggested that folate depletion resulted

from increased demand for the co-factor after induction of drug metabolizing enzymes. As folate deficiency was ultimately proposed to have an impact on drug metabolism, this hypothesis explained why blood phenytoin levels decreased and fit control worsened after correction of folate deficiency in epileptic patients.

In another study published in the Gut in 1972 by Houlihan CM, Scott JM, Boyle PH and Weir DG (Houlihan, 1972) on the effect of phenytoin on the absorption of synthetic folic acid polyglutamate, the study concluded that phenytoin had no adverse effect on the absorption of synthetic polyglutamate in vivo substantiating the work of Baugh and Krumdieck (1969) that showed in vitro that phenytoin did not inhibit the intestinal folate deconjugase enzyme(s) necessary for the breakdown of the folate polyglutamates, a process which occurs before or during folate absorption.

In a study published in 1973 in the Journal of Clinical Pharmacology by Latham AN, Millbank L, Richens A, Rowe DJF (Latham, 1973), on the liver enzyme induction by anti-convulsant drugs, and its relationship to disturbed calcium and folic acid metabolism, serum calcium and folate levels estimated in epileptic patients and related to the urinary excretion of D-glucaric acid. Calcium and folate levels were lowest in those patients who were receiving treatment with pheneturide. This group of patients also excreted a significantly greater amount of D-glucaric acid in their urine, suggesting that pheneturide is a potent liver enzyme inducer and is more powerful in this respect than phenobarbitone, phenytoin, or primidone. The study also supported the hypothesis that the disturbance of both calcium and folate metabolism is caused by liver enzyme induction.

In a study published in 1979 in the Journal of Clinical Investigation by Kelly Deirdre, Weir Berenice Donald and Scott John (Kelly, 1979) on the effect of anti-convulsant drugs on the rate of folate catabolism in mice, it was shown that the rate of catabolism of folate was actually increased after anti-convulsant, in particular phenytoin therapy. For the study, an experimental animal model using mice was developed to determine the rate of catabolism of radioactive hydrogen replaced pteroylglutamic acid by the quantitative estimation of p-aminobenzoylglutamic acid and acetamidobenzoylglutamic acid in the urine. Administration of intramuscular phenobarbitone on the other hand did not affect the rate of catabolism when compared with the controls.

In another review published in 1983 in Therapeutic Drug Monitoring on Phenytoin and folic acid: individualized drug-drug interaction by Berg MJ, Rivey MP, Vern BA, Fischer LJ, Schottelius DD (Berg, 1983), the effect of folic acid supplementation on the disposition of phenytoin and the resultant loss of seizure control in a male folate-deficient epileptic was reported. Due to the increase in tonic-clonic seizures after the initiation of folic acid, the sodium phenytoin dosage was increased until control was achieved. Because of these dosage changes, the Vmax and Km were calculated before and after initiation of the folic acid. The Vmax remained relatively the same, but the Km decreased after folate supplementation. In a Phenytoin-folic acid review published in Drug Intelligence and Clinical Pharmacy in 1984 by Rivey MP, Schottelius DD and Berg MJ (Berg, 1984), it was concluded that the nutrient-drug interaction between folate and phenytoin was a two-way interaction. Folate deficiency resulting from long-term phenytoin therapy was a common occurrence, but progression of the deficiency to a megaloblastic anemia was rare. However, there were data to suggest non-anemic folate deficiency may be detrimental to the patient. Several mechanisms were proposed to explain the ability of phenytoin to deplete body folate. The supplementation of folic acid to folate-deficient patients taking phenytoin was shown to result in lowered serum concentrations of phenytoin, and possibly loss of control of the seizure disorder. Folate appeared to be associated with the hepatic metabolism of phenytoin, although the effect of folic acid supplementation on phenytoin elimination kinetics was suggested to be individualized.

In another review published in The Annals of Pharmacotherapy in 1995 regarding the dual and interdependent drug-nutrient interaction between phenytoin and folic acid by Lewis DP, Van Dyke DC, Willhite LA, Stumbo PJ and Berg MJ (Lewis, 1995), all human studies examining the effects of phenytoin on serum folate concentrations and folic acid supplementation on serum phenytoin concentrations were selected. Case reports were included because of the extensive length of the time needed to study this drug interaction. The information was retrieved from a MEDLINE search of English language literature conducted from 1983 to 1995. Data extracted included gender, dosing, serum folate concentrations, pharmacokinetics and adverse events. The results arrived revealed a decrease in the serum folate concentrations when phenytoin therapy was initiated alone with no folate supplementation. Also, it was found that folic acid supplementation in folate deficient patients with epilepsy changed the pharmacokinetics of phenytoin usually leading to lower serum phenytoin concentrations and possible seizure breakthrough. Folate is hypothesized to be a co-factor in phenytoin metabolism and has been proposed to be responsible for the pseudo-steady-state, a concentration where phenytoin appears to be at a steady state but in reality is not. With simultaneous initiation of phenytoin and folic acid therapy was observed prevention of decreased folate and phenytoin achieving steady state concentrations sooner. It was finally concluded that folic acid supplementation should be initiated each time phenytoin therapy commences because of the hypothesized co-factor mechanism, decreased adverse effects associated with folate deficiency and better seizure control with no perturbation of phenytoin pharmacokinetics.

In a study published in 1997 in Journal of Nutrition by Franklin Carl G, Farlyn Hudson Z and Byron McGuire S Jr. (Carl, 1997) titled Phenytoin-Induced Depletion of Folate in Rats Originates in Liver and Involves a Mechanism That Does Not Discriminate Folate Form studying the mechanism of decrease in plasma concentrations of folate in epileptic patients on the anti-convulsant phenytoin, phenytoin administration was found to have minimal effect on folate concentration as well as the composition of the folate pool in intestinal mucosa. Phenytoin administration did, however, cause a depletion of total hepatic folate, causing the pentaglutamate derivatives of each of the pteridine derivatives to

decline rapidly, with the formyl and dihydro derivatives of the pteridine moiety falling more rapidly than the methyl and methylene / tetrahydro derivatives. The monoglutamate of the methylene / un-substituted tetrahydro derivative increased significantly with time of phenytoin treatment. The mono- and di-glutamate derivatives of the methyltetrahydrofolate increased transiently and significantly in the bile, and the polyglutamate chain length increased significantly in the brain with time of phenytoin treatment. The study concluded that phenytoin inhibits the formation of polyglutamyl folates in rat liver.

In another study published in the Seizure in 2006 by Sener Ufuk, Zorlu Yasar, Karaguzel Oguz, Ozdamar Ozlem, Coker Isik and Topbas Murat (Sener, 2006) on the effects of common anti-epileptic drug monotherapy on serum levels of homocysteine, vitamin B_{12}, folic acid and vitamin B_6, the study revealed that patients receiving phenytoin had significantly lower folic acid levels. A negative correlation between homocysteine and folic acid concentrations was also seen in epileptic patients on anti-epileptic therapy. The duration of anti-epileptic drug use was also correlated to the decrease of folic acid levels In a study published in 2007 in the Indian Journal of Clinical Biochemistry by Itemobong Ekaidem S, Monday Akpanabiatu I, Friday Uboh E and Offiong Eka U (Itemobong, 2007) titled effect of folic acid and vitamin B_{12} administration on phenytoin induced toxicity in rats, the effects of folic acid and vitamin B_{12} on liver integrity of growing Wistar albino rats following therapeutic dose of phenytoin administration were investigated. The activities of serum AST, ALT, ALP were investigated. Serum total protein level and lipid profile were also measured as indices of biochemical changes. The ingestion of phenytoin alone in rats significantly reduced serum protein, while AST, ALT activities increased. Supplementation of phenytoin with oral administration of folic acid resulted in a significant reversal in serum total protein and suppression in serum AST and ALT activities. Vitamin B_{12} supplementation did not afford any significant protection against the effect of phenytoin ingestion but rather phenytoin toxicity was exacerbated in this study. However, the combined effects of vitamin B_{12} and folic acid ameliorated the effects of phenytoin on serum enzymes of experimental rats. The effect of combination of phenytoin with folic acid or folic acid and vitamin B_{12} was an interesting finding. Supplementation of phenytoin with folic acid or combination of these vitamins was recommended for the purpose of ameliorating the adverse biochemical changes which are associated with phenytoin therapy.

In a recent population-based case–control study published in 2007 in the British Journal of Gynaecology: An International Journal of Obstetrics and Gynaecology by Kjær D, Horvath-Puho´ E, Christensen J, Vestergaard M, Czeizel A, Sørensen H, Olsen J (Kjær, 2008) entitled Antiepileptic drug use, folic acid supplementation, and congenital abnormalities with an objective to investigate whether folic acid supplementation in early pregnancy modifies the association between the prevalence of congenital abnormalities in the offspring and maternal use of carbamazepine (CBZ), phenobarbital (PB), phenytoin (PHT), and primidone (PRI) at The Hungarian Case–Control Surveillance of Congenital Abnormalities (HCCSCA) (1980–1996) and its information on children from the Hungarian Congenital Abnormality Registry and the Hungarian National Birth Registry. Children with congenital abnormalities and unaffected children were included. Information on drug exposure and background variables for the mothers were collected from antenatal logbooks, discharge summaries, and structured questionnaires completed by the mothers at the time of HCCSCA registration. The results arrived at revealed that compared with children unexposed to AEDs and folic acid, the odds ratio of congenital abnormalities was 1.47 (95% CI 1.13–1.90) in children exposed to AEDs without folic acid supplementation and 1.27 (95% CI 0.85–1.89) for children exposed to AEDs with folic acid supplementation. The results indicated that the risk of congenital abnormalities in children exposed in-utero to CBZ, PB, PHT, and PRI was reduced but not eliminated by folic acid supplementation at 5–12 weeks from LMP. The statistical precision in the study was limited due to rarity of the exposures, and further studies were warranted.

Risk of folate supplementation in precipitation of breakthrough seizures

The link between epilepsy and folic acid supplementation is however found to be controversial. The well-known teratogenic effects of anti-convulsant drugs are explained on the basis of decreased blood folate levels and have been seen to be prevented with folic acid supplementation during the peri-conceptional period. However, folate supplementation in phenytoin treated patients, as in phenytoin treated pregnant epileptic patients to prevent the risk of neural tube defects and other common teratogenic effects of anti-convulsant drugs, is also not considered to be safe because of the risk of precipitation of seizures in an otherwise stabilized epileptic patients.

In 1976, Smithells et al (Smithells, 1976) suggested that folate deficiency might cause neural tube defects because the mothers of infants with neural tube defects had low blood folate levels. Smithells and co-workers (Smithells, 1983) later found that folic acid supplementation during the peri-conceptional period could potentially reduce the risk of neural tube defects. In 1991, the UK Medical Research Council Vitamin Study (MRC Vitamin Study Research Group, 1991) also supported this hypothesis. There is also accumulating evidence that folic acid supplementation in peri-conceptional period might prevent other major birth defects including congenital heart disease, oro-facial clefts and anomalies of the urinary tract (Botto, 2004, Bailey, 2005, Czeizel, 1998, Myers, 2001). However, this is still controversial since there are also studies that do not show any correlation between folate fortification and the incidence of these birth defects (Botto, 2004).

In 2002, the UK Food Standards Agency decided against the introduction of mandatory folic acid fortification. One reason for this was issue of freedom of choice but interestingly, worry for the possible adverse effects, particularly masking of the diagnosis of vitamin B12 deficiency by prevention of anemia and precipitation of neurologic complications was the main cause (Bailey, 2005, Czeizel, 1998, Myers, 2001, Wald, 2001, Davis, 2002, Abramsky,

2002, Reynolds, 2002). Other issues that were raised were the possible drug interactions particularly with the anti-convulsant medication itself leading to the precipitation of fresh episodes of seizures in an otherwise well-controlled, epileptic patient because of reduction in seizure threshold by lowering serum phenytoin levels, breakthrough seizures; (Campbell, 1996, Ralston, 1970, Grant, 1970, Gibberd, 1981, Chien, 1975, Guidolin, 1998) hypersensitivity reactions, cancer promotion and increase of twinning rate (Bailey, 2005, Czeizel, 1998, Myers, 2001, Wald, 2001, Davis, 2002, Abramsky, 2002, Reynolds, 2002, Campbell, 1996). Another question was that of fetal death as it is a well-known fact that epilepsy with seizures during pregnancy leads to a 2-2.5 folds increase in fetal loss compared to normal subjects (Yerbi, 1997, Czeizel, Bod, 1992) although special care and monitoring during pregnancy may significantly decrease this (Cseh, 1991).

Infact, folic acid was long ago considered as a neurotoxin (Baxter, 1973) and a convulsant (Olney, 1981) if provided in high doses for therapeutic reasons. Chanarin et al (Chanarin, 1960) in 1960 were the first to raise the possibility of a decrease in the efficacy of anti-convulsant medications in case of therapeutic use of folic acid supplementation. Later, Chien et al (Guidolin, 1998) found that some subjects with epilepsy were more sensitive to the therapeutic doses of folic acid administered under certain circumstances. Strauss and Bernstein (Strauss, 1975) also found increased seizure frequency in certain epileptic females treated with anti-epileptic drug, phenytoin. However, Boss et al (Boss, 1980) did not find any hazards of oral doses as high as 1000 mg/day of folic acid. Later, Dansky et al (Dansky, 1987) were also unable to detect any impairment of seizure control in pregnant epileptics using valproic acid along with folic acid supplementation. These differences in the observations are explained on the basis of an intact blood-brain barrier that is said to restrict the entry of folic acid in the brain while on the other hand, after damage of the same, a toxic effect of folic acid might be seen (Hommes, 1973).

Controlled trials of folate therapy for upto 3 months produced conflicting results. There is enough experimental evidence however that folate derivatives have excitatory properties especially when the blood-brain barrier mechanism for the vitamin is circumvented (Reynolds, 1976, Reynolds, 1972, Hommes, 1979). In laboratory animals, intravenous infusions of the sodium salt of folate will only induce seizures in very large doses but if the blood-brain barrier is damaged locally by trauma or, a heat lesion, the dose required for an epileptogenic effect is much lower (Hommes, 1973, Miller, 1979). If the blood-brain barrier on the other hand is circumvented by an intra-ventricular or, intra-cortical administration, all folate derivatives have been seen to be highly epileptogenic (Hommes, 1973, Miller, 1979). Furthermore, the vitamin enhances the kindling model of epilepsy and can be used to kindle seizures directly (Davis, 1973). How exactly folates lead to excitation is unknown but they may do so by blocking or reversing GABA-mediated inhibitions (Reynolds, 2002). Epileptic phenomena produced by folates resemble those induced by disinhibitory compounds such as bicuculline, penicillin or picrotoxin (Spaans, 1970).

The risk of aggravating epileptic seizures is small however because of a restricted entry of the folates by the intact blood-brain barrier but increases gradually with increasing doses given over prolonged periods (Reynolds, 1970).

DISCUSSION

Numerous studies conducted in the past have proposed different reasons for falling serum folate levels on long term administration of phenytoin. While the details of these interactions remain obscure, several potential mechanisms have been proposed as explanations. Folic acid administered at pharmacological doses has been, on the other hand, blamed for a decrease in the serum concentration of phenytoin, possibly due to direct competition between folate and phenytoin for uptake sites, severe enough to precipitate seizures. The use of folic acid as an adjuvant to phenytoin/anti-epileptic therapy therefore mandates further analysis to overcome phenytoin, and folate deficiency associated possible adverse effects of long-term administration of phenytoin while simultaneously regulating the sera levels of folic acid within the safe limits to avoid the precipitation of seizures in this set of medically regulated epileptic patients.

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