Assessment of Risks to Efficacy of Treatment for Certain Medication from an Increase in Folic Acid Intake

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The widespread supplementation of dietary folate has raised concerns over the safety of this agent in large doses over long periods, particularly in relation to interaction with other medications. Though there is considerable anecdotal literature on the potential interactions between folate when given as a supplement, and a variety of medications, this information is largely anecdotal and unsupported by prospective studies. Concerns relate to several broad areas; interaction with antiepileptic drugs (AEDs); interactions with other drugs that inhibit folate metabolism (such as methotrexate); reduction of zinc levels through altered absorption; and masking of cobalamin deficiency.

Concerns over the use of folic acid supplementation go back many years, chiefly in relation to anticonvulsant drug use. This was considered because of the known antifolate effects of several antiepileptic drugs (AEDs), such as Phenytoin, carbamazepine and Phenobarbital, leading to speculation that folate supplementation may counteract the beneficial effects of AEDs. As well folic acid was recognised to be neurotoxic in a number of animal studies, and could provoke seizures in these models. An effect of folic acid on serum Pheytoin levels was demonstrated in some early studies, and breakthrough seizures have been attributed to folic acid supplementation induced reduction in serum anticonvulsant levels.
However, in two authoritative reviews (Morrel 1998; Pennel 2004), the authors agree that folate supplementation is recommended in epileptic women in childbearing age even before considering a pregnancy, with recommended dosages oscillating between 0.4 and 5 mg/day

The evidence though from case reports (Seligmann 1999 for example) and series (Ch'ien 1975) where folic acid supplementation has been implicated in loss of seizure control, has been in relation to very large doses of folic acid, 5mg in the former and up to 150mg intravenously in the latter. These doses are obviously extremely high, and certainly far outside the recommended doses considered in routine dietary supplementation. The study of Ch'ien did not demonstrate any change in clinical state or electroencephalographic (EEG) recordings in the majority of patients though, who received doses of 75mg of folic acid intravenously. Similar studies in patients with Parkinson's disease did not demonstrate any increased frequency of seizures, or other evidence of neurotoxicity.

Large double-blind studies have not demonstrated any increase in seizures when folate supplementation is given to patients with chronic epilepsies (Horwitz 1968; Ralston

1970; Jensen 1970; Baylis 1971; Norris 1971; Mattson 73; Backman 1989; Brown 1991). An exception to this situation may be when the blood brain barrier is disrupted by inflammatory central nervous system disease such as vasculitis, when folic acid may reach brain in concentrations not ordinarily possible (Eros 1998).

In summary, there is no evidence that folic acid supplementation at the recommended dose of 1mg daily is associated with any significant risk of provocation of seizures in people with epilepsy, or of other neurotoxicity. Even the very large doses administered in small studies showed no change in the majority of subjects. A possible exception relates to co-existing inflammatory brain disease, but this is still anecdotal. Levels of anticonvulsant medications, where available, can be checked after initiation of therapy to confirm stability.

Other medications that interfere with folate metabolism, including methotrexate, trimethoprim, and the antiinflammatory agent sulfasalazine have similar anecdotal reports of interaction with folic acid supplements analogous to the situation with the AEDs. Decreased levels of methotrexate have been reported with folate supplementation in a controlled trial, but the dose was high (5mg daily) and no clinical change was observed (Bressolle 2000). These reports of impaired efficacy have not been supported by larger controlled studies, which have not demonstrated a convincing alteration in the efficacy of these agents, but have shown tolerability of these agents may improve with folic acid supplementation (Morgan 1994). There are well known interactions at the renal tubular level between non-steroidal antiinflammatory agents (NSAIDs), including sulfasalazine, and methotrexate (Frenia 1992), but no reports of significant interactions between folate and NSAIDs. Interaction with sulfasalazine appears to be beneficial rather than harmful: an interesting report came from Jansen et al. (2004), who observed that at clinically relevant plasma concentrations, a significant interaction exist between sulfasalazine and reduced folate carrier. The authors concluded that the use of this combination therapy may provide a rationale both for the use of folate supplementation and for spacing administration of these drugs over time. Combined use of sulfasalazine and folate might also reduce the risk of colorectal cancer (Diculescu et al., 2003). In addition, Stella et al. (2000) designed biodegradable, folate linked nanoparticles that when conjugated with folate may act as a potential new drug carrier for tumor cell-selective targeting. Another beneficial pharmacological interaction has been hypothesized between folic acid and SSRIs,as major depression disorder can be poorly responsive to treatment if folate plasmatic concentration is low. However, Alpert et al. (2002) found that folate supplementation produced only a modest effect in SSRIs-refractory patients. Certainly aspirin has been implicated in the low folate levels seen in patients with Rheumatoid arthritis (Alonso-Aperte 2000), though the mechanism is thought to be competition for serum protein carriers. Other antifolate agents such as some antimalarials, which depend on this mechanism for their effect, may also have interaction with folate supplements, but this had not been shown to be clinically relevant in early studies (Tong, 1970). There is some recent evidence to suggest that higher serum folate levels in non-supplemented subjects are associated with higher failure rates of antimalarials in some specific situations (Dzinjalamala, 2005). Some authors (Wang et al., 1999) have analysed the efficacy on antimalaric combinations, such as

pyrimethamine/sulphadoxin, finding thata the efficacy of the interaction these drugs against Plasmodium Falciparum largely dependes on the concentration of exogenous folate.

In summary, drugs with anti-folate effects including some anti-inflammatory agents are known to have interaction with folate, relating to minor reductions in blood levels for some of these agents. The evidence does not support an effect on efficacy of these agents though, and there is no evidence that these are relevant changes at doses of up to 1mg daily. Anecdotal infomrations suggests that there is a perception in the community that folate may intefere with NSAIDs, but again there is no evidence of any significant interaction in this regard.

Folate levels were thought to be influenced by folate, and it has been demonstrated that folate increases albumin bound zinc levels (Agate 2004). This effect was visible even at the ABZn also at zinc concentrations lower than the therapeutic ones. this has not been shown to be a relevant interaction in humans at the levels of up to 1mg daily, but could conceivably be relevant in Zinc deprived subjects.

Finally, some concerns have been recently expressed about possible adverse events related to potentially excessive, long-term folate administration; Kim (2004) claimed that, although an increased risk of developing colorectal cancer is associated with low folate serum level and nutritional intake, exceptionally high supplemental folate levels and folate intervention after microscopic neoplastic foci are established in the colorectal mucosa promote, rather than suppress, colorectal carcinogenesis. Campbell (1996) analysed the potential safety issues related to dietary folate administration in the general population, indicating as theoretical possibilities difficulty identifying cobalamin deficiency, precipitation of neurologic complications of cobalamin deficiency, and lowering of cobalamin levels; folate neurotoxicity; antagonism of drugs that inhibit folate metabolism, in addition to the already mentioned effects on zinc absorption, increased susceptibility to malaria and neurotoxicity. The author, though points out that the evidence supportive of these possible negative effects is mainly based on case reports. In the countries that had a long experience of folate fortification, such as Belgium, UK and Switzerland, no serious negative effects have been reported in the genral population. On the other hand, no documentation is obtainable at the present about long-term exposure to folate, especially in childhood. Despite these doubts, most authors agree that food fortification with folate levels between 140 and 400 □g per 100 g of flour is associated with a substantial improvement of folate status reducing the risk of many potentially preventable diseases, with not sufficiently documented negative effect on other therapeutic regimens.

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