

# RGH Pharmacy E-Bulletin

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A joint initiative of the Patient Services Section and the Drug and Therapeutics Information Service of the Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia. The RGH Pharmacy E-Bulletin is distributed in electronic format on a weekly basis, and aims to present concise, factual information on issues of current interest in therapeutics, drug safety and cost-effective use of medications.

Editor: Assoc. Prof. Chris Alderman, University of South Australia – Director of Pharmacy, RGH

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## Interaction between folate and phenytoin

Phenytoin is a commonly prescribed anticonvulsant medication with a narrow therapeutic index, and is known to have many interactions with other drugs. It has non-linear elimination kinetics resulting from saturable metabolism, which makes safe and effective phenytoin dosing complicated yet crucial. One documented interaction is that between phenytoin and folic acid, a two-way interaction where phenytoin is known to cause folate deficiency (if folic acid is not supplemented), and conversely folic acid decreases serum concentrations of phenytoin.

One proposed mechanism of phenytoin-induced folate deficiency is its inhibition of intestinal conjugase, the enzyme which converts dietary folate from the polyglutamate form to the more readily absorbed monoglutamate. Folate deficiency can contribute to various haematological complications including megaloblastic anaemia and hyperhomocysteinaemia (a risk factor for developing atherosclerosis and venous thromboembolism), and left uncorrected in pregnancy may lead to congenital malformations.

Folate is hypothesised to be a cofactor in the metabolic pathway of phenytoin, and evidence suggests that even low doses of folic acid (1mg daily) given in folic acid deficiency can induce the metabolism of phenytoin, leading to reductions of 4 - 60% in serum concentrations and the possibility of breakthrough seizures.

Where phenytoin is commenced without folic acid supplementation, decreased availability of dietary folate as a cofactor in phenytoin metabolism has been proposed as the cause of a phenomenon known as “pseudo-steady-state”. This is where phenytoin appears to reach steady-state after 7-10 days, but as folic acid is further depleted, phenytoin metabolism decreases and the concentration increases further.

There is some evidence that folic acid supplementation may reduce the incidence and severity of some of the adverse effects of phenytoin, such as gingival hypertrophy, but the extent and clinical significance of this needs to be confirmed. Historically, clinical practice guidelines recommended initiation of folic acid supplementation and phenytoin simultaneously, the intention being to prevent folate deficiency, minimise side effects from phenytoin, achieve steady-state concentrations sooner and avoid adverse changes in phenytoin levels. However, concomitant administration of folic acid and phenytoin is not a prominent feature of current recommendations, nor is baseline measurement of folate levels when starting phenytoin. The manufacturer’s product information simply lists existing phenytoin therapy as a precaution for initiating folic acid, and other references suggest monitoring phenytoin concentrations and clinical effect when folic acid is commenced, ceased or changed.

Awareness of the interaction between phenytoin and folic acid is not new, but this interaction remains a clinically significant one, and bears consideration in patients on long-term phenytoin therapy (to prevent the development of folate deficiency and its associated complications). Similarly, concomitant folic acid therapy may contribute to sub-therapeutic serum phenytoin concentrations, and consequent reduction in seizure control. Being a non-prescription medication in Australia, there is potential for patients to be taking folic acid without the knowledge of their phenytoin prescriber, emphasising the important role of both the GP and the community pharmacist in taking adequate medication histories in order to prevent or manage potential drug interactions.

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**FOR FURTHER INFORMATION – CONTACT THE PHARMACY DEPARTMENT ON 82751763 or email: [chris.alderman@rgh.sa.gov.au](mailto:chris.alderman@rgh.sa.gov.au)**  
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