Folic acid supplementation prevents phenytoin-induced gingival overgrowth in children

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ABSTRACT

Objective: Gingival overgrowth is an important adverse effect of phenytoin (PHT) therapy, occurring in about half of the patients. This study aimed to evaluate the effect of oral folic acid supplementation (0.5 mg/day) for the prevention of PHT-induced gingival overgrowth (PIGO) in children with epilepsy aged 6–15 years on PHT monotherapy for 6 months.

Methods: This was a randomized, double-blind, placebo-controlled trial conducted at a tertiary level hospital from May 2008 to June 2009. Children aged 6–15 years started on PHT monotherapy within last 1 month were eligible for inclusion. Preexisting gingival overgrowth, use of other folic acid antagonists, and macrocytic anemia were exclusion criteria. Trial subjects were randomized to receive either folic acid or placebo. The primary outcome measure was incidence of any degree of gingival overgrowth after 6 months of PHT monotherapy. The trial was registered with clinicaltrials.gov (NCT00781196).

Results: A total of 120 children were recruited, 62 and 58, respectively, in folic acid and placebo arms. The 2 arms were comparable at baseline. Twenty-one percent of patients in the folic acid arm developed PIGO, as compared with 88% receiving placebo ($p < 0.001$). Absolute risk reduction of PIGO by folic acid was 67% (95% confidence interval 54%–80%), and relative risk reduction was 0.76.

Conclusions: Oral folic acid was found to decrease the incidence of PIGO in children on PHT monotherapy, in a statistically significant and clinically relevant manner.

Classification of evidence: This study provides Class I evidence that folic acid supplementation, 0.5 mg/day, is associated with prevention of gingival overgrowth in children taking PHT monotherapy. **Neurology® 2011;76:1338–1343**

GLOSSARY

A&G = Angelopoulos and Goaz; **PHT** = phenytoin; **PIGO** = phenytoin-induced gingival overgrowth.

Phenytoin (PHT) was first used to treat seizures in 1938¹ and gingival hyperplasia as a side effect was recognized the following year.² Community and hospital-based studies have estimated the incidence of PHT-induced gingival overgrowth (PIGO) as 25%–40% and 50%–60%, respectively.^{3–5} Preliminary clinical evidence suggests therapeutic potential of folic acid in PIGO. In an uncontrolled case series of 9 patients, the hyperplasia was completely resolved in 6 and remained unchanged in one after 6 months of therapy.⁶ In another randomized double-blind study, 20 epileptic adults with PIGO were divided to receive either 3 mg folic acid daily or placebo for 16 weeks. Outcome measures included indices of hyperplasia, gingival health, and plaque index. There were no significant differences between groups for any of the indices over time.⁷ There is also some evidence that topical folate significantly inhibits gingival hyperplasia to a greater extent than systemic folic acid.⁸ These studies reflect palliative as opposed to preventive role of folic acid.

In a developing country like ours, PIGO is a significant problem. First, there is increasing cosmetic and self-image awareness and concern. Secondly, due to low cost and familiarity,

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Disclosure: Author disclosures are provided at the end of the article.

PHT is very commonly used, sometimes even in situations where it can be substituted. Finally, a significant proportion of the population catered to by any government hospital usually lacks acceptable dental hygiene. Hence this study was planned to prospectively assess the efficacy of oral folic acid supplementation (0.5 mg/day) for prevention of PIGO in children with epilepsy aged 6–15 years on PHT monotherapy.

METHODS This was a randomized, double-blind, placebo-controlled trial conducted in a tertiary level teaching hospital between May and December 2008.

Participants. Children with epilepsy aged 6–15 years who were started on PHT monotherapy within 1 month from the date of enrollment were eligible for inclusion. Children with preexisting gingival overgrowth due to any other cause, concomitant therapy with other folic acid antagonists for ≥ 2 weeks any time during the last 3 months from the date of enrollment, and macrocytic anemia were excluded. History was obtained including demographic details of the patient and dose and duration of PHT intake. Patients were examined for gingival hyperplasia using Angelopoulos and Goaz (A&G) grading and for oral hygiene using plaque index of Loe and Sillness. The 4 most affected gums (one from each quadrant of the jaws) were selected for evaluation. Each tooth has 4 surfaces—bucco-facial, mesial, distal, and lingual—the interfaces of which define 4 points on which these indices were applied. To quantitatively evaluate degree of gingival overgrowth it is necessary to know the depth of gingival sulcus and to measure the extent to which crown of the teeth has been covered by the overgrown gingiva. This depth was measured using ball-tipped dental probe. Patients also had laboratory evaluations for macrocytic anemia by complete blood count, peripheral blood smear, and mean corpuscular volume, as indicated. All patients were advised regarding oral hygiene in the form of Bass technique of brushing.⁹ Patients were discouraged from undergoing scaling for cosmetic reasons for the duration of participation in the study, as it may alter the plaque index significantly.

Randomization. A printed random number table was used. Two groups were generated using block randomization method, using variable length of blocks. Allocation to the groups was concealed from the investigator (R.A.) assessing gingival overgrowth and plaque index. Patients were randomized to receive either 0.5 mg/day of folic acid or placebo. Trial medication was dispensed in identical capsules, prepacked in identical waterproof plastic pouches of 60 capsules each, coded using the alphabet. Randomization table, allocation details, and trial medication were reserved with a no-interest party.

Outcome measures. The primary outcome measure was incidence of any degree of PIGO in 2 groups after 6 months of PHT monotherapy, as graded using the A&G system.³ Secondary outcome measures included incidence of A&G grade ≥ 2 hyperplasia at the end of 6 months, relationship between PHT dose (in mg/kg/day) and serum PHT levels and occurrence of overgrowth, and time to occurrence of overgrowth. Criteria for protocol violation included withdrawal of PHT for any reason, use of any other antiepileptic drug consecutively for > 7 days, non-

compliance with trial medication or PHT consecutively for > 7 days, and loss to follow-up.

Gingival overgrowth was graded as per the A&G system.³ The definitions used are as follows: grade 0, no hyperplasia, normal gingiva; grade 1, hyperplastic gingiva covering the cervical third or less of the anatomic crowns of the anterior teeth; grade 2, hyperplastic gingiva extended anywhere in the middle third of the anatomic crowns of the anterior teeth; grade 3, hyperplastic gingiva covered more than two-thirds of the anatomic crowns of the anterior teeth. Gingival overgrowth of A&G grade ≥ 2 was deemed cosmetically significant.

Follow-up. Patients were evaluated every 2 months for 6 months. On each visit, they were evaluated for grading of gingival hyperplasia and plaque index. Also, the compliance with medications and oral hygiene measures was assessed using pill count and parental reporting. Dose of PHT (in mg/kg/day) was recorded. At the end of study period, serum PHT levels were obtained.

Sample size estimation and statistical methods. From previous studies,^{3,5} about 50% of patients are likely to develop PIGO in a hospital-based sample. A clinically meaningful reduction in the incidence of PIGO due to intervention was taken as 50%. Keeping an α error of 0.05, power of 80%, and allocation ratio of 1, it was estimated that enrollment of 60 patients in each arm of trial is required.

A Microsoft Excel spreadsheet was used for data entry. Proportions were compared using χ^2 or Fisher exact test and means were compared using t test for independent samples. Ninety-five percent confidence intervals for effect size and relative risk were estimated. The primary analysis was intention-to-treat, worst case scenario. Statistical Package for the Social Sciences (SPSS) version 17.0.1 was used for calculations.

Standard protocol approvals, registrations, and consents. The study was approved by Institutional Ethics committee and was registered with clinicaltrials.gov (NCT00781196) and Clinical Trials Registry of India (CTRI/2008/091/000227). World Health Organization Universal trial reference number is 124525544–30102008324360. Informed parental consent was obtained prior to enrollment for all participants.

RESULTS A total of 120 patients were enrolled in the study, 62 and 58, respectively, in folic acid and placebo arms (figure). The 2 groups were found to be comparable at baseline with respect to demographic and clinical variables (table 1).

Thirteen of the 62 patients (21%) enrolled in the folic acid arm developed PIGO, as compared with 51 of the 58 patients (87.9%) receiving placebo (absolute risk reduction 67%, 95% confidence interval 53.8%–80.1%, $p < 0.001$, number needed to treat 1.5) (table 2). Only 2 (3.23%) of the intervention arm developed severe PIGO (grade 2 or more) vs 8 (13.79%) of the control arm ($p = 0.036$) (table 2).

It was also analyzed whether PHT dose and serum levels differed between those who developed PIGO vs those who did not, in the folic acid and placebo groups. No significant difference in either dose or levels of PHT was found in the folic acid group between those developing and not developing PIGO.

Figure Flow of patients in the study

In the placebo group, serum PHT levels were significantly higher in those developing PIGO (13.38 ± 5.62) as compared to those who did not develop this adverse effect (10.68 ± 1.96) ($p = 0.04$), although the dose of PHT was found not to differ significantly (table 3).

The time trend of development of PIGO was also analyzed. Nearly 16% in the folic acid arm and 67% in the placebo arm had developed PIGO by 2 months of follow-up ($p = 0.000$). This corresponds to nearly 77% of those who eventually developed PIGO in both the groups. By 4 months of follow-up, 21% of the folic acid arm and 83% of the placebo arm had developed PIGO, implying that all of those who eventually developed PIGO in the folic acid arm

had done so by 4 months, and nearly all (94%) in the placebo arm. At every visit, the proportion of patients having plaque indices of 0, 1, and 2 were ascertained for both the arms. Plaque index was found to remain comparable between the 2 arms throughout the follow-up period.

There were 3 protocol violations and one loss to follow-up in the placebo arm and one each in the folic acid arm. All the protocol violations were due to starting of another antiepileptic drug, when these children presented to emergency with a seizure recurrence. Also, 26 patients in the folic acid arm (41.9%) and 23 in the placebo arm (39.7%) required increasing the dose of PHT to achieve seizure control during the course of the study. At the end of the study,

Table 1 Baseline and end-of-trial comparisons between folic acid and placebo arms

	Folic acid	Placebo	p Value
Total enrolled	62	58	
Age, y, mean ± SD	8.7 ± 2.3	8.8 ± 2.2	0.839
Time from PHT start to enrollment, d, mean ± SD	10 ± 4.3	11 ± 4.6	0.218
M/F	37/25	29/29	0.287
Baseline plaque index, 0:1:2	22:30:10	22:24:12	0.699
PHT dose, mg/kg/day, mean ± SD	5.7 ± 0.8	6.0 ± 1.1	0.088
Protocol violations and loss to follow-up (%)	4 (6.5)	2 (3.5)	0.744
No. of patients requiring dose modification (%)	26 (41.9)	23 (39.7)	0.800
PHT dose, mg/kg/day, mean ± SD	6.8 ± 0.9	7.0 ± 1.0	0.319
PHT level, µg/mL, mean ± SD	13.7 ± 6.1 (n = 54)	13.2 ± 5.1 (n = 46)	0.323

Abbreviation: PHT = phenytoin.

mean PHT dose was 6.8 and 7.0 mg/kg/day respectively in intervention and control arms. Serum PHT levels were measured at the end of the study for 54 patients in the folic acid arm and 46 patients in the placebo arm. Mean PHT levels were within the therapeutic range (table 1). Most of the enrolled children had symptomatic seizures due to neurocysticercosis (76%, data not presented).

DISCUSSION The present study prospectively investigated the effect of oral folic acid (0.5 mg/day) on gingival overgrowth induced by PHT in the pediatric age group.

The occurrence of PIGO was found to be significantly decreased with folic acid supplementation from 88% in the control population to only 21% of those receiving folic acid. This amounts to a relative risk reduction to one-fourth of the control population and an absolute risk reduction of 67%, with a number needed to treat of 1.49. Although a 0.5-mg folic acid tablet is not commercially available, using the current price of a 5-mg tablet, the cost of prevention per additional patient for 6-month duration of therapy comes out to be roughly Rs. 215 (US \$5.1). This must be viewed in context of both cosmetic¹⁰ and medical benefits of reduction of PIGO for gingival hygiene.¹¹ A gingival overgrowth of > grade 2 is cosmetically undesirable and creates a dentogingival

pocket for plaque and debris accumulation, further worsening both PIGO and gingival hygiene.¹² This severe PIGO was also significantly reduced from about 14% in the placebo arm to 3% in the folic acid arm ($p = 0.036$). Another study using 5 mg/day of folic acid found that 50% of patients in the intervention arm developed gingival overgrowth as opposed to 60% of controls.¹³ Their finding of more patients with minimal overgrowth in the folic acid group agrees with our finding of less of severe PIGO in the intervention arm as compared to controls.

In the 2 arms, dose and serum levels of PHT were not found to differ significantly among those patients who developed PIGO (table 3). This is a controversial relationship, as some studies have found increased severity of PIGO with increasing PHT dose and serum levels,^{14–16} whereas others have refuted any correlation between severity of PIGO and dose or total serum, free, or even salivary levels of PHT.^{17,18} In the folic acid group, the dose and levels of PHT did not differ significantly between those who developed PIGO and those who did not. In the placebo group, although the dose did not differ, the serum PHT levels were significantly lower in those who did not develop PIGO (mean 10.68 µg/mL) vs those who did (mean 13.38 µg/mL) (table 3). A plausible explanation for this finding would be that in the general population, PHT levels affect occurrence of PIGO, but folic acid supplementation blunts this difference. This proposition is further supported by the fact that mean PHT levels differ significantly between control and intervention arms among those who did not develop PIGO, being 13.45 vs 10.68 µg/mL ($p = 0.006$).

It was observed that by 2 months of follow-up, 67% of the placebo group had already developed PIGO vs 16% of the folic acid group. This corresponds to roughly 76% of those who eventually developed PIGO in both the groups. By 4 months, all of those who eventually had PIGO had developed it in the folic acid arm, whereas nearly all (94%) had done so in the control arm. It means that most of those who develop PIGO do so by 4 months, which is in agreement with the published experience as PIGO usually has been found to be noticeable by 2–3 months and maximally by 4–6 months. A previ-

Table 2 Gingival overgrowth in folic acid and placebo arms at the end of study period

	Folic acid, n (%)	Placebo, n (%)	Effect size (95% confidence interval)	Relative risk (95% confidence interval)	p Value
Any degree of gingival overgrowth	13/62 (21.0)	51/58 (87.9)	66.96 (53.808–80.112)	4.198 (2.571–6.856)	<0.001
Gingival overgrowth ≥ grade II	2/62 (3.2)	8/58 (13.8)	10.56 (0.655–20.465)	4.281 (0.949–19.316)	0.036

Table 3 Relationship of gingival overgrowth with phenytoin dose and serum levels in folic acid and placebo arms

Subgroup	GO	No GO	p Value
Folic acid group, n	13	49	
Dose, mg/kg/day, mean $\pm$ SD	6.1 $\pm$ 1.2	5.76 $\pm$ 0.8	0.216
Levels, μ g/mL, mean $\pm$ SD (n)	15.0 $\pm$ 3.7 (11)	13.5 $\pm$ 2.5 (43)	0.108
Placebo group, n	51	7	
Dose, mg/kg/day, mean $\pm$ SD	6.0 $\pm$ 1.0	5.5 $\pm$ 0.7	0.221
Levels, μ g/mL, mean $\pm$ SD (n)	13.4 $\pm$ 2.8 (41)	10.7 $\pm$ 1.0 (5)	0.040

Abbreviation: GO = gingival overgrowth.

ous study also found that in the folic acid group 6 of the 13 children who eventually had PIGO (46%) had developed it by 3 months and by 6 months the figure reached 8 (62%). In their control group, 60% had PIGO by 3 months and 80% by 6 months.¹³ They have stressed the delay in development of PIGO in the folic acid arm and attributed it to preventive role of folic acid, but we await further studies with a longer follow-up designed to study this aspect. Hence, a significant difference is already established between the folic acid and placebo groups by 2 months of follow-up. PIGO is probably an all-or-none phenomenon; those who eventually do develop PIGO do so within 4 months and also attain maximal severity fairly rapidly, rather than having an increasing severity with the increasing duration of exposure to PHT. This phenomenon is well-characterized at the cellular level, by rapid selection of responder phenotype and augmentation of its biosynthetic activities upon PHT exposure.¹⁹

Our study has some limitations. It would have been desirable to obtain dental photographs of each patient on each visit, thus ensuring very high degree of objectivity in assessment of overgrowth. Measurement of folate levels would also have been desirable. However, it was not available at the institution and a surrogate measure was used as described above.

Oral folic acid supplementation (0.5 mg/day) was found to decrease the incidence of PIGO in children aged 6–15 years on PHT monotherapy, in a statistically significant and clinically relevant manner, on a short-term basis. It also probably decreases the frequency of cosmetically significant PIGO. In this population, frequency of development of PIGO was maximal in the first 2 months of initiation of PHT monotherapy. There was no significant difference between serum PHT levels and PHT dose in mg/kg/day in those who developed PIGO and those who did not. Future basic and clinical research would include replicating the trial with different dose, duration, regimen, or patient profile and studying the effect of folic acid on gingival fibroblast cultures exposed to PHT, as measured by production of matrix

substances including glycosaminoglycans and on selection of responder phenotype. Based on this study, daily folate supplementation should be considered to help minimize the occurrence of PIGO in children.

ACKNOWLEDGMENT

Trial medication and placebo were supplied by Euphoria India Pharmaceuticals, Solan, Himachal Pradesh, India, at a cost of Rs. 12,500, which was borne by the institute. This agency was not involved in design, conduct, or analysis of the trial, nor had any financial transaction with any of the investigators. Dental probes were procured by routine hospital procedures.

DISCLOSURE

Dr. Arya reports no disclosures. Dr. Gulati serves on the editorial board of the *Indian Journal of Pediatrics* and receives research support from the NIH, Autism Speaks, and National Trust. Dr. Kabra serves on scientific advisory boards for the Asian Society of Inherited Metabolic Disorders, Department of Biotechnology, Government of India, and Indian Council of Medical Research; serves on the editorial board of the *Indian Journal of Pediatrics*; and receives research support from Shire plc, Department of Biotechnology, Government of India, and Indian Council of Medical Research, Government of India. Dr. Sahu reports no disclosures. Dr. Kalra receives publishing royalties for *Practical Pediatric Neurology* (Arya Publications, 2005, 2008); retired from her position at All India Institute of Medical Sciences in 2008; and is currently in private practice where she bills for clinical services provided.

Received August 3, 2010. Accepted in final form December 22, 2010.

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Classification scheme requirements for therapeutic questions

Class I. A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II. A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criterion a-e in Class I or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e in Class I. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III. All other controlled trials (including well-defined natural history controls or patients serving as their own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurements.

Class IV. Studies not meeting Class I, II, or III criteria including consensus or expert opinion.

AAN classification of recommendations

A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)

B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.