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# Valproic acid and thrombocytopenia: cross-sectional study

## 瓦爾普洛伊克酸與血小板減少症：交叉研究

**Objectives.** To investigate the relationship between platelet count and serum valproic acid level, age, duration of valproic acid therapy, and polytherapy, and to determine the clinical significance of thrombocytopenia associated with high-dosage valproic acid therapy.

**Design.** Cross-sectional study.

**Setting.** Residential unit for neurologically impaired children and paediatric out-patient clinic, Hong Kong.

**Patients.** Ninety-six neurologically impaired children who were treated with valproic acid between 1 July 1991 and 3 June 1999. The comparison group consisted of 48 children receiving antiepileptic drugs other than valproic acid.

**Intervention.** Low- or high-dosage valproic acid, using the threshold value of  $40 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ .

**Main outcome measures.** Platelet count and liver function, duration of valproic acid treatment, dosage, and trough serum valproic acid concentration.

**Results.** Seventeen (17.7%) patients in the treatment group developed thrombocytopenia, compared with two (4.2%) in the comparison group ( $P < 0.05$ ). The platelet count was negatively correlated to serum valproic acid level and age, and positively correlated to polytherapy. The duration of valproic acid treatment was not a confounding factor in the age-related decrease in platelet count. Children with a trough level of  $>450 \mu\text{mol/L}$  or a daily dose of  $>40 \text{ mg/kg}$  were more likely to develop thrombocytopenia. Thrombocytopenia was mild in most cases.

**Conclusions.** A trough valproic acid level of  $>450 \mu\text{mol/L}$  or a daily dose of  $>40 \text{ mg/kg}$  should alert the clinician to the risk of developing thrombocytopenia. The risk is further increased for older children. The platelet count should be monitored for patients receiving a high concentration of valproic acid who are also receiving drugs that would affect homeostasis, or who are undergoing surgical procedures.

### Key words:

Anticonvulsants/adverse effects;  
Thrombocytopenia/chemically induced;  
Valproic acid/adverse effects

### 關鍵詞：

抗驚厥藥 / 反作用；  
血小板減少症 / 化學性減少；  
瓦爾普洛伊克酸 / 反作用

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**目的：**調查研究血小板數和血清瓦爾普洛伊克酸水平、年齡、瓦爾普洛伊克酸療程、及多重治療之間的相互關係，確定與大劑量瓦爾普洛伊克酸治療相關的血小板減少症的臨床重要性。

**設計：**橫切研究。

**安排：**香港；神經受損兒童住所和兒科門診部。

**患者：**96名從1991年7月1日到1999年6月3日期間，採用瓦爾普洛伊克酸治療的神經受損兒童。對照組是48名接受抗癲癇藥物而不是瓦爾普洛伊克酸治療的兒童。

**用藥：**小或大劑量瓦爾普洛伊克酸，使用分界值  $40 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ 。

**主要結果測量：**血小板數和肝功能，瓦爾普洛伊克酸治療持續時間，劑量和管血清瓦爾普洛伊克酸濃度。

**結果：**在治療組有17名(17.7%)患者得了血小板減少症，而對照組有2名(4.2%)患者得了血小板減少症( $P < 0.05$ )。血小板數與血清瓦爾普洛伊克酸水平和年齡為負相關，對多重治療為正相關。瓦爾普洛伊克酸治療持續期在與年齡有關的血小板數減少中不是一個混淆因素。有大於  $450 \mu\text{mol/L}$  管血清水平或日劑量大於  $40 \text{ mg/kg}$  的兒童更容易得血小板減少症。在大多數案例中血小板減少症是輕微的。

**結論：**當管血清瓦爾普洛伊克酸水平大於  $450 \mu\text{mol/L}$  或日劑量大於  $40 \text{ mg/kg}$  時，臨床醫生應小心病人得血小板減少症的危險。這危險對於年齡較大的兒童會進一步增加。對於接受高濃度瓦爾普洛伊克酸同時還接受影響體內平衡藥物，或處於外科手術程序中的患者，其血小板數應該加以監測。

## Introduction

Valproic acid (VPA) is a commonly used antiepileptic drug. It is widely used as a first-line agent for patients with partial or generalised epilepsy. Thrombocytopenia is one of the most common side effects associated with VPA therapy, with incidences ranging from 1% to 30%.<sup>1-4</sup> It is mild and transient in most cases and usually resolves spontaneously on dosage reduction or withdrawal of the drug.<sup>5,6</sup> Delgado et al<sup>6</sup> and May and Sunder<sup>5</sup> have demonstrated that the platelet count decreases at high serum VPA levels. The platelet count has also been shown to be inversely correlated to VPA dose and plasma VPA concentration.<sup>7</sup>

In a retrospective study of 167 children treated with VPA as monotherapy or polytherapy, the serum VPA level and older age were shown to be the two most important independent predictors for thrombocytopenia.<sup>1</sup> Previous studies adopted various definitions for thrombocytopenia, ranging from a platelet count of  $<75$  to  $200 \times 10^9 / \text{L}$ .<sup>1,8</sup> Peak or random serum VPA levels have also been measured, but they may be more variable and do not reflect the therapeutic range as does the trough level.<sup>1,6</sup> The relationship of thrombocytopenia to older age has not been consistently demonstrated.<sup>6</sup> The duration of VPA therapy may also be a confounding factor in this apparent relationship. Most patients in previous studies received a low to moderate dosage of VPA therapy on an out-patient basis.<sup>1,7</sup> Data for patients who received high-dosage VPA therapy ( $\geq 40 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ ) are scarce.<sup>6,8</sup> The effect of polytherapy on platelet count is not known.<sup>1,6</sup>

In this study, 96 neurologically impaired children who were receiving VPA therapy were recruited. A significant proportion of them (44/96) were given high-dosage VPA (arbitrarily defined as  $\geq 40 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ ), either as monotherapy or polytherapy. The objectives of this study were as follows: (1) to investigate the relationship of thrombocytopenia, defined as a platelet count of  $<150 \times 10^9 / \text{L}$  (normal range,  $150\text{--}450 \times 10^9 / \text{L}$ ), with VPA therapy, age, duration of VPA therapy, and polytherapy; and (2) to determine the

clinical significance of thrombocytopenia associated with high-dosage VPA therapy.

## Methods

### *Patients and treatment*

Ninety-six neurologically impaired children who were receiving VPA therapy between 1 July 1991 and 3 June 1999 were recruited from the Developmental Disabilities Unit (DDU) at the Caritas Medical Centre. All patients were receiving residential care at the hospital. Children with underlying disorders that predisposed them to thrombocytopenia were excluded from the study. The duration of VPA treatment varied from 12 days to 8 years. The data from these patients were compared with those from 48 patients who were given antiepileptic drugs other than VPA. The comparison group consisted of 29 children residing in the DDU and 19 consecutive children who were recruited from the paediatric neurology clinic at the same hospital.

The data extracted included the patients' age, sex, weight, prescribed antiepileptic drugs, and history of bleeding complications. For patients who were receiving VPA, the treatment starting dates were recorded. For patients who were receiving high dosages of VPA, the dates when the dosage was increased to  $\geq 40 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$  were recorded. Since the recommended daily dose of VPA ranged from 20 to  $60 \text{ mg/kg}$ , a dosage exceeding  $40 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$  was arbitrarily defined as a high dosage. The platelet count and levels of serum total bilirubin, aspartate transaminase, and alanine transaminase were obtained for all patients. For those receiving VPA, the concomitant trough serum VPA levels were also obtained. A platelet count of  $<150 \times 10^9 / \text{L}$  was confirmed by light microscopic examination. Levels of liver transaminases, bilirubin, and VPA were measured by enzymatic assay, calorimetric assay, and immunoassay, respectively.

For all patients who were identified to have thrombocytopenia, a thorough clinical examination was performed to ascertain any bleeding tendency. Because reflux oesophagitis occurred frequently in this group

of children, gastro-intestinal bleeding was not regarded as thrombocytopenia-associated bleeding if there were no other signs of mucosal bleeding. For each patient with thrombocytopenia, the previous platelet counts obtained during his or her hospital stay were reviewed to identify any pre-existing cases of thrombocytopenia.

### Statistical analysis

The Statistical Package for Social Science (Windows version 7.5; SPSS Inc., Chicago, United States) was used for the statistical analysis. The percentages of patients with thrombocytopenia and abnormal results of liver function tests were compared between the VPA and the comparison groups by using the Chi squared test. Multiple regression models were used to identify factors that best predicted thrombocytopenia. The variables examined included age, VPA dosage, trough serum VPA level, duration of VPA therapy, and polytherapy.

### Results

Ninety-six children—41 girls and 55 boys—with a mean (standard deviation, SD) age of 9.9 (4.4) years (range, 1.9-20.3 years) who were receiving VPA were recruited into the VPA group. The mean (SD) dosage of VPA used was 44.15 (21.13) mg·kg<sup>-1</sup>·d<sup>-1</sup> (range, 11.45-97.40 mg·kg<sup>-1</sup>·d<sup>-1</sup>). Fifty-eight (60.4%) children were treated with VPA alone and 38 (39.6%) were given VPA together with one or two antiepileptic drugs as follows: carbamazepine (17), clonazepam (4), clobazam (5), diazepam (3), phenobarbitone (1), phenytoin (1), vigabatrin (5), and lamotrigine (8). Seventeen (17.7%) patients had platelet counts of <150 x 10<sup>9</sup>/L. No pre-existing thrombocytopenia was identified among the 17 patients, and none had concomitant neutropenia or anaemia.

Forty-eight children, whose mean (SD) age was 10.0 (5.0) years (range, 1.2-19.6 years), and who were taking antiepileptic drugs other than VPA were enrolled into the comparison group. The antiepileptic drugs used included the following: carbamazepine (41),

clonazepam (3), clobazam (2), diazepam (2), phenobarbitone (1), phenytoin (1), vigabatrin (2), lamotrigine (2), and topiramate (1). Two of the children in the comparison group had platelet counts of <150 x 10<sup>9</sup>/L (P<0.05) [Table 1]. In both these patients, the platelet counts were >100 x 10<sup>9</sup>/L and there was no sign of bleeding.

Multiple regression analysis of platelet count with age, VPA daily dose per kilogram, trough serum VPA level, and polytherapy in the VPA group showed that the platelet count was negatively associated with age and serum VPA level (P<0.001) and positively associated with polytherapy (P<0.05) [Figs 1 and 2]. The standardised beta of age, trough serum VPA level, and polytherapy were -0.42, -0.45, and 0.18, respectively. In the comparison group, the associations between platelet count and age or polytherapy were not statistically significant according to either Pearson's (product moment) correlation or Spearman's rank correlation tests. The VPA dosage was not an independent predictor of thrombocytopenia according to multiple regression. However, it was weakly associated with platelet count when the Spearman's rank correlation test was used (Spearman's rank correlation coefficient,  $r_s$  = -0.21; P<0.05).

The mean serum VPA level of the patients with thrombocytopenia was 564.8 µmol/L, compared with a mean level of 394.6 µmol/L in those patients without thrombocytopenia. Figure 3 shows the frequency distribution according to serum VPA level and VPA dosage in children with and without thrombocytopenia. There were apparent thresholds at a serum VPA level of 450 µmol/L and a daily dose of 40 mg/kg, above which thrombocytopenia became much more common. The linear correlation of serum VPA level with the VPA dosage was weak but statistically significant ( $r_s$  = 0.28; P<0.01).

Because the duration of VPA therapy may have been a confounding factor that led to thrombocytopenia in older children, subgroup analysis was performed for

**Table 1. Demographic and haematological data in the valproic acid and comparison groups**

	Valproic acid group, n=96	Comparison group, n=48
Age (years)*	1.9-20.3 (9.9±4.4)	1.2-19.6 (10.0±5.0)
Sex (M/F)	55/41	30/18
No. of patients receiving monotherapy (%)	58 (60.4)	40 (83.3)
No. of patients receiving polytherapy (%)	38 (39.6)	8 (16.7)
Valproic acid dose (mg·kg <sup>-1</sup> ·d <sup>-1</sup> )*	11.5-97.4 (44.2±21.1)	-
Trough serum valproic acid level (µmol/L)*	101-817 (421.8±156.5)	-
Platelet count (x 10 <sup>9</sup> /L)*	14-572 (262.7±116.8)	108-571 (263.3±111.1)
No. of patients with thrombocytopenia (%)	17 (17.7)	2 (4.2) <sup>†</sup>

\* Results expressed as range (mean±SD)

<sup>†</sup> P<0.05

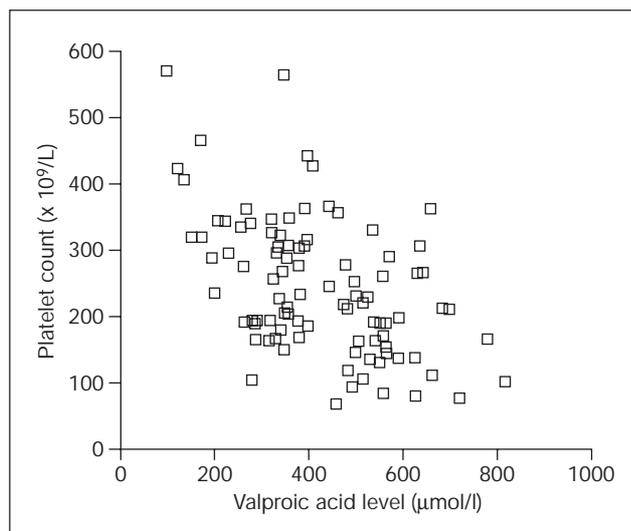


Fig 1. Correlation of platelet count with serum valproic acid level

the 45 children who were receiving high-dosage VPA and for the 51 children who were given low-dosage VPA. The duration of treatment was measured from the first day of VPA therapy for the low-dosage group. For the high-dosage group, the duration was measured from the first day of VPA treatment at a daily dose of  $\geq 40$  mg/kg. Spearman's rank correlation analysis showed that platelet count and treatment duration were not statistically significant for either the low- or high-dosage groups. Among the 22 children who received high-dosage therapy for less than 1 year, eight had already developed thrombocytopenia (Table 2).

Two children in the VPA group who had thrombocytopenia developed generalised petechiae. Both patients responded promptly to a reduced VPA dosage. One of the patients was a 16-year-old Chinese girl with intractable complex partial epilepsy. Her platelet count started to drop below  $50 \times 10^9/L$  when the VPA dosage exceeded  $50 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ . When the VPA dosage was decreased by approximately  $5 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ , there were prompt haematological and clinical responses within 2 weeks in this patient. After resuming VPA  $50 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$  (as her seizure control worsened with the lower dosage), her platelet count again decreased and she developed generalised petechiae, which resolved once more with a reduction in dosage.

No statistically significant Spearman's rank correlation (after Bonferroni correction) was found between

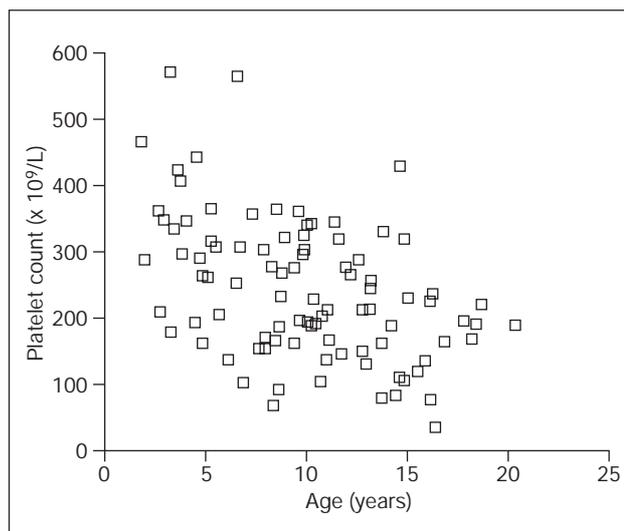


Fig 2. Correlation of platelet count with age

platelet count and liver function, or between trough serum VPA level and liver function.

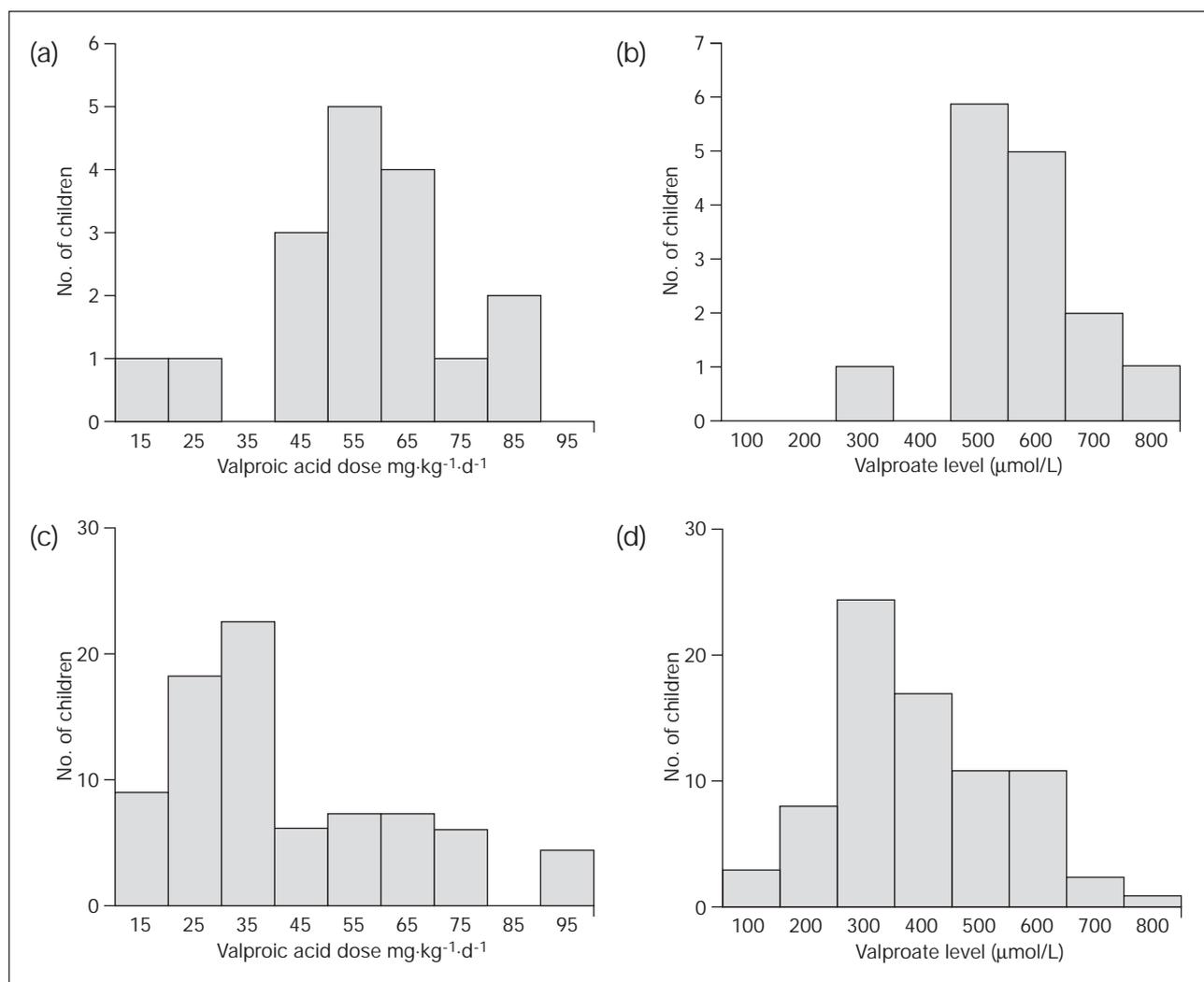
## Discussion

In this study, the trough serum VPA level and age were found to be inversely correlated to the platelet count. Patients with a trough serum VPA level of  $>450 \mu\text{mol/L}$  had a significantly higher risk of developing thrombocytopenia (Fig 3). This finding is consistent with those of previous retrospective studies of children.<sup>1,6</sup> The trough VPA level is more commonly measured than the peak level in daily practice since it is more consistent with the therapeutic effect.<sup>8,9</sup> Our finding suggests it also correlates well with the development of thrombocytopenia. The clinician should be alert to this complication when the trough level is above  $450 \mu\text{mol/L}$ . In this study, 44 (45.8%) of the 96 children were receiving a daily dose of  $\geq 40$  mg/kg, and one-third (15/44) developed thrombocytopenia. A daily dose of  $\geq 40$  mg/kg increased the risk for thrombocytolysis (Fig 3). Although, statistically, VPA daily dose per kilogram was not an independent predictor of thrombocytopenia, a useful guide for clinicians may be to monitor the serum VPA level and platelet count regularly when the daily VPA dose is  $>40$  mg/kg.

Valproic acid-associated thrombocytopenia was generally mild and asymptomatic. Among the 17

Table 2. Duration of high-dosage valproic acid treatment and thrombocytopenia

Duration of high-dosage treatment ( $\geq 40 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ )	<1 year	>1 year
No. of children	22	23
No. of children with thrombocytopenia (%)	8 (36)	7 (30)



**Fig 3. Histograms of valproic acid dosage and serum valproic acid level for children with platelet counts of  $< 150 \times 10^9/L$ , (a) and (b); and  $\geq 150 \times 10^9/L$ , (c) and (d)**

children with thrombocytopenia, 15 were asymptomatic. This proportion is consistent with the findings of previous studies. May and Sunder<sup>5</sup> reported that 12 of 60 patients who were receiving long-term VPA monotherapy developed thrombocytopenia, all of whom remained asymptomatic. Delgado et al<sup>6</sup> reported that only 8 of 64 patients with VPA-associated thrombocytopenia developed signs of bleeding. All of these patients recovered completely after dosage reduction or discontinuation of VPA. For most patients, recovery occurred within 1 week. Thrombocytopenia is usually transient and self-limiting. The interval between the initiation of VPA treatment and platelet nadir is variable among patients with thrombocytopenia, ranging from 8 days to 16 months.<sup>10</sup> Delgado et al<sup>6</sup> has shown that it takes an average of 7.5 months to develop thrombocytopenia in patients with high serum VPA levels.

Among the 96 children in the VPA group in this study, clinically significant thrombocytopenia developed

in only two (2.1%). For both patients, the platelet count increased promptly when the dosage was reduced and there was also a remission of the signs of bleeding. For one patient, resumption of VPA to the previous dosage led to a relapse of clinically significant thrombocytopenia within 2 weeks. This observation suggests that thrombocytopenia tends to develop promptly when the VPA dosage or serum VPA is above certain critical values. A similar phenomenon has been reported.<sup>2,11</sup>

The mechanism of VPA-associated thrombocytopenia is unclear. Barr et al<sup>10</sup> demonstrated that 82% of cases of thrombocytopenia was associated with an increased platelet-associated immunoglobulin (Ig) G level, and that the platelet count is inversely correlated to the level of platelet-associated IgG. The structural similarity between VPA and the fatty acid constituents of cell membranes may lead to an increased incidence of immune thrombocytolysis.<sup>3</sup> Bone marrow examination has revealed normal or slightly increased levels of megakaryocytes, suggestive of

increased peripheral platelet destruction.<sup>12</sup> This proposal, however, does not adequately explain the rapid response to dosage reduction and relapse of thrombocytopenia after the resumption of high-dosage VPA.<sup>6</sup>

Kishi et al<sup>13</sup> have shown that a high serum concentration of VPA is associated with *in vivo* and *in vitro* bone marrow suppression. In their study, pancytopenia recovered after the discontinuation of VPA treatment and concomitant supportive therapy. In this study, the white blood cell and red blood cell lines were not affected in patients receiving high-dosage VPA. While the VPA concentration-dependent thrombocytopenia could be explained by the mechanism of bone marrow suppression, the rare occurrence of pancytopenia suggests that other mechanisms may be involved that render the platelet cell lineage more vulnerable to VPA suppression or damage. It is possible that both immune-mediated peripheral platelet destruction and VPA concentration-dependent suppression of platelet precursors may be operating simultaneously.

In this study, the platelet count was found to be inversely correlated to age in children receiving VPA. We have demonstrated that the duration of VPA treatment is not a confounding factor in this age-related decrease in platelet count. The underlying mechanism remains unclear. It could be because the immune systems of older children are more mature and are thus able to generate a VPA-induced autoimmune thrombocytolysis. Alternatively, older children may be more susceptible to VPA-induced bone marrow suppression.

The platelet count was found to be positively correlated to polytherapy, although the underlying mechanism remains unclear. Carbamazepine was the most commonly used polytherapy drug. The combination of VPA and carbamazepine frequently results in lower serum VPA levels and a decreased incidence of thrombocytopenia.<sup>14</sup> Nevertheless, this mechanism does not adequately explain the positive correlation between platelet count and polytherapy, which is independent of the VPA level in the regression analysis.

No significant correlation was found between serum VPA concentration and liver function. The incidence of fatal hepatotoxicity induced by VPA has been found to be higher for patients of any age who are receiving multiple antiepileptic drugs.<sup>15</sup> Although VPA-associated hepatotoxicity is generally believed to be an idiosyncratic reaction, asymptomatic elevation in hepatic enzymes may be a marker for

early VPA-induced liver damage. It has been suggested that an elevation in aspartate transaminase levels to greater than three times the normal value may warrant a change in drug regimen.<sup>16</sup> Twenty-four children in the VPA group in this study were receiving a VPA dosage of  $>60 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ , the highest dosage being  $97.4 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ . Whereas three patients showed mildly elevated levels of liver transaminase, none had demonstrated a three-fold rise in aspartate transaminase levels. Beydoun et al<sup>8</sup> have shown that high-concentration monotherapy with VPA ( $555\text{--}1040 \mu\text{mol/L}$ ), which exceeds the recommended therapeutic range of  $345$  to  $695 \mu\text{mol/L}$ , is more effective than low-concentration therapy in controlling intractable partial epilepsy. However, the adverse events were significantly higher in the high concentration group, and included tremor, thrombocytopenia, alopecia, asthenia, diarrhoea, vomiting, anorexia, and headache.<sup>8</sup>

Apart from tremor and thrombocytopenia, most other adverse events were mild and did not require an adjustment in VPA dosage. We did not encounter severe side effects that required a major dosage reduction apart from thrombocytopenia. We believe that VPA can be safely increased above the recommended therapeutic range and dosage ( $20\text{--}60 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ ) to achieve better epilepsy control. Further study is required to explore the efficacy and safety of high-concentration VPA treatment in epilepsy refractory to the current therapeutic range.

## Conclusion

This study demonstrates that trough serum levels of VPA and age are the two most important independent predictors of thrombocytopenia. The duration of treatment is not a confounding factor in the latter correlation. Children with a trough level above  $450 \mu\text{mol/L}$  or receiving a dosage of  $\geq 40 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$  are more at risk for thrombocytopenia. The risk is further increased for older children. Platelet count monitoring is recommended for patients receiving high-concentration VPA treatment who are also receiving drugs that would affect homeostasis, or who are undergoing surgical procedures.<sup>17</sup> Thrombocytopenia is usually mild and responds to dosage adjustment.

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