Weight gain with valproate or carbamazepine—a reappraisal

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The use of valproate has traditionally been held to be associated with a greater incidence of weight gain than that of other anticonvulsants. This paper presents an analysis of body weight data gathered during a randomized trial comparing valproate with carbamazepine in 260 children aged 4–15 years with newly-diagnosed epilepsy. There were more reports of weight gain as an adverse event in the valproate group than in the carbamazepine group (22 reports in 14 patients vs. nine reports in five patients). However, amongst the 211 patients (103 on valproate and 108 on carbamazepine) in whom objective weight measurements were taken during treatment, there were no differences between the treatments in percentage weight gain from baseline or incidence of excessive weight velocity. Eight patients reporting weight gain on valproate were switched to carbamazepine because of poor seizure control and/or adverse events including weight gain, but three of the four patients for whom body weight measurements were available continued to gain weight on carbamazepine. It is concluded that weight gain may be erroneously attributed to valproate treatment.

Key words: epilepsy; carbamazepine; sodium valproate; weight gain.

INTRODUCTION

Sodium valproate is a well-established therapy in the treatment of epilepsy. It has been shown to be as effective as carbamazepine in the treatment of both adult-onset and paediatric epilepsy against both generalized and partial seizures. In addition, it has been associated with a lower incidence rate of side-effects necessitating its withdrawal as compared to phenytoin or phenobarbitone in paediatric patients.

Weight gain has traditionally been regarded as a side-effect characteristic of valproate therapy, although its reported incidence has varied widely, ranging from 7.5% to 73.0% in early studies. This may be an unacceptable side-effect for some patients, in particular teenage girls, in whom weight gain may lead to termination of sodium valproate treatment; paediatric studies have also reported weight gain (in from approximately 10% to 44% of patients). Since the medical profession does not associate weight gain with other anticonvulsants (such as carbamazepine) to the same extent, its occurrence in patients on valproate may lead to a switch of maintenance therapy, with the possibility of the patient suffering other side-effects from the new medication.

The reporting of side-effects in clinical practice and open studies may be influenced by patient and clinician expectations, and if a drug is perceived to be associated with a particular effect any occurrence of it during treatment may be more likely to be attributed to the drug. Conversely, weight gain occurring during treatment with a drug for which this side-effect is not expected may be overlooked. This paper reports on objective measures of weight gain, recorded as part of the paediatric EPITEG trial which compared sodium valproate with carbamazepine, in order to investigate the presence and extent of any subjective response.

METHODS

A full description of the paediatric EPITEG trial has been published elsewhere. This paper presents a retrospective analysis of the body weight data recorded during the study.
The open, randomized study was conducted at 63 outpatient clinics in the UK and the Republic of Ireland. Two hundred and sixty children (4–15 years) with newly-diagnosed primary generalized epilepsy or partial epilepsy, with or without secondary generalization, participated in the study. Children with renal, hepatic, or other central nervous system disorders were excluded, as were children with abnormal liver function tests or blood dyscrasias, and girls taking contraceptive medication at entry.

Patients were randomized to receive either sodium valproate (initial dose 200 mg twice daily, increasing by 200 mg daily if clinically necessary, to a maximum of 30 mg/kg daily), or carbamazepine (initial dose 5 mg/kg daily, increasing in the second week of treatment to 10 mg/kg daily, and thereafter as clinically necessary to a maximum of 20 mg/kg daily). Failure of seizure control or occurrence of adverse events permitted cross-over to the alternative therapy. Any child requiring additional anticonvulsant medication was withdrawn from the study. Patients were assessed after one month of treatment, then at 3-monthly intervals for the first year, and at approximately 6-monthly intervals thereafter for the remainder of the trial. The total period of follow-up was 3 years.

Measurements of body weight taken at each visit were used for the present analysis. Patients were excluded if weight data were not available at baseline, or available only at baseline. If a patient crossed to the alternative treatment, only body weight data pertaining to the first treatment were included in the analysis, although changes in weight measured after transfer to the alternative drug were considered on an individual basis.

Since the drop-out rate beyond one year was high, only data for the first 13 months were used. Patients were subgrouped by age (4–6 years, 7–9 years, 10–12 years and 13–15 years) and sex, since growth rates and average body mass indices vary according to these parameters.

Weight velocity was calculated for each patient as the change in body weight over or extrapolated to one year. Weight velocity was classed as 'excessive' if it exceeded the 97th centile expected for a child of that age and sex (as defined by Egger and Brett). If the body weight data for any patient was only available for a period of less than 11 months, but weight velocity extrapolated to one year exceeded the 97th centile, it was classed as 'probably excessive'. The incidence of patients displaying excessive weight velocity was compared between the treatment groups by calculating odds ratios.

Any patient with a body mass index [BMI; weight (kg)/height (m)²] at study entry higher than the 90th centile for their age and sex (as defined by Cronk and Roche) was classed as obese.

RESULTS

Percentage weight gain from baseline

From a total of 260 patients originally enrolled in the EPITEG trial, 211 with adequate body weight records were eligible for this analysis, listing weight measurements for at least one month after baseline. Of the 103 patients in the valproate group and 108 patients in the carbamazepine group, 11 (10.7%) and 11 (10.2%) respectively, were classifiable as obese at study entry.

There was no consistent difference between the two treatment groups with respect to mean percentage changes in body weight from baseline over the four age ranges (Fig. 1).

Incidence of excessive body weight velocity

Body weight velocity was calculated for 203 patients (eight patients, four from each treatment, were excluded either because they were off treatment or no weight measurements were taken after 1 month). The risks of excessive or probably excessive weight velocities analysed by sex and treatment group are shown in Table 1. The data suggest that risk of excessive velocity slightly increases with valproate for males and with carbamazepine for females, however, no real differences could be established between the two drugs.

![Fig. 1: Mean percentage weight gain from baseline in children with epilepsy during treatment with sodium valproate (n = 103) or carbamazepine (n = 108). ×, Sodium valproate; ○, carbamazepine.](image-url)
Weight gain with valproate or carbamazepine

Table 1: Risks of excessive or probably excessive weight velocities by sex and treatment group

<table>
<thead>
<tr>
<th></th>
<th>Sodium valproate</th>
<th>Carbamazepine</th>
<th>Odds ratio</th>
<th>95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (n/N)</td>
<td>% (n/N)</td>
<td></td>
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</tr>
<tr>
<td>Males</td>
<td>32.6 (15/46)</td>
<td>28.0 (14/50)</td>
<td>1.24</td>
<td>0.52, 2.98</td>
</tr>
<tr>
<td>Females</td>
<td>20.8 (11/53)</td>
<td>29.6 (16/54)</td>
<td>0.62</td>
<td>0.26, 1.51</td>
</tr>
</tbody>
</table>

Reported body weight gain

Of the 260 patients originally enrolled in this study, 12 patients (9.2%) who received valproate as initial therapy reported weight gain as an adverse event on 18 occasions, compared with five patients (3.8%) who initially received carbamazepine on nine occasions. A further two patients reported weight gain on four occasions after having been switched from carbamazepine to valproate. Three patients (two on valproate; one on carbamazepine) reporting weight gain as an adverse event were excluded from the present analysis population due to insufficient weight data, while in three other cases (all on valproate) weight gain was not reported until after the 13 month analysis period. Therefore, a total of eight patients (13 occasions) reporting weight gain during valproate therapy, and four patients (five occasions) during carbamazepine therapy, were included in the present analysis. All five of the carbamazepine reports of weight gain and 11 of the valproate reports corresponded to excessive weight velocity.

Crossover between therapies

The trial design permitted patients who failed on first treatment because of poor seizure control, adverse events, or both, to be crossed to the alternative treatment for the remainder of the 3-year trial period. Full details of these treatment failures are given elsewhere.

Eight of the patients who reported weight gain while on valproate were later crossed over to carbamazepine. In two of these cases, no weight data were recorded on either drug; in a further two cases, no objective weight measurements were made after the switch to carbamazepine. Of the remaining four patients, only one showed a pattern consistent with valproate-induced weight gain. This 12-year-old girl was overweight at study entry (65 kg). After gaining a further 5 kg in 6 months of valproate treatment she requested that treatment be stopped. She was transferred to carbamazepine and subsequently lost weight, reaching 52 kg by the 2-year follow-up visit. Another previously obese patient (a boy of 13 years) was transferred to carbamazepine, but continued to gain weight after the changeover. Neither of the other two patients had stopped valproate treatment for weight-related reasons and the change of medication again had no apparent effect on their weight.

DISCUSSION

Various mechanisms have been postulated to explain weight gain in patients taking sodium valproate, however, the present study does not support the perception that weight gain is an effect peculiar to the use of this drug. The present data indicate that valproate and carbamazepine have similar effects on weight when used to treat children with epilepsy. During the study from which the data used was taken more patients reported weight gain with valproate than with carbamazepine; however, analysis of objective measurements of weight, taken as part of the original trial protocol, shows no difference between the treatment groups with respect to percentage weight increase from baseline or incidence of excessive weight velocity. Indeed, in girls (for whom weight gain is often quoted as being an unacceptable side-effect) there was a trend to a lower incidence of excessive weight velocity in the valproate-treated group (see Table 1).

In open studies and clinical practice observer bias cannot be eliminated as it can be in double-blind trials. A perception that sodium valproate is more likely to cause weight gain may lead to observed weight gain in a valproate-treated child being attributed to the drug even though the treatment may have been only a contributory factor. The data reported here show some indication of this effect. Of those reports made during the first 13 months on treatment, where objective weight measurements were available, two during valproate therapy did not correspond to excessive weight velocity. This suggests that in these cases normal growth had been mistakenly interpreted as a side-effect of valproate.

Another possible effect of observer bias in the original study was an apparent under-reporting
of excessive weight gain associated with carbamazepine. The number of such reports associated with carbamazepine was much lower than that with valproate even though there were no differences with the number of patients with excessive and probably excessive weight velocities between the two treatment groups.

The individual records of the patients reporting weight gain during valproate therapy who subsequently changed to carbamazepine, also suggest that valproate may be less important as a cause of weight gain than is generally supposed. Three of the four patients for whom objective weight measurements were available during both treatments showed no dramatic change in their rate of weight gain after cross-over. The fourth patient lost a substantial amount of weight during carbamazepine treatment, eventually reaching a normal weight after having been overweight at study entry. Had her excess weight been due entirely to valproate treatment, it is unlikely that withdrawing the drug would have reduced her weight to less than it was at the start of therapy. Her weight loss may have been caused, at least in part, by other factors such as developmental changes.

The finding of the present report—that the incidence of weight gain associated with valproate treatment may be exaggerated and may be no different from that associated with carbamazepine treatment—is at variance with the conclusions drawn by other studies. In particular, a double blind, randomized trial comparing valproate with carbamazepine in adults found a significantly greater incidence of excessive weight gain associated with valproate vs. carbamazepine. However, that trial utilized patients from a very specific population: predominantly adult male war veterans, 31% of whom had trauma-related epilepsy. The difference between this population and the one used in the present study may explain the disparity between the results.

One obvious drawback of the present study is its open nature. Weight data were not recorded on all study visits in the original trial which led to patients being excluded from the present analysis. Moreover, the irregular frequency with which height data were recorded precluded more detailed analyses involving BMI, rather than weight, as a variable. It also would have been useful to compare data from the adult EPITEG trial, however, weight data are not available to enable this analysis to be made. Notwithstanding, the present study raises serious doubts about the traditionally-held view concerning the incidence of weight gain with this widely-used antiepileptic agent. It is suggested that this issue should be addressed by any future prospective, double blind, randomized trial involving valproate and/or carbamazepine in a wider population of patients.

CONCLUSIONS

This study, the first to compare the effects of sodium valproate and carbamazepine on objective measures of weight gain, found that sodium valproate may be no more likely than carbamazepine to be associated with weight gain when used to treat children with epilepsy. Weight gain due to other factors, such as existing adiposity or a normal growth spurt, may be erroneously attributed to sodium valproate, and that occurring during carbamazepine may be overlooked. Clinicians should consider all possible reasons for an observed increase in weight before deciding to switch the patient to a new anticonvulsant, since inappropriate changing of the patient's medication may result in further side-effects caused by the new drug.

ACKNOWLEDGEMENTS

Members of the Paediatric EPITEG collaborative group who performed the original EPITEG study are listed in the original publication: Verity, C.M., Hosking, G., Easter, D.J. on behalf of the Paediatric EPITEG Collaborative Group. A multicentre comparative trial of sodium valproate and carbamazepine in paediatric epilepsy. Dev. Med. Child Neurol., 1995; 37: 97–108.

REFERENCES


