Long-term developmental outcome of children of women with epilepsy, unexposed or exposed prenatally to antiepileptic drugs: a meta-analysis of cohort studies

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CRD summary

This meta-analysis concluded valproic acid treatment during pregnancy was associated with reduced IQ scores in children of mothers with epilepsy; carbamazepine did not appear to be associated with reduced verbal IQ and full-scale IQ scores. Methodological weaknesses in the included studies and limitations in the review process made the reliability of the authors' conclusions unclear.

Authors' objectives

To estimate intellectual development of children prenatally exposed or unexposed to antiepileptic drugs in terms of intelligence quotient (IQ) scores.

Searching

PubMed, EMBASE databases and Google Scholar were searched from inception to April 2009 without language restrictions. Search terms were reported. Reference lists of retrieved papers were reviewed.

Study selection

Published case control and cohort studies that examined the relationship between exposure to antiepileptic drugs (phenytoin, carbamazepine, valproic acid/valproate and/or barbiturates) during pregnancy and any measure of cognitive function in their offspring and that compared antiepileptic drug use with a control group not exposed to any of the antiepileptic drugs were eligible for inclusion. Case reports, editorials, reviews, studies in which no specific data could be extracted and studies that did not provide sufficient data for analysis were excluded.

Control groups were recruited in different ways by different studies. Where reported, age of participants when the test was performed ranged from six months to 19 years. Mothers with and without epilepsy formed part of the control group. Outcomes of interest were scores of cognitive function measured by Wechsler, Bayley or McCarthy IQ scales or any other measure.

Two reviewers selected studies. A third reviewer made the final decision in cases of unresolved disagreements.

Assessment of study quality

The authors did not state that they assessed quality of the included studies in this review.

Data extraction

Two reviewers independently extracted mean IQ scores for children exposed and unexposed to antiepileptic drugs. It was not reported how any disagreements were resolved.

Methods of synthesis

Mean IQ scores and 95% confidence intervals (CIs) were combined using a random-effects model with inverse variance weighting. Where head-to-head data were not available, data were combined across arms of studies using a random-effects model and the results were compared using a two-tailed t-test with pooled variances. Heterogeneity between trials was assessed by c^2, X^2 and I^2 statistics.

Results of the review

Eleven studies met the inclusion criteria, but only the seven studies (n=1,102 participants) that used IQ testing as a measure of cognitive development were included in the meta-analysis. Five of the seven studies used the Wechsler IQ scale and two studies used Bayley or McCarthy scale. Overall numbers of children included in the meta-analysis were: 67 exposed to valproic acid; 151 to carbamazepine; and 21 to phenytoin. Controls were 494 children born to mothers with epilepsy (n=58) or mothers with epilepsy but not exposed to antiepileptic drugs and healthy mothers without

epilepsy (n=436).

Weighted mean scores of verbal IQ (VIQ), performance IQ (PIQ) and full-scale IQ (FSIQ) were significantly lower in the children exposed to valproic acid: VIQ (mean 83.9, 95% CI 64.2 to 103.6); PIQ (mean 93.7, 95% CI 72.6 to 114.7) and FSIQ (mean 88.3, 95% CI 69.6 to 106.9) compared with children whose mothers had epilepsy but were not exposed: VIQ (mean 97.5, 95% CI 73.3 to 121.7); PIQ (mean 98.6, 95% CI 70.4 to 126.8); and FSIQ (mean 98.7, 95% CI 73.1 to 124.3) or whose mothers did not have epilepsy and were not exposed: VIQ (99.7, 95% CI 87.8 to 111.6); PIQ (mean 100.5, 95% CI 86.1 to 114.8); and FSIQ (mean 99.6, 95% CI 88.1 to 111.2). Intelligent quotient was significantly lower in valproate exposed compared with controls in a subgroup analysis.

For carbamazepine, mean VIQ and FSIQ scores on the Wechsler scale for exposed children were not statistically significantly different from the unexposed children. However, mean PIQ was significantly lower than all-group control ($p<0.002$). Compared with children whose mothers had epilepsy but were not exposed, mean VIQ, PIQ and FSIQ were not statistically significantly different from children who were exposed to carbamazepine. Using the Bayley/McCarthy scale, the mean FSIQ of children exposed to carbamazepine versus children of mothers without epilepsy and who were not exposed were similar (98 versus 102 points).

Authors' conclusions

Exposure to valproic acid in pregnancy was associated with reduced intelligence in children whose mothers were treated for epilepsy; carbamazepine did not appear to be associated with reduced FSIQ and VIQ.

CRD commentary

This review addressed a well-defined question in terms of participants, interventions and study design. It appeared that the authors excluded three studies at the analysis stage which met the a priori inclusion criteria. The search included a range of electronic databases, but no attempts were made to retrieve unpublished studies and the possibility of publication bias could not be ruled out. Two reviewers independently selected studies and extracted data to minimise bias and errors during the review process. There were no apparent attempts to assess study quality. Controls of one study excluded from the meta-analysis were used as part of the control group for the assessment of adverse effects. Given such limitations, the possibility for bias could not be ruled out. The authors stated that because one study was identified for each of phenytoin and phenobarbitone, no formal meta-analysis could be performed for these drugs; these studies could have been reported separately. These issues, together with lack of robust assessment and reporting of clinical variation and statistical heterogeneity in the included studies and limitations in the review process made the reliability of the authors' conclusions unclear.

Implications of the review for practice and research

Practice: The authors stated that prescribing clinicians should inform families of the potential cognitive adverse effects of valproic acid.

Research: The authors stated that further studies were warranted to substantiate these findings.

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