A cost-minimization analysis of phenytoin versus levetiracetam for early seizure pharmacoprophylaxis after traumatic brain injury

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

CRD summary
This study examined the clinical and economic impact of levetiracetam, compared with phenytoin, to prevent early seizures after traumatic brain injury. The authors concluded that phenytoin was cheaper than levetiracetam and, unless levetiracetam was proven to be more effective, phenytoin should be used to prevent early seizures after traumatic brain injury. The cost-minimisation framework was valid, but reliant on the finding of equal efficacy between treatments. Given the low quality of the two sources, further investigation is needed.

Type of economic evaluation
Cost-effectiveness analysis

Study objective
This study examined the clinical and economic impact of levetiracetam, compared with phenytoin, to prevent early seizures after traumatic brain injury.

Interventions
Levetiracetam 1g was compared with phenytoin 300mg. Each treatment was given intravenously twice daily for seven days.

Location/setting
USA/tertiary care.

Methods
Analytical approach:
The evaluation was based on a decision-tree model, with a short time horizon, corresponding to the length of the initial hospitalisation. The authors stated that the perspectives of both the acute care institution and the patient were adopted.

Effectiveness data:
A review of the literature, from 1980 to March 2011, was carried out in the PubMed database to identify the inputs for the model. The evidence was from a retrospective cohort study of 27 patients and a randomised controlled trial of 52 patients. Failure of efficacy (prevention) was the primary input and this was defined as the occurrence of at least one seizure in the early period (up to seven days) after injury. Both studies showed that there was no statistically significant difference in electroencephalographic evidence of seizures between the groups. The rates of adverse events were from the clinical trial and were another important input.

Monetary benefit and utility valuations:
Not considered.

Measure of benefit:
The two treatments were equally effective, so no summary benefit measure was used and a cost-minimisation analysis was carried out.

Cost data:
The economic analysis included the costs of the drugs and routine assessments of serum phenytoin concentration and
serum albumin concentration. The drug costs were from the institution's pharmacy wholesaler, for the normal seven-day in-patient treatment. Patient charges for laboratory work-up were from institutional pricing formulas. All costs were in US $ and the price year was 2011.

Analysis of uncertainty:
One-way sensitivity analyses were carried out on the baseline probabilities of adverse events, the costs or charges for treating these events, and the frequency of laboratory assessment for the phenytoin strategy. The costs of the medical assessment of deterioration in mental status (computed tomography of the head, magnetic resonance imaging, electroencephalograph, and complete blood count) were included in an alternative scenario. A Monte Carlo simulation of 1,000 hypothetical patients was run to calculate the mean outcomes for the two strategies.

Results
Phenytoin produced a statistically significant higher rate of gastrointestinal upset, deteriorating mental status, and anaemia.

From the perspective of the health care institution, the mean cost per patient was $151.24 with phenytoin and $411.85 with levetiracetam. From the patient perspective, the mean charge per patient was $2,302.58 with phenytoin and $3,498.40 with levetiracetam.

For both perspectives, phenytoin saved costs, compared with levetiracetam, in all sensitivity analyses, even when making unfavourable assumptions. The cost of treating mental status deterioration was the most influential input.

Authors’ conclusions
The authors concluded that phenytoin was cheaper than levetiracetam and, unless levetiracetam was proven to be more effective, phenytoin should be used to prevent early seizures after traumatic brain injury.

CRD commentary
Interventions:
The selection of the comparators was appropriate. Phenytoin was the most commonly used prevention and the only one endorsed by a professional organisation, namely the American Academy of Neurology. Levetiracetam had recently been shown to be similar in efficacy and safety to phenytoin, but the economic implications of the two drugs had not been explored.

Effectiveness/benefits:
The clinical data were from two studies of different quality; one was retrospective and the other was a randomised controlled trial. Both studies had very small samples. Differences in adverse events, but not in treatment efficacy, were found in the clinical trial. The model parameters were varied in the sensitivity analysis.

Costs:
The economic analysis was satisfactorily performed. Appropriate cost categories were included and different sources of data were used, depending on the perspective. The unit costs were reported, with some key data on resource consumption. The price year was explicitly stated, allowing reflation exercises. The impact of varying key economic inputs was appropriately investigated in the sensitivity analyses.

Analysis and results:
The results were clearly presented. A synthesis of costs and benefits was not relevant because a cost-minimisation analysis was conducted. The uncertainty was partly investigated, by varying some key parameters, and the findings were robust. The main issues for the study were the quality of the clinical sources and the use of a cost-minimisation analysis. If the adverse events had an impact on the patients’ quality of life, phenytoin and levetiracetam would produce different quality-adjusted life-years, favouring levetiracetam. The findings were specific to the authors' setting and cannot be directly transferred to other settings.

Concluding remarks:
The cost-minimisation framework was valid, but reliant on the finding of equal efficacy between treatments observed in the two published studies. Given the low quality of these two studies, further investigation is needed to corroborate the
authors’ conclusions.

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