Cost-minimization analysis of phenytoin and fosphenytoin in the emergency department

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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.

Health technology
The use of fosphenytoin, a drug approved by the Food and Drug Administration in 1996 for the treatment of patients with seizure disorders.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with acute seizure disorders presenting at the emergency department, with the exception of patients in status epilepticus.

Setting
The setting was a hospital emergency department. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness evidence and resource use data were gathered in 1998. The price year was 1999.

Source of effectiveness data
The effectiveness evidence was derived from a published study (see Other Publications of Related Interest).

Modelling
A decision analytic model was developed to estimate the expected costs and the frequency of adverse events associated with the two drug treatments. The effectiveness, in terms of stopping seizures, was assumed to be equal for both the drugs. Patients in status epilepticus, and those for whom intravenous phenytoin would not be administered, were excluded from the analysis.

Outcomes assessed in the review
The outcomes assessed in the review, and used as input parameters in the decision model, were mainly the clinical data on the rates of several adverse events. These were collected prospectively and retrospectively from the single study.

Study designs and other criteria for inclusion in the review
The study selected for the effectiveness evidence was a prospective unblinded clinical trial, in which 256 patients were
randomised to receive phenytoin on odd-numbered days and fosphenytoin on even-numbered days of each month.

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
Not reported.

**Methods used to judge relevance and validity, and for extracting data**
Not reported.

**Number of primary studies included**
The effectiveness evidence was derived from a single study.

**Methods of combining primary studies**
Not applicable, given that only one study was used to derive the effectiveness data.

**Investigation of differences between primary studies**
Not applicable.

**Results of the review**
In the phenytoin group, the only adverse event was vein burning (9.1%). In the fosphenytoin group, the adverse events were hypotension (0.5%), infiltration (0.5%), burning legs and buttocks (2.5%), pruritus (7.4%), tongue swelling (0.5%) and vein burning (0.5%).

**Measure of benefits used in the economic analysis**
The two drug treatments were considered equally effective, therefore a cost-minimisation analysis was undertaken. The authors used the frequency of the adverse events to calculate the costs for treating the same adverse events.

**Direct costs**
Discounting was not carried out given the short duration of the treatment. The unit costs and resource quantities were reported separately. The boundary adopted was that of the hospital. The costs and the quantities were estimated from actual data. The total costs of the treatments were derived through the decision model. The costs of the treatment with the two drugs included medical accessories, wholesale prices from the drugs, and personnel costs. The costs of the medical accessories were derived from cost data from a purchasing organisation encompassing over 1,000 hospitals. The wholesale prices for the drugs were gathered from the 1999 Drug Topics Red Book. The personnel costs were obtained from institutional salary data. The costs of treating adverse effects were also considered and included. The resource use data were gathered in 1998. The price year was 1999. The costs and resources related to administering the drug were omitted because they were common to both treatments.

**Statistical analysis of costs**
No statistical analysis of the costs was reported, although the costs were treated stochastically.

**Indirect Costs**
The indirect costs were not included.

**Currency**
US dollars ($).

**Sensitivity analysis**
Sensitivity analyses (one-way and multi-way) and Monte Carlo simulations were performed. These were used to investigate the variability in the data and to assess the robustness of the model. Almost all the variables in the model were varied. A scenario analysis, based on the effectiveness data from a different clinical trial, was also carried out.

**Estimated benefits used in the economic analysis**
See the 'Effectiveness Results' section.

**Cost results**
The average annual salary was $43,576 for a nurse, $145,475 for a physician and $57,678 for a pharmacist. Phenytoin cost $1.84 for one dose, while fosphenytoin cost $180 for one dose. The costs of treating adverse events were $4.23 for ataxia and vertigo, $4.23 for hypotension, $144.07 for infiltration, $2.41 for burning on legs and buttocks, 16.71 for pruritus, $4.23 for vein burning, and $671.22 for purple glove syndrome. The total expected cost of administering phenytoin was $5.39, compared with $110.14 for fosphenytoin. The cost difference was $104.76. When the personnel costs were excluded, the cost of phenytoin was $5.31 and the cost of fosphenytoin was $108.68. The expected difference in cost was $103.38. The sensitivity analyses showed that the base-case analysis results were fairly robust to reasonable variations in the model parameters. Monte Carlo simulation and scenario analysis indicated that phenytoin remained the preferred drug.

**Synthesis of costs and benefits**
Not relevant due to the cost-minimisation analysis carried out.

**Authors' conclusions**
The administration of phenytoin in patients with seizure disorders was associated with substantial cost-savings in comparison with fosphenytoin.

**CRD COMMENTARY - Selection of comparators**
The reason for the choice of the comparator was clear. Phenytoin was selected because it represented the prior drug of choice for patients with seizure problems presenting at a hospital emergency department. You should consider whether it is considered a widely used technology in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness measures were derived from a single published study, which was based on a randomised clinical trial. The authors recognised that the study was not blinded, and this could have resulted in some bias in the data collection. Also, effectiveness was assumed to be equal in terms of the incidence of stopping seizures; the time to stop was not considered important in this context. However, this highlights the problem of considering effectiveness separately to adverse events. In health outcome terms, there was considered to be a difference between the treatments in that this difference was reflected in the difference in cost to treat the adverse events. Finally, it should be noted that only one study was used to provide the effectiveness evidence, and it is unclear what the strategy was for locating relevant studies.
Validity of estimate of measure of benefit
This is not applicable due to the cost-minimisation analysis conducted, although it might be questionable whether the drugs are equal in effectiveness in terms of seizure cessation. Also, the difference in terms of all health outcomes (including adverse events) was not accounted for.

Validity of estimate of costs
All the costs relevant to the perspective adopted appear to have been included in the analysis. The costing appears to have been fully reported. Extensive sensitivity analyses were performed on the cost data, thus enhancing the external validity of the study. However, some specific cost estimations (i.e. cost associated with purple glove syndrome) were not accurate, as the authors acknowledged, due to the lack of data.

Other issues
The issue of the generalisability of the results to other settings was partially addressed by performing several sensitivity analyses. Further, the authors made appropriate comparison of their findings with those of other studies. However, the authors reported some limitations. These were mainly due to the design of the study used as the source of the effectiveness data. The authors’ conclusions were in keeping with the scope of the study.

Implications of the study
Intravenous phenytoin provides the greatest value from the provider’s perspective. The results are mainly applicable to patients who receive a single dose of phenytoin or fosphenytoin. Further research is necessary to determine the frequency of delayed infusion-related reactions with phenytoin.

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Other publications of related interest

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MeSH
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