Cost-effectiveness of oral phenytoin, intravenous phenytoin, and intravenous 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 oral phenytoin (poP), intravenous phenytoin (ivP), and intravenous fosphenytoin (ivF) for the treatment of patients presenting to the emergency department (ED) with seizures and sub-therapeutic phenytoin concentrations. poP was administered in increments of 400 mg every 2 hours until a dose of 20 mg/kg was reached. Dosing for the intravenous routes was 18 mg/kg for phenytoin and 18 mg/kg phenytoin equivalents for fosphenytoin. The infusion rates were initiated at 50 mg/minute (ivP) and 150 mg/minute (ivF) for each drug, respectively, and were adjusted downward according to a preset protocol.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients receiving maintenance phenytoin therapy for an existing seizure disorder, who had presented to the ED with a seizure in the past 48 hours and a serum phenytoin concentration less than 5 microg/mL.

Setting
The setting of the study was a hospital ED. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness evidence and resource use data came mainly from a study published in 2004. The price year was not reported.

Source of effectiveness data
The effectiveness evidence was derived from a single study, the results of which had been published elsewhere (Swadron et al., see Other Publications of Related Interest).

Link between effectiveness and cost data
The costing was performed prospectively on the same sample of patients as that used in the effectiveness analysis.

Study sample
There was limited information on the sample selection method as most of the details of the trial had been published elsewhere. It was not reported whether power calculations had been conducted. A sample of 45 patients was included in
the analysis. There were 16 patients in the poP group, 14 in the ivP group, and 15 in the ivF group.

Study design
This was a prospective, randomised clinical trial that was carried out at a single centre. Details of the methods of randomisation and blinded assessment of the outcomes were not provided. The patients were observed for 24 hours from the time of initiation of study medication for drug administration, pharmacokinetic sampling at predetermined times, and observation of adverse events (AEs). No patient appears to have been lost to the follow-up assessment. The AEs were treated according to a standardised algorithmic approach.

Analysis of effectiveness
The analysis of the clinical study appears to have been conducted on an intention to treat basis, as all of the patients included in the initial study sample were accounted for in the effectiveness analysis. The outcomes used in the study were the rates of AEs and the time to AE resolution. AEs included ataxia, disorientation, dizziness or headache, hypotension, pruritus, nausea or vomiting, nystagmus, phlebitis, and tachycardia. The recurrence of seizures was also recorded, but it was not included in the analysis because the difference among groups was not statistically significant. The baseline comparability of the study groups was not discussed.

Effectiveness results
The rates of AEs for poP were 25% (range: 6.8 - 59.5) for ataxia, 12.5% (range: 1.6 - 38.3) for disorientation, 37.5% (range: 15.2 - 64.5) for dizziness or headache, 12.5% (range: 1.6 - 38.3) for nausea or vomiting, and 18.8% (range: 4 - 45.7) for nystagmus.

The rates of AEs for ivP were 14.3% (range: 1.8 - 42.4) for ataxia, 14.3% (range: 1.8 - 42.4) for disorientation, 28.6% (range: 8.4 - 58.1) for dizziness or headache, 14.3% (range: 1.8 - 42.4) for hypotension, 0% (range: 0 - 23.2) for nausea or vomiting, 42.9% (range: 17.7 - 71.2) for nystagmus, 78.6% (range: 49.2 - 95.4) for phlebitis, and 0% (range: 0 - 23.2) for tachycardia.

The rates of AEs for ivF were 0% (range: 0 - 21.8) for ataxia, 13.3% (range: 1.7 - 40.4) for disorientation, 40% (range: 16.3 - 67.7) for dizziness or headache, 6.7% (range: 0.2 - 32) for hypotension, 80% (range: 51.9 - 95.7) for pruritus, 26.7% (range: 7.8 - 55.1) for nausea or vomiting, 20% (range: 4.3 - 48.1) for nystagmus, 20% (range: 4.3 - 48.1) for phlebitis, and 6.7% (range: 0.2 - 32) for tachycardia.

The time to AE resolution (minutes) was 35 (range: 25 - 45) for ataxia, 58.5 (range: 12.6 - 104.4) for disorientation, 63.4 (range: 3.4 - 123.4) for dizziness or headache, 7.5 (range: 2.5 - 12.5) for hypotension, 18.3 (range: 7.5 - 29) for pruritus, 18.5 (range: 5 - 32) for nausea or vomiting, 45.9 (range: 20.2 - 71.6) for nystagmus, 19.9 (range: 11.6 - 28.2) for phlebitis, and 5 (range: 0 - 100) for tachycardia.

Clinical conclusions
The results of the effectiveness analysis were used as model inputs.

Modelling
A decision tree was constructed to determine the costs associated with the three loading approaches under examination. The tree was mainly based on the probability of adverse events associated with each alternative. The structure of the tree was depicted.

Measure of benefits used in the economic analysis
The summary benefit measures used were the number of AEs per person and the time to safe ED discharge.
Direct costs
Discounting was not relevant since the costs were incurred during a short timeframe. The unit costs were not presented separately from the quantities of resources used for all cost items. The health services included in the economic evaluation were hospital care (including drug administration and the treatment of AEs) and salary. The cost/resource boundary of the hospital was adopted.

The cost of care was determined using a micro-costing approach. Salary data and cost of care were both obtained from the hospital administrative databases. Resource use was based on data derived from the clinical trial and from time and motion studies. The time and motion studies were performed by randomly selecting 6 nurses from the ED staff and timing their performance for starting an intravenous line, setting up the cardiac monitor and intravenous pump for drug administration, and preparing the medication for administration. Physician time was calculated similarly. Only nursing time was considered for poP, given that it requires minimal preparation time and its AEs are typically transient and do not require additional supplies.

The price year was not reported. The three alternative scenarios considered in the cost analysis were the base-case (only costs of care; excluding salary), labour scenario (including costs of care and salary), and triage scenario (lower urgency area of ED). Under the latter scenario (triage), the patients were treated in a minor care area rather than at a monitored bed. In this case, poP was expected to generate revenue for the hospital.

Statistical analysis of costs
Power calculations were carried out in the preliminary phase of the study to determine the adequate sample size to detect a minimum difference of 30% in cost between the three groups. A sample of 180 patients would have been required. However, an interim analysis revealed that, after the enrolment of the first 45 patients, a statistically significant difference in costs had already been achieved. Statistical tests were carried out to test the statistical significance of differences in the costs.

Indirect Costs
The indirect costs were not included.

Currency
US dollars ($).

Sensitivity analysis
Sensitivity analyses were carried out to deal with the uncertainty arising from variability in the data used in the decision model. Univariate sensitivity analyses were performed for all model inputs. Probability values were varied within the range reported in the trial (95% confidence interval), while the cost data were varied by 50 to 200% of their base-case values. Monte Carlo simulations were also carried out, the results of which were used to construct acceptability curves for various thresholds of what was considered cost-effective. All the sensitivity analyses were performed on all three cost scenarios.

Estimated benefits used in the economic analysis
The number of AEs per person was 1.06 with poP, 1.93 with ivP, and 2.13 with ivF. The time to safe ED discharge was 6.4 hours with poP, 1.7 hours with ivP, and 1.3 hours with ivF.

Cost results
The total costs in the base-case were $2.83 with poP, $23.48 with ivP, and $176.79 with ivF.

The total costs in the labour scenario were $40.06 with poP, $84.31 with ivP, and $238.67 with ivF.
The total costs in the triage scenario were -$297.17 with poP, $23.48 with ivP, and $176.79 with ivF.

**Synthesis of costs and benefits**
An incremental cost-effectiveness ratio was calculated to combine the costs and benefits of the three strategies under evaluation. In all scenarios, poP dominated the other strategies in terms of cost per AE avoided. The cost per hour of ED time saved was:

- in the base-case, $4.39 with ivP over poP, $383.28 with ivF over ivP, and $34.11 with ivF over poP;
- in the labour scenario, $9.41 with ivP over poP, $385.90 with ivF over ivP, and $38.94 with ivF over poP; and
- in the triage scenario, $81.46 with ivP over poP, $383.28 with ivF over ivP, and $105.07 with ivF over poP.

The one-way sensitivity analysis showed that no variation in model inputs led to a change in the preferred strategy. Similarly, poP remained the dominant strategy in most Monte Carlo simulations (in the case of AEs as effectiveness outcomes). Different results were found when the time to safe ED discharge was considered. In particular, in the base-case, with a threshold of $2 per hour of ED saved, poP was the preferred strategy more than 95% of the time. With a threshold between $2 and $14, both poP and ivP were favoured and the preferred option depended on patient- or institution-specific details. Beyond a threshold of $14, ivP was preferred 95% of the time. Similar results were observed in the labour scenario, while poP was always the preferred option in the triage scenario.

**Authors’ conclusions**
Oral phenytoin (poP) was the most cost-effective phenytoin loading strategy for patients presenting to the emergency department (ED) with low concentrations and seizure disorders. However, in settings where rapid discharges from the ED were desirable, it could be preferable to use intravenous phenytoin (ivP) at an estimated additional average cost of about $20 per patient.

**CRD COMMENTARY - Selection of comparators**
The selection of the comparators appears to have been appropriate since the most commonly used phenytoin treatment options were considered in the analysis. Dosages and administration procedures were reported. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The analysis of effectiveness was based on data derived from a clinical trial, which was appropriate for the study question. Most of the details on the methods and design were not reported because the trial had been published elsewhere. However, the internal validity of the study appears to have been high because of the randomised design. Although the sample size was small, significant differences in the main outcome measures were observed. Most of the data derived from the clinical trial were varied in the sensitivity analysis, which further enhanced the validity of the estimates.

**Validity of estimate of measure of benefit**
The summary benefit measures used in the economic analysis were specific to the interventions under examination. They do not appear to be comparable with the benefits of other health care interventions. The summary benefit measures were obtained from the clinical trial. The impact of the interventions on quality of life was not investigated, but the authors stated that differences in quality of life among the three options were not to be expected. The use of a more generalisable measure would have been helpful.

**Validity of estimate of costs**
The authors restricted the perspective of the study to hospital costs. It appears that all the relevant categories of costs
have been included. The source of data and the methods used to determine the costs associated with each intervention were reported. Alternative scenarios were considered in order to reflect different patterns of phenytoin provision. However, details of the unit costs and the quantities of resources used were not presented separately for all cost categories. The price year was not reported, which makes reflation exercises in other settings difficult. The cost analysis was powered to detect statistically significant differences in costs among the interventions. Further, statistical tests of the costs were conducted and the cost estimators were varied in the sensitivity analysis.

Other issues
The authors compared their findings with those from other studies and discussed possible explanations for differences in the conclusions reached. The issue of the generalisability of the study results to other settings was addressed by conducting sensitivity analyses and considering alternative cost scenarios. The authors noted some limitations to the validity of their study. First, differences in seizure rates could not have been detected because the study was not powered for such a specific outcome, which would have been clinically relevant. Second, the triage scenario was not actually implemented and the analysis did not consider possible insufficiencies and administrative duties associated with a normal ED encounter. The authors also pointed out the difficulties in obtaining data pertaining to the indirect costs in their study setting.

Implications of the study
The authors recommended the use of poP loading at their institution in cases in which patients did not otherwise require monitoring. ivF use was restricted to status epilepticus of cases in which the time required to load should be kept to the absolute minimum.

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