Economic analysis of tirilazad mesylate for aneurysmal subarachnoid hemorrhage:
ecological evaluation of a phase III clinical trial in Europe and Australia

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
Tirilazad mesylate (Freedox, Pharmacia and Upjohn Inc., Kalamazoo, Michigan), a synthetic 21-aminosteroid compound for the treatment of subarachnoid hemorrhage.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
Male and female patients with subarachnoid hemorrhage.

Setting
Hospital. The economic study took place in 41 neurosurgical centres in Australia, New Zealand and nine European countries (Austria, Belgium, Denmark, England, France, Sweden, Germany, Italy, Portugal).

Dates to which data relate
Effectiveness and resource data were from a trial conducted from December 1991 to May 1993. 1993 prices were used.

Source of effectiveness data
Effectiveness data were derived from a single study

Link between effectiveness and cost data
The costing was undertaken prospectively alongside the effectiveness study.

Study sample
1023 patients were randomised to one of four treatment groups:

(1) placebo (vehicle),
(2) tirilazad at 0.6 mg/kg,
(3) tirilazad at 2.0 mg/kg, and
(4) tirilazad at 6 mg/kg of body weight per day for 8 to 10 days.

Randomisation was stratified by centre to achieve a balance in the frequency of administration of other ancillary therapies such as antifibrinolytic drugs. All patients received concomitant treatment with nimodipine. All patients were at least 18 years of age, had a SAH confirmed by CT scan or lumbar puncture, had an angiographically confirmed saccular aneurysm as the cause of hemorrhage and were able to begin treatment with the study drug within 48 hours of the onset of SAH.

Study design
Randomised controlled trial (multinational). Eight patients (three patients randomised to vehicle, one to 0.6 mg, three to 2 mg and one to 6 mg/kg of tirilazad) were dropped from the study prior to receiving study medication and were excluded from the analysis.

Analysis of effectiveness
The analysis was based on intention to treat. The primary outcome (occurrence of vasospasm) and the secondary outcomes, Glasgow Outcome Scale (GOS) score and death, were assessed three months after randomisation.

Effectiveness results
Use of tirilazad at 6mg/kg was associated with a reduction in the probability of death in the sample as a whole (p=0.002) and with a greater frequency of recovery on the Glasgow Outcome Scale 3 months after SAH. Improved outcomes were demonstrated to be greater in men, (p=0.0001).

Clinical conclusions
The addition of intravenous tirilazad at a dosage of 6 mg/kg is associated with an improvement in overall outcome and a reduction in mortality at 3 months in patients with aneurysmal subarachnoid hemorrhage (SAH), especially in men.

Measure of benefits used in the economic analysis
The benefit measures were deaths averted, life years and quality-adjusted years of life (QALYs) saved.

Direct costs
Quantities and costs were analysed separately, from the societal perspective. Only health service costs were considered: total number of days in hospital, the number of imaging studies (transcranial Doppler, angiograms, computed tomography scans, and magnetic resonance images), the number and types of surgical procedures and medication use. Quantities were prospectively measured in the trial. Unit cost data were collected in six countries (out of 11). For the five countries with missing unit costs, averages of the costs from the other six countries were used. Values for employment were derived from wage and salary data from all 11 countries. Unit costs from the different countries were converted into US dollars using purchasing power parities. 1993 prices were used.

Statistical analysis of costs
To assess differences in costs within the hospital and at 3 months, univariate tests of means were employed (i.e. analysis of variance for comparisons of all four groups and Student’s t-tests for pairwise comparisons). Multivariable ordinary least-squares regression was also used to assess differences in costs within the hospital. Cost outcomes of interest (e.g. hospital costs among men) were predicted on the basis of several explanatory variables measured at randomisation (e.g. treatment group, country, neurograde of the subarachnoid hemorrhage) for the sample as a whole, for women and for men.

Indirect Costs
Daily residence costs were assessed at 3 months for patients living at home with supervision or dependent on others and for those living in minimal care, skilled care, or long-term rehabilitation facilities. Also daily employment value was assessed at 3 months for full-time and part-time workers and homemakers.

**Currency**

US dollars ($).

**Sensitivity analysis**

A one-way sensitivity analysis was carried out. This was performed on the assumed drug price (ranging from $125 to $150 per 150mg) and on unit costs for the hospital resource utilization using the unit costs from a single country to value all resource utilisation (i.e. six separate analyses) and using the average unit costs among all six countries). 95% confidence intervals for the comparison of costs and outcomes using the bootstrap procedure. Also sensitivity analysis was performed on the translation of deaths averted into gains in life expectancy with and without adjustments for quality of life.

**Estimated benefits used in the economic analysis**

Use of tirilazad at 6mg/kg reduced the probability of death in the sample as a whole (p=.002) and in men (p=0.0001). Life expectancies among survivors ranged from 0.5 to 25.5 years undiscounted (0.48 years to 14.23 years discounted).

**Cost results**

Mean costs within the hospital averaged $20,341 (SD +/- $17,239) in the sample as a whole, $19,569 (+/- $15,156) among women and $21,835 (+/- $20,743) among men. Most costs were associated with length of stay, which averaged $13,673 (+/- $14,296). Costs associated with tirilazad (6mg/kg per day) averaged $3,258 (+/- $891) for the sample as a whole and $3,460 (+/- $806) for men. At 3 months, the daily employment values for the sample as a whole were $21.1 for vehicle, $23.7 for tirilazad 6mg/kg per day, $21.3 for tirilazad 2mg/kg per day and $23.5 for tirilazad 0.6mg/kg per day. At 3 months, daily residence costs for the sample as a whole were $37.3 for vehicle, $38.3 for tirilazad 6mg/kg per day, $32.9 for tirilazad 2mg/kg per day and $34.8 for tirilazad 0.6mg/kg per day.

**Synthesis of costs and benefits**

The cost per death averted was $29,615 in the sample as a whole and $26,924 in men. Cost per year of life saved and cost per quality-adjusted year of life saved were below $50,000 if those who survived until the end of the trial, lived on average 0.6 years and 0.8 years respectively. These ratios fell to below $30,000 if they lived on average 1 and 1.2 years. For men, the ratios fell below $50,000 if those who survived until the end of the trial, lived on average 1.1 years and 2.4 years. The cost per year of life saved did not fall below $27,500 per year of life saved and the cost per quality-adjusted year of life saved did not fall below $36,400.

**Authors’ conclusions**

The authors concluded that, although tirilazad treatment increased costs of care, tirilazad is associated with significant reductions in mortality and has a cost-effectiveness ratio that compares favourably with other interventions.

**CRD COMMENTARY - Selection of comparators**

Whilst the choice of comparators used was not explicitly justified, they appear to represent variations of usual practice.

**Validity of estimate of measure of benefit**

The study was based on a multinational randomized controlled trial. However, the trial only provided data for up to three months and may not provide an accurate representation of costs and outcomes in the long term. Further, the clinical results of the multinational trial conflict with those from a similar parallel North American protocol and merit
further investigation. Gender differences may be explained by differences in the pharmacokinetics of tirilazad. As with many other economic analyses alongside trials, the secondary clinical endpoint (in this case, mortality) was used as the primary outcome in the economic assessment.

Validity of estimate of costs
Adequate details were given of the sources of estimates of resource use and prices and the price date. However, the authors acknowledged that data limitations exist associated with the collection of resource use and employment status based on a single observation at the 3 month visit.

Other issues
The costs data may not be generalisable to other countries outside those in which data were collected, although this study presents an interesting and sound approach to the analysis of data from multinational clinical-economic trials.

Implications of the study
Tirilazad mesylate therapy is associated with significantly increased survival, increased cost of care, and ratios of cost per death averted, cost per year of life saved and cost per quality-adjusted year of life saved that compare favourably with other life and death interventions. However, the efficacy results of tirilazad in the international protocol conflict with those of the similar North American protocol and further clinical studies of this therapy are needed.

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Other publications of related interest

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