Pharmacoeconomic assessment of propofol 2% used for prolonged sedation

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 propofol 2% (Diprivan 2%) for patients under mechanical ventilation who required prolonged sedation. Propofol 1% (100 to 200 mg) was used to induce sedation and, once the desired hypnotic level was attained, propofol 2% was started at a dose ranging from 1 to 6 mg/kg per hour.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients requiring mechanical ventilation for more than 24 hours. Patients were excluded on the basis of age (younger than 14 years), pregnancy, coma of any etiology (such as trauma, metabolic, renal or hepatic trauma), chronic liver disease, or a history of alcohol or drug abuse. Patients who required the administration of neuromuscular blocking agents were also excluded.

Setting
The setting was secondary care. The economic study was carried out in Toledo, Spain.

Dates to which data relate
The effectiveness data associated with the intervention group related to August 1997 to February 1998. The effectiveness and cost data associated with the initial study of propofol 1% and midazolam were obtained from a study published in 1997. The price year was not stated.

Source of effectiveness data
The effectiveness data for the propofol 2% group were derived from a single study, while the effectiveness data for the control groups were obtained from a study published by the same authors (see Other Publications of Related Interest).

Link between effectiveness and cost data
The costing seems to have been carried out on the same sample population as that used in the effectiveness analysis.

Study sample
No power calculations were performed in the planning phase of the propofol 2% study, in order to assure a certain power. No details were given of the propofol 1% and midazolam study other than the sample size. There were 52 patients in the group that received propofol 2%, 54 in the group that received propofol 1%, and 54 in the group that
received midazolam. One of the patients receiving propofol 2% was excluded because she remained under permanent mechanical ventilation. Therefore, 51 patients were finally analysed within this group. The authors did not report any evidence that the study sample was representative of the study population.

Study design
A randomised controlled trial (RCT) had been conducted before to compare propofol 1% with midazolam. In this clinical study, a group was selected to analyse the effects of propofol 2% and this was compared with the earlier evaluation of propofol 1%. Thus, this was a comparative study with a historical control. It was carried out in a single centre. The patients were followed up until death, therapeutic failure (i.e. triglyceride concentration greater than 500 mg/dL), or extubation. Extubation was performed when the patient reached a level of 2 on the Ramsay scale of sedation and met at least one of the following criteria: a vital capacity greater than 10 mL/kg, the capability to double minute volume on request, a respiratory rate of less than 35 breaths/minute, and PaO2 of greater than 60 torr with an FIO2 of less than or equal to 0.4. The duration of follow-up ranged from 1 to 14 days.

Analysis of effectiveness
All but one of the patients in the propofol 2% group were included in the analysis. It was not possible to say from the article whether or not all the patients who entered the RCT were included in that analysis. The primary health outcomes assessed in the effectiveness analysis for both propofol 2% and propofol 1% patients were:

- the number who reached weaning from mechanical ventilation,
- the number who died (and the mortality rates),
- the number with therapeutic failure,
- the number who were unable to achieve an adequate level of sedation, and
- the number who presented with hypertriglyceridaemia.

The authors also assessed the mean duration of sedation;

the extubation times for those patients who reached weaning, in terms of the hours from discontinuation of the drug infusion to first T-bridge trial, hours from first T-bridge trial to extubation, and total number of hours from discontinuation of the drug infusion to extubation; and

the daily dose required for each of the sedative regimens (propofol 2%, propofol 1% and midazolam).

The only clinical data reported on midazolam were the duration of sedation, the numbers who reached weaning and time to extubation.

The authors stated that the patient groups were comparable at analysis in terms of their age, weight, Acute Physiology and Chronic Health Evaluation (APACHE) II score, duration and level of sedation (Ramsay scale), Therapeutic Intervention Score System (TISS) score, gender, and admission diagnosis. However, the midazolam and propofol 1% groups were more similar as a result of the randomisation.

Effectiveness results
The mean duration of sedation was 122.4 hours (standard deviation, SD=89.2) for patients receiving propofol 2%, 141.7 hours (SD=89.4) for patients receiving midazolam, and 139.7 hours (SD=84.7) for patients receiving propofol 1%.

The numbers of patients that reached weaning from mechanical ventilation were 28 (54.9%) with propofol 2%, 25 (46.2%; p>0.10) with propofol 1% and 27 with midazolam.
Thirteen of the propofol 2% patients died (mortality rate 25.5%) versus 11 of the propofol 1% patients (mortality rate 20.4%; p>0.10). The mortality rate associated with midazolam was similar to that for propofol 1%.

Therapeutic failure occurred in 10 (19.6%) propofol 2% patients and 18 (33.4%; p>0.10) propofol 1% patients. The rate of therapeutic failure associated with midazolam was similar to that for propofol 1%.

Eight (15.7%) propofol 2% patients were unable to achieve an adequate level of sedation versus 7 (13%; p>0.10) propofol 1% patients.

The number patients who presented with hypertriglyceridaemia was significantly lower for propofol 2% (2 patients, 3.9%) than for propofol 1% patients (11 patients, 20.4%; p=0.016).

The average time from discontinuation of the drug infusion to extubation was 32.3 hours (SD=27.6) for propofol 2% patients, 97.9 hours (SD=54.6) for midazolam patients, and 34.8 hours (SD=29.4) for propofol 1% patients. There were no statistically significant differences between the times for propofol 2% and propofol 1% patients. However, the times were statistically significantly shorter for propofol 2% patients and propofol 1% patients in comparison with midazolam patients (p<0.0000).

The daily doses required for propofol 2% patients were significantly higher than for propofol 1% patients during the first 48 hours, (p<0.05). During the first 24 hours, the doses were 4.3 mg/kg per hour (SD=1.2) for propofol 2% patients versus 3.1 mg/kg per hour (SD=1.4) for propofol 1% patients. During the second 24 hours, the doses were 4.4 mg/kg per hour (SD=1.2) for propofol 2% patients versus 3.5 mg/kg per hour (SD=1.5) for propofol 1% patients. There were no significant differences in the doses required between propofol 2% and propofol 1% for periods longer than 48 hours.

**Clinical conclusions**

The mortality rates, rates of therapeutic failure, and rates of inability to achieve the desired level of sedation were similar for both propofol sedative regimens. However, compared with propofol 1%, propofol 2% gave a lower rate of hypertriglyceridaemia and required a significantly higher dose during the first two days of sedation. The extubation times for propofol 2% and propofol 1% were similar, while those for midazolam were significantly longer in comparison with propofol.

**Modelling**

A model was used to estimate the costs of the therapies. Details of the model were published elsewhere (Barrientos-Vega et al, see Other Publications of Related Interest). The authors reported that a predictive model was used.

**Measure of benefits used in the economic analysis**

No summary measure of benefit was used in the economic analysis. The study was therefore categorised as a cost-consequences analysis.

**Direct costs**

Most of the resource quantities were reported separately from the costs. The direct costs considered in the study appear to have been those of the hospital. These included the cost of the sedative regimens (propofol 2%, propofol 1% or midazolam), the cost of the intensive care unit (ICU) for the duration of mechanical ventilation, and the ICU cost during weaning. It seems that the direct costs were estimated from the same study, published in 1997, from which the authors obtained the cost model. The average costs were reported for each type of patient and sedative regimen (either propofol 2% or propofol 1%), according to the reason for study termination (i.e. death, therapeutic failure or extubation). The average costs per patient (independent of the reason for study termination) for propofol 2% and propofol 1% patients were also reported. Discounting was not performed, but it was not relevant since the costs were incurred during a short time (approximately 2 weeks). The price year was not stated. The authors may have adjusted the costs of the sedative regimens (propofol 1% and midazolam) for inflation, using a rate of 2.1%.
Statistical analysis of costs
The means and SDs were reported for some of the resource quantities and costs. The costs of the sedatives were compared using Student’s t-test.

Indirect Costs
No indirect costs were reported.

Currency
US dollars ($).

Sensitivity analysis
A sensitivity analysis was performed to compare the variation in the net savings generated with propofol versus midazolam when the sedation period varied.

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

Cost results
The average cost per patient was $9,057 for patients receiving propofol 2% and $8,758 for patients receiving propofol 1%.

For those patients who achieved extubation, the cost per patient was $9,740 for the sedative regimen with propofol 2%, and $9,589 for the sedative regimen with propofol 1%.

The ICU cost per patient during weaning was $1,744 (+/- 1,418) in the propofol 2% group, $5,287 (+/- 2,947) in the midazolam group, and $1,880 (+/- 1,590) in the propofol 1% group.

The ICU cost per patient during sedation was $939 (+/- 684) in the propofol 2% group, $378 (+/- 342) in the midazolam group, and $1,047 (+/- 794) in the propofol 1% group.

Synthesis of costs and benefits
Not applicable due to the cost-consequences approach adopted.

Authors’ conclusions
Propofol (either 1% or 2%) was more cost-effective than midazolam. The longer the sedation period, the less cost-effective were the propofol options. The greater the proportion of patients reaching weaning, the more cost-effective the propofol options. Propofol 2% and propofol 1% were similar in terms of their efficacy and rapid wake-up times (which were more rapid than those for midazolam), although propofol 2% had a higher cost. However, as the authors stated, this higher cost may be offset by the reduced frequency of hyperglyceridaemia with propofol 2% in comparison with propofol 1%.

CRD COMMENTARY - Selection of comparators
A justification was given for the comparators chosen. Propofol 1% and midazolam are two of the most frequently used drugs in the authors’ setting for patients under mechanical ventilation who require continuous sedation. You must decide whether these health technologies are widely used in your own setting for this purpose.
Validity of estimate of measure of effectiveness
The study seems to have been a prospective comparative trial with historical controls obtained from a study published by the same authors. It is hard to rule out the possibility of selection bias and confounding due to the study design. The authors did not provide evidence that the study sample was representative of the study population, neither did they report how the patients were selected for inclusion in the study. The authors stated that the patient groups were comparable at analysis in terms of their age, weight, APACHE II score, duration and level of sedation, TISS score, gender, and admission diagnosis. However, the propofol 1% and midazolam groups were more similar due to the randomisation procedure.

Validity of estimate of measure of benefit
No summary measure of health benefit was reported. The study was therefore categorised as a cost-consequences analysis.

Validity of estimate of costs
The perspective adopted was that of the hospital, which may have been appropriate for the health technologies under study. The authors reported that the cost of ICU after extubation was not included in the model because it was considered to be independent of sedation. In addition, the costs of the follow-up of patients developing hypertriglyceridaemia were not considered in the economic analysis, but were relevant. These costs may be greater for the sedative regimen with propofol 1% since the rate of hypertriglyceridaemia was higher among these patients than for propofol 2% patients. Most of the resource quantities were reported separately from the costs, which can facilitate reflation exercises to other settings. However, this would be difficult since the price year was not reported. Statistical analyses were performed for some resource quantities and some costs, but not for the final costs per patient considered in the economic evaluation. Discounting was not carried out, which was appropriate as the costs were incurred in less than two years.

Other issues
The authors made some comparisons of their findings with those from other studies. The issue of the generalisability of the results was not addressed. The authors' conclusions reflected the scope of the analysis.

Implications of the study
The authors recommended the use of reasonable sedation guidelines in order to improve sedation in critically ill patients. They proposed the use of propofol 1% for patients with short sedation times (until 4 or 5 days) because hypertriglyceridaemia is unlikely to appear during that short period of treatment.

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None stated.

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Other publications of related interest


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