Continuous infusion of lorazepam versus midazolam in patients in the intensive care unit: sedation with lorazepam is easier to manage and is more cost-effective

Swart E L, van Schijndel R J, van Loenen A C, Thijs L G

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 long term sedation, specifically using either lorazepam (maximum dose of 4mg/h) and midazolam (maximum dose of 60 mg/h), to accommodate mechanical ventilation in patients.

Type of intervention
Supportive care.

Economic study type
Cost-effectiveness analysis.

Study population
Adult patients between the ages of 18 and 85 admitted to an intensive care unit, and who would require mechanical ventilation for at least three days. Patients were excluded for a number of reasons: indication of neurotrauma or tetanus, comatose, needed muscle relaxants, history of allergic reaction to the sedatives or mechanically ventilated for less than 24 hours due to either early extubation or death.

Setting
Hospital intensive care unit. The economic analysis was conducted in Amsterdam, The Netherlands.

Dates to which data relate
Dates of the clinical study were not reported. Correspondence with the author after this abstract was written has indicated that the price year was 1997.

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

Link between effectiveness and cost data
The cost data were collected prospectively using the same population sample as in the clinical analysis.

Study sample
Initially 75 patients were included in the study, of which 11 (14.67%) were excluded. 5 of these died within 24 hours; a further 6 were excluded for other reasons, none of which were related to the sedatives taken. Of the remaining 64 patients, 31 were in the lorazepam group and 33 in the midazolam group. There were 20 men in the lorazepam group and 19 men in the midazolam group. The mean age of patients in the lorazepam group was 61 +/- 13 (range: 22-78) years and in the midazolam group 54 +/- 18 (range: 20-83) years. Power calculations were not used to determine sample
size.

Note: correspondence with the author after this abstract was published has indicate that power calculations were, in fact, carried out. The power analysis was based on detecting a 30% difference with a significance level of 0.05 and a power of 90%. A 30% difference in the percentage of time that a patient was sedated at the desired level was considered clinically relevant by the participating intensive care doctors. The estimated variance was 15%.

Study design
This was a single centre double blind randomised controlled trial. The duration of treatment follow up was 24 hours following the end of sedation and extubation or until death (mean number of hours 141 (range: 24 - 583)). There was no loss to follow up.

Analysis of effectiveness
The analysis of effectiveness was based on treatment completers only. The primary health outcome used was physician satisfaction that patients were sedated to a desired level. In addition, therapeutic failure rates were recorded. At analysis both treatment groups had similar demographic and clinical characteristics.

Effectiveness results
Time spent at a desired level of sedation was significantly higher in the lorazepam group than in the midazolam group (87% compared with 66%) (p<0.0001). There was one treatment failure in the lorazepam group compared with three in the midazolam group. There was also no difference in recovery time periods, following discontinuation of treatment, for patients in either group.

Clinical conclusions
It was concluded that lorazepam was a suitable alternative to midazolam for the long-term sedation of patients requiring mechanical ventilation, and also that it was better when managing dose adjustments in patients.

Measure of benefits used in the economic analysis
Since the effectiveness analysis demonstrated that the performance of the two drugs was similar, the economic analysis was based on the difference in costs only.

Direct costs
The average cost per day was estimated for both drugs. Other costs relating to the infusion of both drugs were considered to be identical and therefore were not included in the analysis. The quantity of study medication used per patient was also recorded. Costs relating to adverse events and complications associated with treatment were not included. Quantities and item costs were reported separately. Neither the source of cost data nor the price years used appears to have been stated. Costs were determined from the perspective of a third party payer and were not discounted, which was appropriate given the short duration of the analysis.

Indirect Costs
Not included.

Currency
US Dollars ($). Conversion rate 1.7 Dutch guilders = $1.

Sensitivity analysis
Not conducted.

**Estimated benefits used in the economic analysis**
Not applicable.

**Cost results**
The average cost of lorazepam per day was significantly lower than that of midazolam, $6.56 for lorazepam compared with $73.31 for midazolam (p<0.0001).

**Synthesis of costs and benefits**
Not applicable.

**Authors’ conclusions**
The authors concluded that lorazepam was an appropriate alternative to midazolam when sedating patients for a long period within an intensive care unit. Furthermore patients on lorazepam were found to be more easily managed, and using the drug would present an opportunity to significantly reduce costs.

**CRD COMMENTARY - Selection of comparators**
A justification was given for the comparators used, namely that both drugs lorazepam and midazolam were in use for the sedation of patients at the study institution. However you, as a user of the database, should decide whether these drugs are representative of current practice in your own setting.

**Validity of estimate of measure of benefit**
The analysis of effectiveness was based on a double blind randomised controlled trial which was appropriate for the study question and, furthermore, the study sample was representative of the study population. Patients were shown to be comparable at baseline analysis. The analysis of effectiveness was based on treatment completers only, which might have introduced some bias. From the trial the effectiveness of both drugs was reported to be similar although the proportion of time in an appropriate state of sedation was greater in the lorazepam group. The economic analysis, therefore, only included costs (cost-minimisation analysis).

**Validity of estimate of costs**
Only direct costs associated with the intervention drug use were included in the analysis, and other direct costs as well as indirect costs were not estimated. The authors did not include in the analysis the additional costs associated with infusion, as they were identical. Costs of adverse events and complications were not included. Although some costs appear to have been omitted, this is unlikely to have affected the authors’ conclusions. Quantities of both drugs used and length of sedation time were reported separately from costs. The source of cost estimates used in the analysis were not stated. Cost results may not be generalisable to other settings or countries.

**Other issues**
The authors compared the results of their study with those of other studies examining the sedation effects of benzodiazepines, although this was limited as they noted that it was previously unknown whether both the drugs were equally effective in reaching an appropriate degree of sedation. The issue of generalisability to other study settings was not addressed.

**Implications of the study**
Given the limitations of this study, further research is needed to establish the cost-effectiveness of lorazepam compared
with midazolam.

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