Impact of goal-oriented and model-based clinical pharmacokinetic dosing of aminoglycosides on clinical outcome: a cost-effectiveness analysis

van Lent-Evers N A, Mathot R A, Geus W P, van Hout B A, Vinks A A

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
Goal-oriented and model-based clinical pharmacokinetic dosing of aminoglycosides was compared with the current practice of "suboptimal" and non-guided therapeutic drug monitoring of aminoglycoside therapy.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients aged over 18 years and eligible for aminoglycoside therapy for a suspected or proven Gram-negative infection, either on admission or during their stay. Immunocompromised patients, patients with severe renal insufficiency and cystic fibrosis patients were excluded.

Setting
The setting was hospital and the economic analysis was carried out in the Netherlands.

Dates to which data relate
Effectiveness, resource use, and cost data were collected from July 1994 to December 1995. The price year was not reported.

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

Link between effectiveness and cost data
The costing was carried out prospectively on the same patient sample as that used in the effectiveness analysis.

Study sample
The authors reported that a minimum of 200 patients was calculated to be necessary to detect a statistically significant difference in hospital stay between the two study groups (alpha of 5%; beta of 20%). Two hundred and seven ATM patients and 225 control patients were analysed; 232 patients were evaluable. The main reason for exclusion of patients was a gentamicin treatment of less than 48 hours. The ATM group comprised 105 patients and 127 patients with non-guided TDM were followed up as controls. The proportion of women in each group was around 50%. Age and weight of patients was 67 years and 69 kg on average.
Study design
This was a prospective cohort study carried out at four teaching hospitals. The duration of follow-up was not reported. There was no loss to follow-up. The authors did not report whether staff assessing outcomes were blinded.

Analysis of effectiveness
The analysis of the clinical study was based on intention to treat. Primary health outcomes used in the analysis were duration of the patient's febrile period, incidence of nephrotoxicity and ototoxicity, and morbidity or mortality. Groups were comparable at analysis in terms of the proportion of women, age, weight, and serum creatinine level. There were more patients with sepsis in the ATM group than in the non-guided TDM group (27% versus 15%; p<0.05) and fewer patients with a skin/soft tissue infection (0% versus 14%; p<0.01). Amoxicillin was used less in ATM patients than in the non-guided TDM patients (10% versus 20%; p<0.05), as was clindamycin (1% versus 9%; p<0.05).

Effectiveness results
A significantly higher loading dose was administered to ATM patients compared to the non-guided TDM group (202 versus 136 mg; p<0.001).

Maintenance dosages in ATM patients were significantly higher (175 versus 127 mg; p<0.001). This resulted in significantly higher peak concentrations (10.6 versus 7.6 mg/L; p<0.001).

The dosage interval was significantly longer in the ATM group (19 versus 14 hours; p<0.001) and gave better target trough concentrations (0.7 versus 1.4 mg/L; p<0.001).

The proportion of dose adjustments was 48.6% with ATM and 80.4% with non-guided TDM, (p=0.016).

There was a trend towards lower mortality in the ATM group (9 of 105 versus 18 of 127 patients died; p=0.26) that was significant for ATM patients admitted to the hospital with an infection (1 of 48 versus 9 of 62 patients died; p=0.023).

There was significantly less nephrotoxicity in the ATM patients compared to non-guided TDM patients (2.9 versus 13.4%; p<0.01).

The number of days with signs of infection was 4.8 with ATM and 3.4 with non-guided TDM (p=0.003).

The number of febrile days was 2.8 with ATM and 2.3 with non-guided TDM (p=0.024).

Clinical conclusions
The authors argued that a goal-oriented, model-based aminoglycoside dosing strategy contributes to achieving desired target serum concentrations in patients with a suspected or proven Gram-negative infection and treated with an aminoglycoside.

Measure of benefits used in the economic analysis
The outcome measures used in the economic analysis were survival and number of days alive after discharge from the hospital.

Direct costs
Direct costs were not discounted due to the short time horizon of the study (less than one year). Quantities and costs were reported separately. Direct costs related to costs of hospitalisation and major diagnostic and therapeutic interventions. The quantity/cost boundary adopted was that of the hospital. Diagnostic and therapeutic interventions were valued using the Dutch reimbursement system. The price year was not reported. The length of hospital stay was 20 days with ATM and 26.3 days with non-guided TDM, (p=0.045). The number of days of aminoglycoside therapy was 5.9 with ATM and 8.0 with non-guided TDM, (p<0.001).
Statistical analysis of costs
Costs between groups were compared using the Student t test or analysis of variance for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables.

Indirect Costs
Indirect costs were not included.

Currency
Dutch guilders (Dfl).

Sensitivity analysis
Uncertainties surrounding the cost-effectiveness results were expressed using cost-effectiveness probability ellipses.

Estimated benefits used in the economic analysis
The difference in Kaplan-Meier survival of ATM over non-guided TDM was 5.6%. The difference in the number of days alive after discharge from the hospital of ATM over non-guided TDM was 8.3%.

Cost results
The total costs were Dfl 16,862 with non-guided TDM compared to Dfl 13,125 with ATM, (p =0.027) for patients with a suspected or proven Gram-negative infection during their hospital stay. Total costs were Dfl 11,743 with non-guided TDM compared to Dfl 8,883 with ATM, (p=0.007) for patients admitted to hospital with a suspected or proven Gram-negative infection.

Synthesis of costs and benefits
ATM combined additional effectiveness with savings and, hence, was cost-effective. ATM was most cost-effective for patients who were admitted to the hospital with a suspected or proven Gram-negative infection.

Authors' conclusions
The authors concluded that goal-oriented, model-based dosing of aminoglycosides resulted in higher antibiotic efficacy, shorter hospitalisation, and reduced incidence of nephrotoxicity. By combining efficacy with savings, ATM offered a significant alternative to usual care.

CRD COMMENTARY - Selection of comparators
The justification of the comparator was that it represented current practice. You, as a user of this database, should decide if these health technologies are relevant to your setting.

Validity of estimate of measure of effectiveness
The analysis was based on a prospective cohort study based on a sequential design, which was appropriate for the study question. The study sample was representative of the study population. The authors reported demographic characteristics of patients in each group and showed that the groups were comparable in terms of demographic characteristics. However, the infections diagnosed in the treatment groups were significantly different. Thus, in order to eliminate the influence of bias and confounding variables, more investigation may be warranted using a matched control cohort design or randomised controlled trial.
Validity of estimate of measure of benefit
The estimation of benefits was obtained directly from the effectiveness analysis.

Validity of estimate of costs
More details about the source of costs could have been provided. Some good features of the cost analysis were that all relevant direct cost categories were included and that quantities and costs were reported separately. Moreover, the authors conducted statistical analyses on quantities and costs. However, the price year was not reported, making reflation exercises to other settings difficult. Costs of diagnostic and therapeutic interventions were based on the Dutch reimbursement system, which may limit their generalisability to NHS-type healthcare systems.

Other issues
The authors made appropriate comparisons of their findings with those from other studies. The authors did not seem to present their results selectively. The study considered patients aged over 18 years and eligible for aminoglycoside therapy for a suspected or proven Gram-negative infection and this was reflected in the authors’ conclusions. The authors examined the generalisability of the results by calculating cost-effectiveness probability ellipses. This approach was based on the assumption that average costs and average effects were normally distributed. The authors used a region-specific population model and not a model based on the average white population. The authors did not investigate how the results differed by characteristics of the pharmacokinetic model (parametric versus non-parametric methods, amount of pharmacy staff time).

Implications of the study
The authors concluded that goal-oriented, model-based dosing of aminoglycosides resulted in higher antibiotic efficacy, shorter hospitalisation, and reduced incidence of nephrotoxicity. By combining efficacy with savings, ATM offered a significant alternative to usual care. The results confirmed that the current practice of non-guided TDM results in suboptimal peak serum concentrations for many patients. More research is needed to examine how cost-effectiveness is related to the characteristics of the pharmacokinetic model.

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