Outcome assessment of minimizing vancomycin monitoring and dosing adjustments
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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
A method for the monitoring of vancomycin, based on a simplified dosing nomogram (NM), was compared with traditional approaches using serum peak, trough concentrations and traditional pharmacokinetic methods. The vancomycin therapies were administered for the treatment of gram-positive infections. The ND dosing was derived using the actual body weight and creatinine clearance (Clcr), estimated using the Cockroft and Gault equation. Vancomycin regimens that predicted a minimum drug concentration of 5 to 20 microg/mL in serum were prescribed. The standard regimens of 500 or 1,000 microg/mL given at usual intervals of 6, 8, 12 and 24 hours were used in the NM.

Type of intervention
Treatment.

Economic study type
Cost effectiveness analysis.

Study population
The study population comprised relatively young male and female patients with gram-positive infections to whom vancomycin was prescribed. Patients whose actual body weight and/or estimated Clcr were outside the NM (Clcr less than 30 mL/minute, weight less than 50 kg) were excluded.

Setting
The setting was a university-affiliated, level 1 emergency trauma centre. The economic analysis was carried out at the Detroit Receiving Hospital and University Health Centre, Detroit, USA.

Dates to which data relate
The effectiveness and resource use data related to the period January 1995 to October 1996 for the traditional monitoring group, and to the period November 1996 to May 1997 for the NM group. The price year was not reported.

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

Link between effectiveness and cost data
The costing was undertaken retrospectively for the traditional pharmacokinetic dosing group, and prospectively for the NM dosing group.

Study sample
The study sample comprised 240 patients, 120 in each group. The mean age of the patients in the traditional pharmacokinetic dosing group was 47 (+/- 16) years, and 76 were men. The mean age of the patients in the NM dosing group was 49.2 (+/- 16.8) years, and 78 were men. No power calculations were reported. All patient treated in the respective study periods were considered for inclusion in the study.

**Study design**
This was a case-control study carried out in a single centre. No randomisation was carried out. The study compared two groups of patients treated by traditional and NM dosing approaches, respectively. The average length of therapy was 8.6 (+/- 7.2) days for the pharmacokinetic group and 9.9 (+/- 9.4) days for the NM group. No loss to follow-up was reported.

For the NM patients, if the vancomycin were to be continued after day 5, blood to determine a single trough concentration was drawn on day 5. If the trough concentration was within the range 5 to 20 microg/mL, no change in therapy was made. If the trough concentration was below 5 microg/mL, the dosing interval was decreased to the next standard interval. If the trough concentration was above 20 microg/mL, either the dose was cut by 50% (i.e. 1,000 microg decreased to 500 microg) or the dosing interval was increased to the next standard interval (i.e. from 6 to 8 hours or from 12 to 24 hours). In cases where an adjustment was made, the trough concentration was measured again after 3 days.

**Analysis of effectiveness**
The clinical outcomes were:

- **cure**, i.e. complete resolution of all the signs and symptoms of infection;
- **improvement**, i.e. the resolution of or lack of progression in most signs and symptoms;
- **failure**, such as the persistence or progression of all signs and symptoms after 5 days' therapy, death due to infection, and/or the inability to complete vancomycin therapy due to adverse effects; or
- **indeterminate**, i.e. extenuating circumstances precluding classification as either cure or failure.

The average number of days taken to eradicate the organism was also assessed.

Nephrotoxicity was defined as an increase in serum creatinine of 0.5 mg/dL or 50%, whichever was greater, on two consecutive occasions during vancomycin therapy. The occurrence of cases of ototoxicity was also assessed. The microbiologic outcomes were classified as cure, failure, or indeterminate.

Cure was defined as at least one of the following: elimination of the original causative organism(s) from the same site, absence of appropriate material for culture (i.e. sputum), or the repeated aspiration of fluid was not clinically justified).

Failure or persistence was defined as the failure to eradicate the original causative organism(s) from the same site.

Indeterminate was defined as at least one of the following: no evaluation because of death, withdrawal from vancomycin before the follow-up cultures could be obtained, and incomplete microbiological data.

Finally, NM was validated using those patients dosed by NM who had trough concentrations measured on the specified dosing regimen. The patient samples were comparable in terms of their age, gender, underlying disease states (diabetes, cancer, HIV, burns), the length of therapy, the number of days in the intensive care unit, and concomitant nephrotoxic agents.

**Effectiveness results**
No difference was found between the pharmacokinetic and NM groups for the clinical outcomes. For the pharmacokinetic group, the rate of cure was 45%, the rate of improvement was 35%, the rate of failure was 13.3%, and the rate of indeterminate was 6.7%. The corresponding rates for the NM group were 44.3% (cure), 39.6%
(improvement), 8.5% (failure) and 7.5% (indeterminate). The microbiological response was assessed for 56 patients in the pharmacokinetic group and 37 patients in the NM group. No statistically significant differences were found between the two groups. For the pharmacokinetic group, the rate of cure was 46.4%, the rate of failure or persistence was 26.8%, and the rate of indeterminate was 26.8%. The corresponding rates for the NM group were 37.8% (cure), 29.7% (failure or persistence) and 32.4% (indeterminate).

The average number of days to eradicate the organism was 3.2 (+/- 3.2) in the pharmacokinetic group and 4.4 (+/- 5.3) in the NM group, (P=0.3).

There was no difference in overall nephrotoxicity when assessing all other concomitant nephrotoxins. For patients who received vancomycin alone, a higher but not statistically significant difference in the rate of nephrotoxicity was observed in the NM group, compared with the pharmacokinetic group. The rate of nephrotoxicity was 8.6% (3 out of 35) in the NM group and 3.1% (1 out of 32) in the pharmacokinetic group. The therapy was not discontinued in any patient, and the renal function returned to baseline before discharge from the hospital. No cases of ototoxicity were observed.

Of the 77 patients who were included in the validation of NM, 72 patients (94%) had a trough concentration in the target range. The NM was most reliable in patients with a Clcr above 90 mL/minute.

**Clinical conclusions**

The authors concluded that simplified NM-based monitoring of vancomycin proved to be as effective as the traditional pharmacokinetic monitoring methods in terms of several outcome measures. The NM-based approach did not compromise the patient outcome or the ability to make changes in therapy.

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

The health outcomes were left disaggregated and no summary measure of benefits was used in the economic analysis. Thus, a cost-consequences analysis was carried out.

**Direct costs**

The costs were analysed from the perspective of the health care provider. The direct costs were for vancomycin, drug preparation and administration, serum concentration determinations, initial pharmacokinetic consultations and follow-up evaluations. The unit costs were reported. The costs were derived from data obtained from the clinical study. The pharmacist's time for the initial consultation and follow-up evaluation for pharmacokinetic and NM dosing were treated as deterministic data. Discounting was unnecessary as the length of the intervention was less than one year. The resource use data were gathered from January 1995 to October 1996 for the traditional monitoring group, and from November 1996 to May 1997 for the NM group. The price year was not reported.

**Statistical analysis of costs**

Statistical analyses of the total costs were carried out to test for statistical significance of the results.

**Indirect Costs**

No indirect costs were evaluated.

**Currency**

US dollars ($).

**Sensitivity analysis**
No sensitivity analysis was performed.

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

**Cost results**
NM patients tended to receive a lower dose (1.9 +/- 0.7 g/day) than those in the pharmacokinetic dosing group (2.2 +/-1 g/day). The acquisition cost of 1 g of vancomycin was $6.32. The cost of preparing and administering one dose was $3.35. The unit cost of measuring the serum concentration was $5. The cost of the pharmacist's time was $28.71/hour. The initial consultation took 40 minutes of the pharmacist's time for a patient in the pharmacokinetic group, and 15 minutes for one in the NM group. The follow-up evaluation was 15 minutes for the pharmacokinetic approach and 5 minutes for the NM approach.

The total drug cost per patient was not statistically significantly different between the groups, $195.22 (+/-191.12) in the NM group versus $189.54 (+/-157.66) in the pharmacokinetic group, (p=0.7). However, the costs of concentration measurement were statistically lower for the NM patients, both per patient and per month. The costs per patient were $5.41 (+/-9.48) in the NM group versus $9.79 (+/-10.03) in the pharmacokinetic group, (p=0.001). The costs per month were $232.5 (+/-50.74) in the NM group versus $403.75 (+/-70.97) in the pharmacokinetic group, (p=0.009).

**Synthesis of costs and benefits**
No synthesis of the costs and the benefits was performed.

**Authors' conclusions**
The use of a simplified nomogram (NM)-based approach for monitoring vancomycin was as effective as the traditional pharmacokinetic monitoring methods. Costs-savings were associated with the simplified approach in terms of the costs of concentration measurement.

**CRD COMMENTARY - Selection of comparators**
A justification was given for the choice of the NM as a possible alternative to the traditional pharmacokinetic dosing, namely, the improved current formulation of the drug and the lack of evidence linking concentration to outcome above certain levels. You should decide whether the traditional pharmacokinetic dosing is the appropriate widely used health technology in your setting.

**Validity of estimate of measure of effectiveness**
The analysis used patient samples recruited in different time periods. Power calculations were not performed and randomisation was not carried out. The role of confounding and bias cannot be excluded, even though the patient groups were shown to be comparable at baseline and statistical analyses were carried out. The authors stated that the study sample consisted of relatively young and predominantly male patients. This could restrict the generalisability of the results to different populations. These issues tend to limit the internal validity of the analysis.

**Validity of estimate of measure of benefit**
The authors did not derive a summary measure of health benefit. The analysis was therefore categorised as a cost-consequences study.

**Validity of estimate of costs**
All the cost categories relevant to the perspective adopted appear to have been included in the analysis. The resource use was not reported separately, except for the daily mean dose of vancomycin. The unit costs of vancomycin,
preparation, the pharmacist’s time and the serum concentration determination were reported. The pharmacist’s time
necessary to manage dosing in the traditional and NM alternatives, which is one of the main drivers of cost difference,
was fixed in the analysis. No sensitivity analyses to examine the influence of the unit costs and pharmacist’s time were
reported. The price year was not explicitly reported.

**Other issues**
The authors made appropriate comparisons of their findings with those from other studies. The study involved
relatively young and mostly male patients, and this was reflected in the authors’ conclusions. The issue of the
generalisability of the study’s results to other settings was not addressed and sensitivity analyses were not carried out.
These limited the external validity of the analysis. The authors do not seem to have presented their results selectively.

**Implications of the study**
The authors suggest that vancomycin dosing based on a NM is a reasonable and simpler approach than traditional
pharmacokinetic monitoring. However, empiric therapy doses using traditional pharmacokinetic methods should be
used when the patients do not fall within specific limits.

**Source of funding**
None stated.

**Bibliographic details**
Karam C M, McKinnon P S, Neuhauser M M, Rybak M J. Outcome assessment of minimizing vancomycin monitoring

**PubMedID**
10221365

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adult; Aged; Anti-Bacterial Agents /administration & dosage /economics /pharmacokinetics; Drug Administration
Schedule; Female; Health Care Costs; Hospitalization; Humans; Male; Middle Aged; Treatment Outcome; United
States; Vancomycin /administration & dosage /economics /pharmacokinetics

**AccessionNumber**
21999000481

**Date bibliographic record published**
31/10/2002

**Date abstract record published**
31/10/2002