Antimicrobial practice

Impact of glycopeptide therapy after hospital discharge on inpatient costs: a comparison of teicoplanin and vancomycin

Peter G. Davey*, Richard South* and Mo Malek*

*Pharmacoeconomics Research Centre, Ninewells Hospital and Medical School, Dundee DD1 9SY, *Marion Merrell Dow Ltd, Lakeside House, Stockley Park, Uxbridge UB11 1BE, †Pharmacoeconomics Research Centre, Department of Economics, University of St Andrews, St Andrews, UK

Data were collected prospectively from 59 patients receiving vancomycin and 20 patients receiving teicoplanin. The mean daily drug cost was £52.40 for teicoplanin and £31.13 for vancomycin; the 95% Confidence Intervals (CI) for the difference in mean drug costs varied between £14.40 and £28.10 in favour of vancomycin. Use of a loading dose of teicoplanin significantly increased mean daily drug costs if the duration of treatment was less than 10 days. Costs of preparation, administration and monitoring were consistently higher for vancomycin than for teicoplanin and inclusion of these costs reduced the difference in mean daily costs to £13.01 (95% CI £6.10 to £19.90). In Dundee 11 of 20 patients who received teicoplanin had received some of their treatment after discharge from the hospital and a survey of UK hospitals confirmed that teicoplanin treatment after discharge is being used in a wide range of conditions. The median proportion of teicoplanin treatment in Dundee given after discharge was 28.4% for each patient who received the drug: the median proportion of non-inpatient therapy was 50% per patient of those who received any teicoplanin treatment after discharge. Assuming that teicoplanin costs £20 per day more than vancomycin, use of teicoplanin implies an investment of £70.42 to gain one hospital day through earlier discharge of patients receiving teicoplanin.

Introduction

Glycopeptides are increasingly important antibiotics for the treatment of Gram-positive infection in hospitals because of changes in the epidemiology of infection and of drug resistance amongst Gram-positive bacteria. The increasing use of implanted devices in hospital medicine has resulted in a parallel increase in the prevalence of infections caused by coagulase-negative staphylococci which are often resistant to β-lactam drugs (Goldmann et al., 1973; Sugarman & Young, 1989; Mouton et al., 1990; Refsahl & Andersen, 1992; Knudsen et al., 1993). At the same time, the prevalence of β-lactam resistance has increased amongst other Gram-positive organisms such as Staphylococcus aureus and Enterococcus faecalis (Maple, Hamilton-Miller & Brumfitt, 1989; Dornbusch et al., 1990; Baquero, Martinez-Beltran & Loza, 1991; Mulgrave, 1991; Cohen, 1992).
In most countries, teicoplanin and vancomycin are the only two glycopeptides available for treatment of Gram-positive infection. Vancomycin was introduced in the 1950s and the availability of generic formulations has led to a steady decrease in price. For example, in the United Kingdom the price has fallen from £26.72/g in 1992 to £21.38/g in 1993 and £17.32/g in 1994 (source Monthly Index of Medical Specialties). However, the hospital cost of treatment with vancomycin is increased by its adverse effects. Monitoring of serum vancomycin concentrations is recommended because of dose-related nephrotoxicity and ototoxicity. Both the link between vancomycin serum concentrations and toxicity, and the need for therapeutic drug monitoring have been questioned (Cantu, Yamanaka-Yuen & Lietman, 1994). Nonetheless, monitoring at least of pre-dose concentrations is generally recommended (Saunders, 1994). In contrast, given the lack of any real evidence for dose-related adverse effects of teicoplanin (Wilson, Gruneberg & Neu, 1993), monitoring has never become firmly established: few laboratories offer teicoplanin assays as a routine service and it has never been our practice to measure serum concentrations, despite recommendations in the data sheet to consider monitoring for patients with impaired renal function. Vancomycin must be administered by controlled iv infusion over 1 h because more rapid infusion causes release of histamine from mast cells, resulting in vasodilation and potential circulatory collapse, the red man syndrome (Editorial, 1990). Teicoplanin does not share these adverse effects and can be safely administered as a rapid bolus iv injection or im injection. This, together with the fact that teicoplanin administration always requires only a single daily injection, increases the possibility that patients who are receiving teicoplanin can be safely discharged from hospital.

The aims of this study were to document the hospital costs of administration of vancomycin and teicoplanin, to assess current levels of non-inpatient use of teicoplanin in the United Kingdom and the likely impact on hospital costs.

Patients and methods

Patients

Data on hospital costs of glycopeptide treatment were collected from the clinical haematology and orthopaedic infection units in Dundee Teaching Hospitals Trust. Most patients in the clinical haematology unit received vancomycin for suspected infection involving Hickman central intravenous lines. However, selected patients were being treated with teicoplanin in order to allow earlier discharge from hospital. Clinical data were recorded for all haematology patients treated with glycopeptides from October 1992 to March 1993. In contrast, teicoplanin was routinely used for treatment of orthopaedic infections caused by β-lactam resistant staphylococci or enterococci. Clinical data were available for patients treated with teicoplanin since 1991. In addition, some patients with orthopaedic infections were entered into a multicentre randomised trial which included vancomycin.

Additional data about administration of teicoplanin to patients after discharge were obtained by a retrospective survey involving centres throughout the UK. Centres known to prescribe teicoplanin were contacted and asked to complete a standardised clinical record for any patients who had received all or part of their treatment as an outpatient or at home.

These data are observational and do not involve any randomised allocation of patients to treatment groups. The purpose of this study was to observe routine clinical
practice with each drug rather than to conduct an experimental comparison between them. All patients received teicoplanin or vancomycin intravenously.

**Definitions**

Intravenous treatment following discharge (non-inpatient treatment) may be given either as outpatient or home treatment. Outpatient treatment requires the patient to return to the hospital where treatment is prepared and administered by hospital staff. Home treatment is prepared and administered in the home by the patient, the patient’s family, a friend or a nurse. Alternative settings include the general practitioner’s surgery, the cottage hospital or nursing home.

**Hospital costs**

Drug acquisition costs were taken from MIMS, February 1994. Consumables and staff time required for preparation and administration of teicoplanin or vancomycin were measured by direct observation. Previously published definitions of preparation and administration time were applied (Malek *et al.*, 1992). For vancomycin infusions, administration time was the total time required to connect and disconnect the infusion. Costs of consumables, vancomycin assay and staff time were obtained from Dundee Teaching Hospitals Trust in February 1994.

**Statistics**

Data were analysed with Minitab 8.0 or SAS. For medians the spread of the sample is indicated by the inter quartile range (IQR). Estimates of a population median and its 95% Confidence Intervals (95% CI) were made by Minitab using a method based on calculation of Walsh averages. In general the median has been used as the best estimate of central tendency for continuous distributions (Polgar & Thomas, 1991). However, the mean has been used as the best estimate of average costs because we believe that it is necessary to incorporate all values in the analysis of costs (Polgar & Thomas, 1991).

**Results**

**Drug administration and preparation costs**

*Patient demographics.* Data were collected from 79 patients in Dundee, of whom 20 received teicoplanin and 59 received vancomycin. Median ages (years) were 66 (IQR 38–72) and 49 (IQR 31–65) respectively \((P = 0.0331, \text{Mann Whitney test})\). The overall age range was similar: 20–83 years for teicoplanin and 18–79 years for vancomycin. Of the 20 patients who received teicoplanin, 11 (55%) were treated for orthopaedic infections and nine (45%) were haematology patients, whereas four (7%) of the patients who received vancomycin had orthopaedic infections and the remaining 55 (93%) were haematology patients.

*Drug acquisition costs.* A loading dose of teicoplanin was given to 14 (70%) of patients, who received twice the maintenance dose in the first 24 h of treatment. The maintenance dose was 200 mg in four patients (20%), 400 mg in 14 patients (70%) and
600 mg in two patients (10%). The maintenance dose was 6 mg/kg rounded to the nearest 200 mg. The average daily drug acquisition cost for teicoplanin therefore depends on three factors: the maintenance dose, the use of a loading dose and the duration of treatment. If a loading dose is given to all patients, then the average daily drug cost for a maintenance dose of 400 mg daily ranges from £64.13 for a 5 day treatment course to £54.51 for a 50 day treatment course.

No patient received a loading dose of vancomycin. Dose adjustments were made during treatment in 22 (39%) patients; the number of dose adjustments was one for 10 patients (17%), two for six patients (10%), three for four patients (7%) and four for three patients (5%) making a total of 46 dose adjustments. Of these, 24 resulted in an increase in dose, 20 in a decrease in dose. In the remaining two cases the daily dose remained the same but the dosing interval was changed from 12 to 24 hourly (e.g. from 500 mg bd to 1000 mg od). All dose adjustments were made to the nearest 500 mg vancomycin but because some patients received two or more different doses, the calculated daily dose (total dose/duration of treatment) is not always divisible by 500. The median calculated daily dose was 2000 mg (IQR 1636–2000) and the overall range was from 667 to 3000 mg.

The average daily drug cost for teicoplanin was £52.40, whereas for vancomycin it was £31.13, a difference of £21.27 per day (Table I). The distribution of drug costs shows little overlap between vancomycin and teicoplanin (Figure 1(a)).

**Preparation, administration and monitoring costs.** Vancomycin was administered twice daily to most patients; 26 (44%) received at least part of their treatment as a once daily regimen. An average of 21.8% of each patient’s treatment days were once daily (for each patient the number of once daily days was divided by the total duration of treatment). Preparation and administration of vancomycin was observed on 32 occasions. On 25 of these, two vancomycin injections were prepared simultaneously, in which case the total preparation time was divided by two. The median preparation time was 4.75 min (IQR 3.5–5.5, total range 2.0–7.5). Median administration time was 7.0 min (IQR 5.5–8.0, total range 4.0–8.0). Teicoplanin preparation and administration was observed on ten occasions. Preparation time was quite variable because rapid reconstitution leads to frothing which then has to be allowed to settle before the drug can be administered: median 10.0 min (IQR 9.5–13.0, total range 5.0–14.0). In contrast, administration time was extremely consistent: median 2 min (IQR 1.5–2.0, total range 1.0–2.0). The total preparation and administration time for the two drugs is therefore almost identical (about 12 min).

<table>
<thead>
<tr>
<th>Drug costs (per day)</th>
<th>Teicoplanin</th>
<th>Vancomycin</th>
<th>Mean difference</th>
<th>95% CI of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>£52.40</td>
<td>£31.13</td>
<td>£21.17</td>
<td>£14.40 to £28.10</td>
</tr>
<tr>
<td>Preparation,</td>
<td>£0.76</td>
<td>£8.96</td>
<td>−£8.20</td>
<td>−£7.17 to −£9.24</td>
</tr>
<tr>
<td>administration and</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>monitoring costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total costs (per day)</td>
<td>£53.01</td>
<td>£40.09</td>
<td>£13.01</td>
<td>£6.10 to £19.90</td>
</tr>
</tbody>
</table>
These data have been used to construct a range of likely daily preparation and administration costs for teicoplanin and vancomycin (Table II). Teicoplanin is always given as a single bolus injection and the only variation in consumables which was encountered was in the use of a heparin/saline flush. In contrast, vancomycin may be given as either one or two infusions per day and there are several important sources of variation in the daily cost, notably the potential cost of assays and the cost of staff time (Table II). Taking range extremes for teicoplanin and vancomycin, the difference in daily preparation and administration costs could vary from £24.22/day in favour of teicoplanin (£25.16-£0.94) to £0.97/day in favour of vancomycin (£2.50-£1.91).

The observed mean difference in preparation, administration and monitoring costs in the present study was £8.96/day in favour of teicoplanin (Table I). The observed range of vancomycin preparation, administration and monitoring costs was from £2.16 to £18.48/day. The major determinant of variation was the number of assays performed. No assay was performed for 19/59 (32%) of the patients and the range was from one to 23 samples assayed per patient. The orthopaedic patients were monitored twice weekly initially and then weekly. Protocols for the haematology patients recommended monitoring twice weekly but monitoring was sometimes not carried out, particularly for short treatment courses.
The difference in total daily costs was £13.01/day in favour of vancomycin (Table I). There is considerably more overlap between the daily costs of the two regimens when all costs are included (Figure 1(b)).

**Non-inpatient treatment**

**Dundee patients.** The median duration of vancomycin treatment was 8 days (IQR 4–18 days, overall range 1–47 days). The median duration of teicoplanin treatment was 27 days (IQR 9–54 days, overall range 2–190 days) and 11 of the 20 patients received part of their treatment after discharge from the hospital. The median proportion of treatment administered on a non-inpatient basis was 28.4% (95% CI 7.7%–46.0%; range 0%–92.3%). For the 11 patients who received at least part of their treatment after discharge, the median proportion of non-inpatient treatment was 50%. Non-inpatient treatment was used more frequently in the orthopaedic patients (eight out of 11 vs three out of nine haematology patients). Treatment was administered to all eight orthopaedic patients at home (by a relative in seven patients and by a district nurse in one patient). All three haematology patients received their treatment by returning to the ward as outpatients. No complications related to iv cannulae occurred and there were no apparent adverse events due to treatment after discharge.

**National survey of non-inpatient treatment.** Data were collected from 55 adult patients from other UK centres of which 48 were haematology or oncology patients. Of the remaining seven patients, three were treated for bone or joint infections, two for endocarditis and two for wound infection. The median duration of non-inpatient treatment was 5 days (IQR 3–9 days; total range 1–70 days). The median proportion of non-inpatient treatment was 98% (IQR 63%–100%, total range 22%–100%).

For the 48 haematology patients, treatment was administered at home for 15 patients; in 13 it was self administered, in one administered by a family member and in one by a nurse at home. The remaining 33 haematology patients returned to the ward to receive outpatient treatment. Home treatment was administered by a general practitioner or family member to two of the seven patients with other diagnoses; the remaining patients returned to the ward for outpatient treatment. As with the Dundee patients, there were

---

**Table II. Range of daily preparation, administration and monitoring costs**

<table>
<thead>
<tr>
<th></th>
<th>Unit cost (£)</th>
<th>Teicoplanin</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>minimum</td>
<td>maximum</td>
</tr>
<tr>
<td></td>
<td>(£)</td>
<td>n</td>
<td>cost (£)</td>
</tr>
<tr>
<td>IV line</td>
<td>1.77</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Syringe</td>
<td>0.07</td>
<td>1</td>
<td>0.07</td>
</tr>
<tr>
<td>Needle</td>
<td>0.01</td>
<td>1</td>
<td>0.01</td>
</tr>
<tr>
<td>Water</td>
<td>0.10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hepsal</td>
<td>0.28</td>
<td>0</td>
<td>0.28</td>
</tr>
<tr>
<td>Wipe</td>
<td>0.01</td>
<td>1</td>
<td>0.01</td>
</tr>
<tr>
<td>Minibag</td>
<td>0.86</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Assay</td>
<td>19.60</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Time (h)</td>
<td>8.50</td>
<td>0.10</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Total: £0.94       £2.50       £1.91       £25.16
no clinical problems associated with the iv cannulae and no apparent adverse effects of non-inpatient treatment.

**Economic model for treatment after discharge**

Early discharge of patients saves resources which may be used to provide care to other patients, either by allowing more admissions or by reallocating staff to the care of other patients. Whatever use is made of the resource, early discharge of patients does not necessarily reduce hospital costs, particularly in the short term. Assuming that the hospital cost of teicoplanin exceeds vancomycin, the decision maker needs to estimate the value of saving one day in hospital in order to decide which treatment to use.

Suppose that the total daily cost of teicoplanin is £20 greater than vancomycin and that 28.4% of the treatment is given after discharge (this was the median for the Dundee patients including those who received all treatment as inpatients). If $D$ is the duration of treatment, then the total cost of treatment is $D \times £20$ and the number of days saved is $0.284 \times D$. In order to justify choosing teicoplanin, the decision maker must believe that the value of gaining one hospital day is at least £70.42 because:

\[
\text{Implied value of gaining 1 day in hospital} = \frac{\£20 \times D}{0.284 \times D} = £70.42
\]

This simple equation can be used to compare the implications of choosing teicoplanin or vancomycin over a wide range of assumptions about differences in daily cost, the value of gaining inpatient days and the proportion of non-inpatient treatment (Figure 2).

![Figure 2. Sensitivity analysis of the implied value of gaining days in hospital by early discharge of patients receiving teicoplanin. Difference in daily drug cost: ■, £10; +, £20; *, £30.](image-url)
The present analysis did not include costs of District Nurse or General Practitioner time. If home administration of iv drugs requires regular community support then funding from the provider unit may be required, which in turn should be included in any cost analysis.

Discussion

The daily cost of both regimens is extremely variable (Figure 1). For teicoplanin the major factors are the maintenance dose and the use of a loading dose. The latter is particularly important when the duration of treatment is less than 10 days. Administration of teicoplanin by the im route would reduce costs slightly because iv cannulae would not be required. However, the cost of cannulae was not included in the present analysis as it was assumed that they may have been inserted for other purposes (Table II). The costs of preparation, administration and monitoring of vancomycin are consistently higher than teicoplanin but are also extremely variable and are particularly influenced by the number of assays which are performed. The manufacturer's data sheet recommends monitoring of vancomycin by measurement of peak and trough serum concentrations, but a recent review has questioned whether vancomycin assays are required at all, doubting the relationship between serum concentrations and adverse events (Cantu et al., 1994). Nonetheless, a recent randomised controlled study showed that therapeutic drug monitoring of vancomycin therapy of haematology patients was associated with a reduced incidence of renal dysfunction (Calvo et al., 1994). The cost of a vancomycin assay estimated by our laboratory (£19.60 per sample) is similar to a published estimate from the Netherlands (65.45 NLG = £23.80) (Gyssens et al., 1991) but the cost is likely to vary considerably between laboratories (Vacani, Malek & Davey, 1993). For all of these reasons, the total daily cost of both regimens is highly variable (Figure 1) and we have used a range of differences in daily drug cost in our sensitivity analysis (Figure 2). Other hospitals should make their own estimates based on local practice and assay costs.

We have not estimated the cost of adverse events. Debate still continues about the clinical significance of vancomycin ototoxicity or nephrotoxicity (Goetz & Sayers, 1993). There is general agreement that the red man syndrome is a significant complication of vancomycin treatment which can be avoided by careful attention to infusion rate and, if necessary, premedication of the patient (Editorial, 1990). Early reports of circulatory collapse associated with vancomycin infusion (Newfield & Roizen, 1979; Dajee et al., 1984) prompted investigation and definition of the mechanism, which is histamine release from mast cells (Editorial, 1990). The problem can be reduced by slow infusion of vancomycin, although in a prospective controlled study, eight out of 17 paediatric patients showed clinical signs of histamine release after slow vancomycin infusion (Wallace, Mascola & Oldfield, 1991). The problem can be virtually eliminated by pre-treatment of patients with diphenhydramine (Editorial, 1990; Wallace et al., 1991) but this is rarely done in the UK and did not occur in any of the patients that we reported. The main cost of the red man syndrome is the cost of educating staff about the safe administration of vancomycin, which is clearly necessary, given that 23% of resident medical staff in a recent US survey did not know whether vancomycin should be given as a bolus injection or iv infusion (Cheng, Nimphius & Hennen, 1992).

Surprisingly in the present study, vancomycin was administered once daily for at least part of the course of treatment in 44% of patients. Once daily treatment is a major
advantage when considering regimens for treatment after discharge (Tice, 1991) and once daily outpatient infusion of vancomycin may well be suitable in selected patients. Nonetheless, safe administration of vancomycin outside the hospital would be difficult and would require temporary provision of infusion pumps in the patient’s home. We therefore believe that teicoplanin is the glycopeptide of choice for home administration.

Home iv administration is widely used in the USA, where it has been estimated that 250,000 patients are treated annually (Rubinstein, 1993). Antibiotic treatment is one of the commonest indications but others include parenteral nutrition, cytotoxic chemotherapy, administration of blood products and pain control (Thickson, 1993). Gram-positive infections account for 60% of infections treated with antibiotics at home (Rubinstein, 1993). In the UK, iv therapy is used less frequently than oral administration of antibiotics in hospital, in marked contrast to most other countries (Halls, 1993). It is therefore unwise to extrapolate too much from American experience to the UK. Nonetheless, we believe that iv antibiotic treatment in non-hospitalised patients will increase in the UK.

The savings achieved through non-inpatient iv administration depend on the proportion of treatment administered outside the hospital, the cost of providing training or staff for preparation or administration and on the value attached to gaining a hospital day. The median proportion of non-inpatient treatment achieved in Dundee (28.4%) was well below that generally reported in the US, where about 60% of patient treatment is usually administered outside the hospital (Craven, 1993; Williams et al., 1993). This proportion will doubtless increase and in some patients in the UK survey, the entire course of teicoplanin was administered outside the hospital. Treatment after discharge in Dundee has grown without specific provision or costing of support services. In the US it has been estimated that training of each patient requires 4 h of pharmacy time (Swenson, 1981) and future studies should include a more comprehensive estimate of costs. It is important to quantify indirect costs (financial costs falling outside the health service) in addition to direct healthcare resource costs (Thickson, 1993). Future studies should also clarify the risk of complications of home iv treatment (Jauregui, Martin & Hageage, 1987; Burks, Fliegelman & Sokalski, 1989; Graham, 1993). Overall estimates from the USA suggest that iv antibiotic administration costs $700/day in hospital compared with $220/day at home (Craven, 1993). The principal component of saving is the cost of a hospital day, which is much easier to identify in the US system of reimbursement (Finkler, 1982) than in the UK (Lowson, 1993a,b,c). The overall average cost of a day in hospital depends on the setting and can vary from about £150 on a chronic care ward to over £500 in an intensive care unit. Unfortunately these average costs give little or no indication of the savings which can be achieved by earlier discharge (Finkler, 1982; Lowson, 1993a,b,c; Shulkin et al., 1993; Whynes & Walker, 1995). Nonetheless, we believe that it will be possible to realise some of these savings in the long term in the UK system. In the short term we believe that it is more realistic to use an implied value to demonstrate the implications of using teicoplanin for treatment after hospital discharge (Figure 2).

References


(Received 17 February 1995; returned 15 May 1995; revised 11 July 1995; accepted 18 September 1995)