Continuous versus intermittent infusion of vancomycin for the treatment of Gram-positive infections: systematic review and meta-analysis

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CRD summary
This review concluded that (in treating Gram-positive infections) there was less risk of nephrotoxicity associated with continuous infusions of vancomycin than with intermittent infusions. This was not conclusive: larger RCTs were needed to compare the methods across a range of outcomes. The conclusion reflects the uncertainty of review findings based on small mostly observational studies and is probably reliable.

Authors' objectives
To compare the effectiveness of continuous versus intermittent infusion of vancomycin in adults with Gram-positive infections.

Searching
MEDLINE, EMBASE and Cochrane databases were searched from 1956 to May 2011. Search terms were reported. There were no language restrictions. References of identified studies were checked.

Study selection
Randomised controlled trials (RCTs) and observational studies of vancomycin treatment in adults aged at least 18 years with Gram-positive infections were eligible for inclusion. Primary outcomes were nephrotoxicity rate and overall mortality. Secondary outcomes were clinical failure, adverse events and vancomycin serum drug exposure (defined in the review).

Included studies looked at patients infected with MRSA (methicillin-resistant Staphylococcus aureus) or methicillin-resistant coagulase-negative staphylococci; infections in the included studies were bacteraemia or pneumonia, severe hospital-acquired osteomyelitis or post-surgery infections in cardiac patients. Dosages of vancomycin (in both continuous and intermittent infusions) and whether they were calculated by patients' body mass or not, and the target serum concentrations all varied between studies. Treatment duration ranged from six to 101 days.

Two reviewers independently assessed the studies for inclusion in the review.

Assessment of study quality
RCTs were assessed using the criteria of the Cochrane Effective Practice and Organisation of Care group. Observational studies were assessed using the Newcastle-Ottawa tool. Additional criteria on reporting of intervention delivery (performance bias) and assessment of outcomes (detection bias) were also assessed for observational studies.

Two reviewers independently assessed the quality of the studies. Disagreements were resolved by discussion or consulting a third reviewer.

Data extraction
Data were extracted on the intervention administration (infusion type, dose, use of bolus, duration and any dosage adjustments) and population characteristics (type of hospital ward and type and aetiology of the infection). The vancomycin minimum inhibitory concentration (MIC) for the type of bacteria involved was noted. Outcome data for vancomycin serum concentration, area under the curve values and clinical outcomes were extracted. Relative risks with 95% confidence intervals were calculated for clinical outcomes.

Two reviewers independently performed the data extraction using a standardised database. Disagreements were resolved by a third reviewer.

Methods of synthesis
Pooled relative risks (dichotomous outcomes) or standardised mean differences (continuous outcomes) were calculated.
together with 95% confidence intervals using a fixed-effect model meta-analysis. Heterogeneity between studies was assessed using the $I^2$ statistic (considered significant where $I^2>50\%$). Plans to stratify analyses based on type of infection, clinical setting, use of a bolus and whether dosages were adjusted based on serum concentration of vancomycin were not adopted due to the small number of studies included.

**Results of the review**

Six studies (one RCT and five observational studies) with a total of 443 patients were included in the review. The quality of the RCT was reasonable although it was unclear whether allocation concealment was adequate. The most common issue in the observational studies was that outcomes were not determined by a blinded assessor.

There was no difference in the mortality rates between patient groups treated with continuous and those treated with intermittent vancomycin infusions (RR 1.03, 95% CI 0.68 to 1.57; four studies; $I^2=0\%$). There was a statistically significant benefit in reduced nephrotoxicity for patients treated with continuous infusions (RR 0.63, 95% CI 0.43 to 0.94; five studies; $I^2=0\%$). More patients required dialysis in the intermittent vancomycin treatment groups in two trials that reported this but the differences were not statistically significant. Definitions of nephrotoxicity varied between studies. Treatment failure was reported by two studies; both found no significant difference between the groups. Reporting of adverse events data was variable and incomplete but three studies indicated that adverse events were more frequent and more diverse in groups treated with intermittent infusions.

Vancomycin exposure (area under the serum-concentration time curve over 24 hours, vancomycin trough concentration and vancomycin steady-state concentration) was assessed but no pooled estimates were calculated due to high heterogeneity. Area under the curve was comparable in the continuous and intermittent infusion groups (two studies). There was incomplete reporting of the serum concentrations in the review.

**Cost information**

One of the included studies reported that per-patient costs for 10 days of vancomycin treatment were significantly lower for continuous compared to intermittent infusions. The estimates included the costs of serum vancomycin determination.

**Authors' conclusions**

There was a significantly lower risk of associated nephrotoxicity when vancomycin for the treatment of gram-positive infections was administered as a continuous infusion than when it was administered as an intermittent infusion. RCTs were required to define the impact on mortality and on pharmacodynamic activity (the ratio of area under the curve to minimum inhibitory concentration).

**CRD commentary**

The review addressed a clear question supported by appropriate inclusion criteria. The authors searched three relevant databases. All stages of the review process were carried out in duplicate which reduced the possibility of reviewer error and bias. Study quality was assessed using tools appropriate to their design. The synthesis was reasonable.

The authors’ conclusions were based on both the results of their analyses and limitations of the included evidence. They correctly noted that their findings rested on small observational studies and recommended that larger RCTs be conducted in order to reduce the uncertainty around their findings. This caution is an appropriate reflection of the evidence base.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated a need for multicentre RCTs with adequate sample sizes and strong methodology to compare continuous with intermittent infusions of vancomycin in patients with Gram-positive infections. There was a need for cost-effectiveness analysis.

**Funding**

None.
Bibliographic details

PubMedID
22028203

DOI
10.1093/jac/dkr442

Original Paper URL
http://jac.oxfordjournals.org/content/67/1/17.abstract

Indexing Status
Subject indexing assigned by NLM

MeSH
Anti-Bacterial Agents /administration & dosage /adverse effects; Gram-Positive Bacterial Infections /drug therapy; Humans; Infusions, Intravenous /methods; Renal Insufficiency /chemically induced; Vancomycin /administration & dosage /adverse effects

AccessionNumber
12012016210

Date bibliographic record published
07/06/2012

Date abstract record published
24/09/2013

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.