Double trouble: how big a problem is redundant anaerobic antibiotic coverage in Veterans Affairs medical centres?

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Objectives: To assess the prevalence of, and the variation in, avoidable use of metronidazole in the Veterans Affairs (VA) healthcare system

Methods: Barcode Medication Administration (BCMA) data were retrospectively assessed for all patients hospitalized between January 2006 and December 2010 in acute-care wards of all VA medical centres (VAMCs) with complete BCMA data and at least 10 acute-care non-intensive care unit (ICU) beds. Potentially avoidable metronidazole days of therapy (DOT) were defined as the administration of metronidazole with another anti-anaerobic antibiotic on the same day for at least two consecutive days during the same hospitalization. Metronidazole was not considered redundant in combination with another anti-anaerobic agent within 28 days after a positive test for Clostridium difficile and during hospitalizations associated with discharge diagnosis codes for cholecystitis or cholangitis.

Results: A total of 128 VAMCs satisfied the inclusion criteria. Over the study period there were a total of 782 821 DOT of metronidazole (57.4 DOT per 1000 patient-days), of which 183 267 (23.4%) fulfilled the criteria for avoidable metronidazole DOT. The percentage of avoidable metronidazole DOT remained stable over the study period (22.8% in 2006 and 22.9% in 2010) despite a decrease in overall metronidazole use. There was wide variation in the percentage of avoidable metronidazole DOT among facilities (2010: median 20.3%, IQR 15.3%–29.4%). Piperacillin/tazobactam was the most commonly administered drug on avoidable metronidazole DOT (56.8%).

Conclusions: Potentially avoidable use of metronidazole affected about a quarter of all days when metronidazole was given. The combination of metronidazole with piperacillin/tazobactam was particularly common and represents a possible target for antibiotic stewardship interventions.

Keywords: antibiotic stewardship, anaerobes, metronidazole, inappropriate antibiotic use

Introduction

Inappropriate use of antibiotics is a common problem in hospitals around the world, contributing to antimicrobial resistance, Clostridium difficile infection (CDI), increased costs and drug-related adverse effects.1,2 Unnecessary combinations of antibiotics with overlapping spectra are part of this problem.1,3,4 The CDC recommend that antimicrobial stewardship programmes (ASPs) review instances of double coverage for anaerobic pathogens. This practice is promoted in the ‘Get Smart for Healthcare’ programme as an ‘easy’ target for ASPs since it is relatively straightforward to identify inappropriate use of anaerobic agents without time-intensive chart review. It is commonly accepted that there is no indication to combine metronidazole with another anti-anaerobic agent, with the exception of patients with CDI and certain biliary infections.5 Although most ASPs probably encounter redundant anaerobic coverage regularly, it remains difficult to measure without patient-level electronic data. In addition, the magnitude of practice variation among different facilities remains unclear. We therefore utilized the wealth of Barcode Medication Administration (BCMA) data from Veterans Affairs (VA) hospitals to assess the prevalence of, and the variation in, this practice throughout the VA healthcare system.
Methods

VA is the largest integrated healthcare system in the USA operating 152 VA medical centres (VAMCs). All VAMCs implemented BCMA in 2000, which enables users to document the administration of medications at the bedside through the scanning of barcode labels. BCMA data are logged electronically with information about the type of drug, administration time, route, etc. Recently, BCMA data have become available for research through the VA Informatics and Computing Infrastructure (VINCI).

We retrospectively assessed BCMA data for all patients hospitalized between 1 January 2006 and 31 December 2010 in acute-care wards of all VAMCs with complete BCMA data and at least 10 acute-care non-intensive care unit (ICU) beds over the study period. This research complies with all Federal guidelines and VHA policies relative to Human Subjects and Clinical Research.

Antibiotic use was expressed as ‘days of therapy’ (DOT), which is defined as the administration of a single antibiotic on a given day independent of the number of doses, the strength of the dose administered or the route of administration. DOT and patient-days (PDs) were calculated using a midnight census approach.

Definition of redundant anaerobic coverage

We defined potentially avoidable metronidazole DOT as the administration of enteral or parenteral metronidazole with any of the following agents on the same calendar day for at least two consecutive calendar days during the same hospitalization:

(i) penicillin/β-lactamase-inhibitor combinations (ampicillin/sulbactam, amoxicillin/clavulanate, ticarcillin/clavulanate or piperacillin/tazobactam)
(ii) carbapenems (meropenem, ertapenem, doripenem or imipenem)
(iii) moxifloxacin, clindamycin, cefoxitin, cefotetan or tigecycline

We stipulated two consecutive days of therapy to account for days when therapy was merely switched.

Metronidazole was not considered redundant in combination with the antibiotics above in the following situations:

(i) administration within 28 calendar days after obtaining a stool sample that tested positive for C. difficile toxin
(ii) all administrations during a hospitalization associated with either of the two following ICD-9-CM diagnosis codes: 575.0 (cholecystitis) or 576.1 (cholangitis)

Our main outcome measure was the percentage of avoidable metronidazole DOT out of all metronidazole DOT. Data were analysed using STATA version 11 (Stata Corp., College Station, TX, USA). Descriptive statistics were used to summarize variables.

Results

Of 152 VAMCs, 128 met the inclusion criteria for this study. Twenty facilities were excluded for not offering acute-care services; one was excluded for having less than 10 acute-care beds; and three were excluded for incomplete BCMA data. Over the study period there were 2.43 million unique hospitalizations in included wards, accounting for over 13.63 million PDs.

There were a total of 782821 DOT of metronidazole (57.4 DOT per 1000 PDs) in all 128 hospitals over the study period, of which 183267 (23.4%) fulfilled the criteria for avoidable metronidazole DOT. While overall metronidazole use decreased over the study period (from 64.1 DOT per 1000 PDs in 2006 to 50.9 DOT per 1000 PDs in 2010), the overall percentage of avoidable metronidazole DOT remained relatively stable (22.8% in 2006 and 22.9% in 2010; Figure 1). Avoidable metronidazole use was also higher in ICUs (35.9% of metronidazole DOT versus 19.4% in the non-ICU setting).

We observed wide variation in the percentage of avoidable metronidazole DOT among facilities. In 2010, this ranged from 2.5% to 58.7% (median 20.3%, IQR 15.3%–29.4%). Overall, potentially avoidable metronidazole was administered in 34190 hospitalizations (1.4% of all hospitalizations).

When we examined anaerobically active agents commonly used with metronidazole, piperacillin/tazobactam was by far the most common drug administered (56.8% of all avoidable metronidazole DOT), followed by imipenem (15.1%) and moxifloxacin (12.4%). The median duration of avoidable metronidazole use was 4 days (IQR 3–7 days).

Discussion

The results of this study show that: (i) about 1 in every 4 days of metronidazole treatment in VA facilities represents potentially redundant anaerobic coverage; (ii) there is significant variation in avoidable metronidazole use among facilities; and (iii) the combination of piperacillin/tazobactam with metronidazole is the most common example of redundancy.

Only a handful of single-centre studies have assessed the prevalence of avoidable anaerobic drug use, making it difficult to put the results of this study into perspective. A recent study at the Hospital of the University of Pennsylvania analysed unnecessary metronidazole use in patients receiving ampicillin/sulbactam over two years: 41 of 1783 admissions (2.3%) fulfilled their definition of inappropriate use.

We observed marked variation in the percentage of avoidable metronidazole use among facilities. While the overall percentage of avoidable metronidazole use remained stable over the study period, some individual facilities demonstrated decreases (data not shown), which might be attributable to antibiotic stewardship interventions. It is also noteworthy that, despite a decrease...
in overall metronidazole use (presumably in part through increased use of oral vancomycin from 7.2 DOT per 1000 PDs in 2006 to 11.7 DOT per 1000 PDs in 2010, likely for treatment of CDI), there was no decrease in the percentage of metronidazole use identified as potentially avoidable.

The reasons for the redundant use of metronidazole are unclear. One potential explanation is that many prescribers are unaware of the overlapping spectra of antibiotic activity. While most facilities perform anaerobic susceptibility testing only on a limited basis, multicentred susceptibility surveys of clinically important anaerobic bacteria continue to report susceptibilities in excess of 99% for piperacillin/tazobactam and carbapenems. Prescribers may also perceive little harm from using multiple antibiotics, believing that ‘more is better’. Some redundant metronidazole use might also represent CDI ‘prophylaxis’, which, although neither recommended nor supported by evidence, could still be influencing practice. In our dataset a history of CDI within the previous year was rare (1.4% of all hospitalizations with potentially avoidable metronidazole use). A subset of physicians might also feel compelled to add metronidazole to another antibiotic with anaerobic activity for better abscess penetration in the case of severe anaerobic infections. Only 2.3% of hospitalizations with potentially avoidable metronidazole use, according to our definition, had a discharge diagnosis from intra-peritoneal abscess.

The negative impact of metronidazole overuse is difficult to estimate. Resistance to metronidazole is currently not a major clinical problem and it is unclear whether redundant anaerobic coverage increases the risk of CDI. Unnecessary antibiotic use is associated with increased drug costs, but since metronidazole is relatively inexpensive, overall costs are likely to be less important than adverse events. While metronidazole can have serious side effects (such as neurotoxicity), when given in high doses or over prolonged periods, the frequency of these side effects is unclear and difficult to ascertain.

Nevertheless, frequent use of redundant anaerobic therapy could be a marker of antibiotic prescribing quality in general. Addressing this problem may have the collateral benefit of increasing overall awareness of the need for appropriate antibiotic use, regardless of the clinical domain.

Our analysis has some limitations. Detailed chart review might have identified more cases where double therapy was justified, such as for patients with CDI whose tests were performed outside the VA or for patients with biliary tract infections not recorded in discharge diagnoses. We also did not check for the presence of diagnoses where metronidazole is the treatment of choice, such as amoebiosis and giardiasis, but these infections are likely to be rare in the VA inpatient population. On the other hand, our methods underestimated total avoidable anaerobic coverage, since we did not consider double anaerobic coverage with drugs other than metronidazole (e.g. the combination of clindamycin with another anti-anaerobic agent, outside the setting of necrotizing fasciitis). Finally, the particular patient population in VA hospitals limits the external generalizability of our findings. However, to our knowledge, this is the largest study so far examining the issue of redundant anaerobic coverage using patient-level antibiotic administration data over an extended period.

A substantial proportion of all metronidazole use in VA facilities likely represents redundant anaerobic antibiotic coverage. Since the use of metronidazole for anaerobic infections was first studied in a VA facility in the 1970s, investigating practice and implementing policies to encourage more rational use of metronidazole, and antibiotics in general, in the VA network of medical centres seems particularly apropos.

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Transparency declarations
None to declare.

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