Metronidazole stewardship initiative at Christchurch hospitals—achievable with immediate benefits
Sharon J Gardiner, Sarah CL Metcalf, Paul KL Chin, Matthew P Doogue, Simon C Dalton, Stephen T Chambers

ABSTRACT

AIMS: To evaluate an antimicrobial stewardship (AMS) initiative to change hospital prescribing practice for metronidazole.

METHODS: In October 2015, the Canterbury District Health Board (CDHB) AMS committee changed advice for metronidazole to promote two times daily dosing for most indications, prioritisation of the oral route and avoidance of double anaerobic cover. Adoption of the initiative was facilitated via change in prescribing guidelines, education and ongoing pharmacy support. Usage and expenditure on metronidazole for adult inpatients were compared for the five years pre- and two years post-change. Other district health boards (DHBs) were surveyed to determine their dosing recommendation for metronidazole IV.

RESULTS: Mean annual metronidazole IV use, as defined daily doses per 1,000 occupied bed days, decreased by 43% post-initiative. Use of non-IV (oral or rectal) formulations increased by 104%. Total savings associated with the initiative were approximately $33,400 in drug costs plus $78,200 per annum in IV giving sets and post-dose flushes. Twelve of 20 (60%) DHBs (including CDHB) endorse twice daily IV dosing.

CONCLUSIONS: In addition to financial savings, reduction in IV doses has potential benefits, including avoidance of IV catheter-associated complications such as bloodstream infections. Approaches to metronidazole dosing vary across DHBs and could benefit from national coordination.

Metronidazole is a synthetic nitroimidazole developed in the 1950s to treat urogenital infections caused by the parasite, Trichomonas vaginalis.1 Its activity against anaerobic bacteria was later discovered serendipitously in 19622 and now forms the basis for most of its use in hospitalised patients.

Metronidazole has a unique pharmacological profile that includes rapid concentration-dependent bactericidal action against susceptible anaerobic bacteria3,4 and low resistance rates within these organisms.5 It also has an excellent oral bioavailability (>90%), favourable penetration to the site of infection and a long half-life (by antimicrobial standards) of eight hours.6 However, despite more than 50 years of use and an established role in the treatment of anaerobic infections, there is no consensus on the ideal dosing strategy for metronidazole administered intravenously (IV). Indeed, international guidelines on the treatment of intra-abdominal infections in adults endorse a two-fold variation in daily dose (1,000–2,000mg) administered at four different dose intervals (6-, 8-, 12- or 24-hourly) (Table 1).7–12 An antimicrobial stewardship (AMS) perspective is needed to rationalise these regimens, which are not equivalent in terms of cost or administration complexity, and may differ in both efficacy and adverse effects.

Canterbury District Health Board (CDHB) had a long history of dosing metronidazole IV as 500mg every eight hours, and orally (PO) as 400mg three times daily, for treatment of anaerobic bacterial infections.
In 2015, our AMS committee considered literature recommendations for metronidazole dosing together with contemporary knowledge of pharmacokinetic-pharmacodynamic relationships, risk of bloodstream infections with IV access, administration issues and cost. A multifaceted AMS initiative was developed for adult inpatients at CDHB and comprised:

1. Prioritisation of the oral route, with the IV route only to be used in the presence of compromised gastrointestinal absorption, or a patient designated ‘nil by mouth’,
2. Twice daily dosing for most indications, as PO 600mg twice daily or IV 500mg 12-hourly,
3. Avoidance of unnecessary duplication of anaerobic cover, by not co-administering metronidazole with amoxicillin+clavulanic acid, carbapenems (eg, meropenem), clindamycin, moxifloxacin or piperacillin+tazobactam. 

*Clostridium difficile*-associated diarrhoea, *H. pylori* eradication regimens and sexual/reproductive health indications other than pelvic inflammatory disease were excluded from this initiative.

The purpose of this paper is to describe the multipronged AMS initiative undertaken to change prescribing practices at CDHB and the resultant impact on metronidazole usage and expenditure.

### Methods

After consultation with senior medical officers, and nursing and pharmacy staff from relevant areas such as general surgery, the following initiative was implemented in October 2015:

1. Updating online CDHB antimicrobial guidelines for intra-abdominal infections, sepsis, pelvic inflammatory disease and deep neck space infections to reflect the twice daily dosing strategy and prioritisation of the oral route,
2. Updating the e-prescribing and administration system used at CDHB to include the new dosing guidelines,
3. Verbal education sessions for medical, nursing and pharmacy staff,
4. Written bulletins and a poster disseminated to clinical staff,
5. Pharmacist support of the initiative via ongoing education on the wards,
6. Ward drug stocks were altered to improve access to metronidazole 200mg oral tablets for the 600mg oral dose.

Metronidazole usage and expenditure from 1 October 2010 until 30 September 2017 (five years pre- and two years post-initiative) were assessed with data extracted from the hospital pharmacy dispensing software (ePharmacy, v1.7, DXC Technology, Virginia) into Microsoft Excel (2013).

### Table 1: Recommended metronidazole IV dosing strategies for intra-abdominal infections.

<table>
<thead>
<tr>
<th>Source</th>
<th>1,000mg per 24h</th>
<th>1,500mg per 24h</th>
<th>2,000mg per 24h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>500mg q12h</td>
<td>1,000mg q24h</td>
<td>1,500mg q8h</td>
</tr>
<tr>
<td>Infectious Diseases Society of America7</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Surgical Infection Society (USA)8</td>
<td>Y*</td>
<td>Y*</td>
<td>Y</td>
</tr>
<tr>
<td>World Society of Emergency Surgery9</td>
<td></td>
<td></td>
<td>y</td>
</tr>
<tr>
<td>Therapeutic Guidelines of Australia10</td>
<td>Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Zealand Formulary11</td>
<td></td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>Metronidazole datasheet12</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>

*with a loading dose of 1,000mg IV.
Systemic metronidazole use was determined from issues to ward imprests and to individual patients for adult inpatients to reflect the population targeted by the initiative. Adult inpatients were those admitted to Christchurch, Christchurch Women’s, Burwood or the Princess Margaret Hospitals after exclusion of psychiatric, paediatric and day stay areas as per established local method.13

All formulations administered to treat systemic infections were included: 500mg/100mL IV infusion bags, 200mg tablets, 400mg tablets, 200mg/5mL suspension and 500mg rectal suppositories. Topical and vaginal formulations were excluded. Use was expressed as defined daily doses (DDD) per quarter and per year normalised to 1,000 bed days. This was calculated for the individual formulations, for IV versus non-IV routes of administration, and for total systemic metronidazole use. Expenditure was determined using the pharmacy purchasing price per unit. This was essentially static (less than 10% variation) over the seven-year study period for the 200mg tablet (NZ$0.10), 400mg tablet (NZ$0.18), 200mg/5mL suspension 100mL (~NZ$25.63) and 500mg suppository (~NZ$2.60). The metronidazole IV 500mg infusion bag changed from a price of $2.46 to $1.39 in February 2015. Costs of administration consumables was taken simplistically as $6.63 per IV dose for the cost of a giving set (Alaris secondary set, CareFusion, Switzerland) and 100mL sodium chloride 0.9% infusion bag (post-dose flush).

Between September and November 2017, the other 19 New Zealand district health boards (DHBs) were surveyed electronically and via telephone to determine the dosing strategy used for metronidazole IV and, where relevant, the date when a twice daily dosing strategy was adopted.

Results

This AMS initiative was associated with a 43% decrease in metronidazole IV use (Table 2 and Figure 1), which translates to around 11,800 avoided IV doses annually (data not shown). By contrast, non-IV administration of metronidazole increased by 104%, largely due to a 339% increase in use of the 200mg tablets. Thus, the proportion of metronidazole-administered IV decreased from 80% prior to the initiative to 52% post-initiative.

Mean annual expenditure on metronidazole in adult inpatients decreased by 59% following the initiative, with additional savings in consumables and nursing time. The total saving was approximately $111,600 per year, comprising $33,400 and $78,200 in drug cost and consumables, respectively.

Eleven of the 19 remaining DHBs reported a 12-hourly dosing strategy for metronidazole IV. Hence, 60% (12 of 20) of all DHBs (including CDHB) now recommend twice daily dosing. All of these advise a dose of 500 mg 12-hourly while one DHB recommended 15mg/kg 12-hourly, a two-fold greater dose (ie, 1,000mg 12-hourly for a 70kg person). The earliest adopter reported that twice daily dosing was included in their guidelines since the 1990s. The remaining 11 DHBs (including CDHB) changed to 12-hourly between 2011 and 2017.

Table 2: Mean annual metronidazole usage and expenditure for adult inpatients for the five years before and after commencement of the initiative in October 2015.

<table>
<thead>
<tr>
<th></th>
<th>DDDs per 1,000 occupied bed days (mean usage per year)</th>
<th>Expenditure (unadjusted mean cost per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>200mg tablets</td>
<td>3.1</td>
<td>13.6</td>
</tr>
<tr>
<td>400mg tablets</td>
<td>3.9</td>
<td>1.3</td>
</tr>
<tr>
<td>200mg/5mL susp</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>500mg suppository</td>
<td>0.05</td>
<td>0.07</td>
</tr>
<tr>
<td>Total non-IV</td>
<td>7.6</td>
<td>15.5</td>
</tr>
<tr>
<td>500mg IV</td>
<td>29.9</td>
<td>16.9</td>
</tr>
<tr>
<td>Total non-IV + IV</td>
<td>37.5</td>
<td>32.4</td>
</tr>
</tbody>
</table>

*Changes ≤5% are arbitrarily reported as unchanged
Note: susp = suspension, IV = intravenous
Discussion

This AMS initiative to avoid unnecessary metronidazole IV doses in CDHB public hospitals was associated with a 43% decrease in use of the IV formulation and a 104% increase in use of the non-IV route. Despite overall metronidazole use decreasing minimally (14%), the shifts in route of administration resulted in substantial healthcare savings. Drug costs were 59% lower post-initiative resulting in savings of $33,400 per annum. An additional $78,200 was saved in consumables through avoidance of 11,800 IV doses annually. Additional benefits and savings that we have not quantified relate to nursing time, avoided complications of IV access such as bloodstream infections and facilitated discharge from hospital.

While there is a lack of clinical trials comparing outcomes with different dosing strategies, the concept of giving metronidazole twice daily is not new. In 1989, Earl et al stated that IV 500mg or PO 400mg twice daily had been used at their hospital for “many years” with “apparent success”. They reported that this regimen produced adequate metronidazole serum concentrations in 48 surgical patients, defined as a trough concentration above both 2mg/L and the minimum inhibitory concentration (MIC) of most relevant anaerobes. Nearly three decades later, Sprandel et al determined that the probability of attaining a target area under the concentration-time curve (AUC$_{0-24h}$/MIC ratio ≥ 70 was ≥ 99.8% for 1,000mg and 1,500mg daily for organisms with an MIC <2mg/L. However, for an MIC of 4mg/L, this decreased to 28.5% and 80.0%, respectively, showing an advantage for the higher dose. Almost all (213/218) of the B. fragilis isolates studied had MICs <1mg/L, and the remaining five isolates had MICs of 2mg/L. This is in keeping with New Zealand research. Collectively, these studies support an IV dose of 1,000mg per 24 hours as achieving satisfactory concentrations in most circumstances. Given the formulation available in New Zealand (a 100mL infusion bag containing 500mg), we elected to give this in two divided doses, in line with the Therapeutic Guidelines of Australia. In the absence of a 500mg oral dose formulation, we chose an oral dose of 600mg to achieve similar concentrations to the IV dose and for clinicians to replace IV with oral metronidazole with confidence in similar outcomes.

The data used in this analysis has limitations as it was derived from pharmacy dispensing software. It reflects ‘mass' shifts in stock from pharmacy to clinical areas rather than dispensings, prescriptions or administrations to patients. While the assumption is that this stock movement reflects usage in patients it is undoubtedly less accurate than information obtained from electronic prescribing and administration software. This has only been used for a short time at Canterbury DHB and cannot,
therefore, be used to assess changes in usage over a long period of time. However, e-prescribing data for the six months to September 2017, shows that 81% of metronidazole IV is prescribed as 12-hourly on our general surgical wards (data not shown).

The slow change observed in New Zealand DHBs and variability in guidelines suggests that AMS in New Zealand would benefit from national guidance and a coordinated approach. All of our DHBs are under-resourced for AMS, and only half employ dedicated staff to manage AMS in New Zealand public hospitals. While we believe that AMS programmes should be driven with a quality rather than financial focus, it is clear that this initiative provides a compelling economic case for employing staff dedicated to AMS.

Competing interests:
Nil.

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