Metronidazole q12 Hours Literature Summary

Rationale:

Metronidazole is a concentration-dependent bactericidal antimicrobial[1]. It is frequently given in pediatrics as a once daily medication for the indication of appendicitis as well as every 12 hours for other indications in adults.

Pharmacokinetic support:

Half-life of ~8hrs in adults and is metabolized to a hydroxy metabolite with a half-life of 11.6 hours which has 30-65% activity of the parent compound.[2]

Earl 1989: JAC 1989[3]

Paired blood samples were examined from 48 patients undergoing major surgery that were receiving metronidazole at an interval of 12 hours after steady state (mean doses 9th and 6th PO and IV, respectively).

Patients: 25 patients were given 400 mg PO q12h and 23 patients 500 mg IV BID for either prophylaxis or treatment

Results: trough serum conc. oral 3-11 mg/L (mean 5.5 mg/L) and intravenous (IV) 2-15 mg/L (mean 6.7 mg/L); peak concentrations were oral 10-26 mg/L (mean 17.4 mg/L) and IV 13-28 mg/L (mean 23.6 mg/L).

Conclusion: **The trough concentrations are well in excess of the MICs for the majority of obligate anaerobes and thus the 12-hourly regimen achieves and maintains therapeutic serum concentrations**. The reduction from 8hr regimen to 12hr represents substantial cost savings the drug budget.

Microbiologic support:

Snydman 2017: Anaerobe 2017[4]

Seven medical centers (including Duke University) reported data for *Bacteroides* and *Parabacteroides* isolates collected from 2010 to 2012.

Table 1
Activity of antimicrobial agents against *Bacteroides* species in the United States 2010–2012.

Species	Antimicrobial agents	MIC range (μg/mL)	MIC_{50}	MIC_{90}	Percent resistant[a]
All isolates tested (n=779)	Ampicillin/Sulbactam	≤0.5–>128	2	16	3.1%
	Cefoxitin	≤2–>128	8	32	5.9%
	Chloramphenicol[b]	>2–≤8	≤8	≤8	0.0%
	Clindamycin	≤0.5–>16	2	>16	33.2%
	Ertapenem	≤0.12–16	0.5	2	1.8%
	Imipenem	≤0.06–16	0.25	0.5	0.8%
	Linezolid	≤0.5–16	2	4	1.0%
	Meropenem	≤0.12–16	0.25	1	1.5%
	Metronidazole	≤1–2	≤1	2	0.0%
	Moxifloxacin	≤0.5–>16	2	>16	28.5%
	Piperacillin/Tazobactam	<0.5–>256	2	16	1.2%
	Tigecycline	≤0.06–32	0.5	4	2.4%

On review of individual isolates, there were no outliers with the above. **The 779 isolates in this study demonstrated a metronidazole MIC_{90} of 2.** No isolate was resistant according to the CLSI cutoff of ≤ 8.

Table 1. Review of Studies

Author/Year	Design	Intervention	Inclusion/Exclusion	Results
Beique 2016[5]	Retrospective chart review, IDWeek 2016 Poster	500 mg q12 vs q8h	**Inclusion**: prescribed metronidazole for appy or divert Exclusion: drug on admission, prescribed both frequency, ≤ 24h of therapy, concomitant infection, or chronic GI disease	**30-d readmit:** appy: 1/20 pts q12 vs 1/25 pts q8h, **(p=1)** divert: 1/15 pts q12 vs 0/21 pts q8, **p=0.4** **Resolution rate no difference** appy p=0.43; divert p=0.28
Soule 2018[6]	Retrospective, pre/post study 2014 -2016	500 mg q12h vs q8h	**Inclusion**: > 18 yo and received at least 3 days of metronidazole Exclusion: use of anaerobic coverage > 24h before metronidazole, concurrent anaerobic coverage, pathogen resistance, or pregnancy	**Clinical cure: 83% both groups, p=1.0.** No difference in duration of antibiotics, LOS, escalation of therapy, microbiologic cure, or mortality
Shah 2021[2]	Multi-center retrospective study 2016-2020	500 mg q12h vs q8h	**Inclusion**: bacteremic with obligate anaerobe Exclusion: < 72h metronidazole, > 72h other anaerobic coverage, *C. difficile*, and CNS infection	85 pts, 32 q8h and 53 q12h **All cause 30-d death: 15.6% q8h vs 9.4% q12h, p=0.49** **No diff in post-infection days of hospitalization, 30-d readmission due to infection, or repeat positive cultures**

Appy: appendicitis; CNS: central nervous system; divert: diverticulitis; GI: gastrointestinal; LOS: length of stay; pts: patients; yo: years old

1. Beique 2016: Comparison of Metronidazole q12h to q8h in Combination with Other Antibiotics on the Clinical Outcome and Readmission Rate of Patients with Appendicitis and Diverticulitis. IDWEEK 2016 – Poster
    a. Antimicrobial stewardship initiative recommending q12h during weekly rounds on surgery team
    b. Objective: determine if 500 mg q12h differs from q8h in appendicitis or diverticulitis for 30-day clinical outcomes and readmission rates
    c. Design: Retrospective chart review of patients with appendicitis or diverticulitis prior to and after 03.2015
    d. Results: Of 200 patients with appendicitis, 45 were included and of 120 patients with diverticulitis, 36 were included. 82% of appendicitis were treated surgically and 92% of diverticulitis were treated medically
        i. 30-day readmission rate did not differ for appendicitis (1/20 patients q12h vs 1/25 patients q8h, p=1) or diverticulitis (1/15 patients q12h vs 0/21 patients q8h, p=0.4)
        ii. Resolution rate did not differ for appendicitis p=0.43, diverticulitis p=0.28
2. Soule 2018
    a. Post intervention period started July 2015
        i. Q12h dosing was utilized for all indications except *C. difficile*, CNS, or parasitic/amoebic infections
    b. Clinical cure defined as improvement or resolution of principle sign/symptom of infection with normalization of WBC (> 4,000 and < 12,000) at the end of therapy or discharge
    c. Clinical failure defined as presence of any of the following: no resolution of signs and symptoms of infection, escalation of antibiotics, or no microbiological cure.
    d. Stats: 80% response and alpha 0.05, 82 pts in each group for power of 0.8 and difference of 20%
    e. Baseline: patients in the q8h group were older (62.5 years vs 53.9 years, p=0.002). 24-29% were obese and 5% vs 10% q8h and q12h, respectively were admitted to the ICU
        i. 89% and 79% for complicated intra-abdominal infection and source control in 26% and 31%, q8h and q12h, respectively

3. Shah 2021
    a. 781 bacteremic due to an obligate anaerobe identified by MALDI-TOF from 08.2016 to 07.2020
        i. Excluded if did not get metronidazole, metronidazole duration < 72hrs, received both frequencies, > 72hrs of other anaerobic coverage, concomitant *C. difficile*, CNS disease, or infected with resistant anaerobe
        ii. Decision to use q12h or q8h interval was by the provider
    b. Results:
        i. *B. fragillis* in 42.4% of cases
        ii. Total patients with source control: 12/32 (37.5%) q8h and 19/53 (35.8%) q12h
            1. Of the patients who were managed surgically, 67.7% (21/31) of patients achieved source control within 5 days of positive blood cultures

Summary:

Due to metronidazole trough levels with every 12 hour dosing being higher than current anaerobic isolate MICs, every 12 hour dosing represents an attractive option for limiting drug exposure and potentially reducing cost and adverse effects. Additionally, there are three clinical studies that demonstrate equivalent outcomes for patients dosed at an every 12 hour and 8 hour interval.

Recommendations

Utilize every 12 hour metronidazole dosing for IV and oral with the following exceptions:

1. Pediatric patients: no data and low use, continue to utilize current dosing
2. More frequent dosing for *C. difficile*, CNS, or parasitic/amoebic infections, which may require higher concentrations of metronidazole
3. May consider more frequent dosing (q8h) for complicated infections without source control such as undrained large abscesses or infections involving prosthetic material (e.g. aortic grafts, aortoenteric fistulae, etc)

References

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