Technigram

Minimum Inhibitory Concentrations (MIC) for Cephalosporin Compounds and Their Active Metabolites for Selected Mastitis Pathogens

Based on publication: Cortinhas CS, Ruegg PL, Oliveira L, et al. *AJVR* 2013;74(5).[1]

Abbreviations and Definitions

MIC: Minimum inhibitory (MIC) concentration is the lowest concentration of a particular antibiotic that inhibits growth of a particular bacterial isolate over 24 hours in the laboratory, under standardized conditions.

MIC_{50}: MIC inhibiting growth of 50% of bacterial isolates tested.

MIC_{90}: MIC inhibiting growth of 90% of bacterial isolates tested.

Study Design

This study compared the MICs of the parent antibiotics ceftiofur and cephapirin to their respective metabolites, desfuroylceftiofur and desacetylcephapirin.

MIC break points to classify bacterial isolates for susceptibility and resistance were based on Clinical and Laboratory Standards Institute (CLSI) guidelines, and are as follows:

Antibiotic	Sensitive	Intermediate	Resistant
Ceftiofur	≤2 µg/mL	4 µg/mL	≥8 µg/mL
Cephapirin	≤8 µg/mL	16 µg/mL	≥32 µg/mL

There are no guidelines for the metabolites, and in the paper, the authors assumed the same break points as for the parent antibiotics. Mastitis isolates (n = 488) tested were previously collected from 2005 to 2010 from Wisconsin dairy farms. Isolates were from both subclinical and clinical intramammary infections. The tables at the end of this document contain MIC data from the research.

Key Points

- When infused into an udder, ceftiofur is partly metabolized to desfuroylceftiofur, and cephapirin is partly metabolized to desacetylcephaprin.
- These metabolites retain antibacterial activity, but may not be as effective as the parent antibiotic.
- The effectiveness of an antibotic infused into a mastitic quarter may depend on the degree of metabolism that has occurred. Up to 80% of the parent ceftiofur may be metabolized at a 24-hour interval, and 50% of cephapirin at a 12-hour interval after dosing.[2,3]
- There is a difference in the MIC_{50} and MIC_{90} between the parent drug and the major metabolite.
- One hundred percent of *Staphylococcus aureus* isolates were sensitive to ceftiofur, but only 5.1% of isolates were sensitive to desfuroylceftiofur. All isolates (100%) were classified as sensitive to both cephapirin and desacetylcephapirin.
- Ninety-seven percent of coagulase-negative staphylococci (CNS) isolates were sensitive to ceftiofur, but only 34.3% of isolates were sensitive to desfuroylceftiofur. One hundred percent of isolates were sensitive to both cephapirin and desacetylcephapirin.
- One hundred percent of *Streptococcus dysgalactiae* isolates tested were sensitive to ceftiofur, desfuroylceftiofur, cephapirin and desacetylcephapirin.
- The percentage of *Streptococcus uberis* isolates sensitive to the compounds were as follows: ceftiofur (94%), desfuroylceftiofur (92%), cephapirin (100%) and desacetylcephapirin (100%).
- Ninety-five percent of *E. coli* isolates were sensitive to ceftiofur and 91% to desfuroylceftiofur. Fifty-one percent of isolates were sensitive to cephapirin, and no isolates were sensitive to desacetylcephapirin.
- Cephapirin and desacetylcephapirin have superior MIC performance against Gram-positive mastitis pathogens, whereas ceftiofur and desfuroylceftiofur have superior activity against *E. coli*.

Conclusion

This paper demonstrated there can be a significant difference in the MIC between the parent and metabolite of cephalosporin antibiotics for certain mastitis pathogens.

This difference in MIC becomes significant when there is a major shift in the sensitivity of the mastitis pathogen between the parent antibiotic and the metabolite.

The lack of correlation between MIC results and clinical outcome in the treatment of mastitis may be explained by the difference in MIC between parent antibiotic and the major active metabolite.

The determination of the most appropriate antibiotic to treat a mastitis pathogen should ideally be based on MIC testing of both parent and metabolites, and adjust for the proportion of each in the udder over the dosing interval.

References

[1] Cortinhas CS, Ruegg PL, Oliveira L, et al. Minimum inhibitory concentrations of cephalosporin compounds and their active metabolites for selected mastitis pathogens. *AJVR* 2013;74(5):683–690.

[2] Freedom of Information Summary, NADA 141-238, Spectramast® LC.

[3] Gorden PJ , van der List MJ, Lehman FD, et al. Elimination kinetics of cephapirin sodium in milk after an eight-day extended therapy program of daily intramammary infusion in healthy lactating Holstein-Friesian cows. *J. Dairy Sci* 2013;96:4455–4464.

Table 1. Percentage of *Staphylococcus aureus*, *E. coli* and coagulase-negative staphylococci isolates classified as sensitive, intermediate or resistant for ceftiofur, desfuroylceftiofur, cephapirin and desacetylcephapirin.*

Bacteria	Antimicrobial	Type of mastitis	No. of isolates	Susceptible isolates (%)*	Intermediate isolates (%)	Resistant isolates (%)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
S. aureus	Ceftiofur	Clinical	48	100	0	0	0.50	1.00
		Subclinical	50	100	0	0	0.50	1.00
	Desfuroylceftiofur	Clinical	48	8.3	42.9	33.3	4.00	8.00
		Subclinical	50	2.0	28	70.0	8.00	16.00
	Cephapirin	Clinical	48	100	0	0	0.12	0.25
		Subclinical	50	100	0	0	0.25	0.25
	Desacetylcephapirin	Clinical	48	100	0	0	0.25	0.50
		Subclinical	50	100	0	0	0.25	0.50
Coagulase-negative staphylococci	Ceftiofur	Subclinical	99	97	0	3.0	0.50	1.00
	Desfuroylceftiofur	Subclinical	99	34.3	45.5	19.2	4.00	8.00
	Cephapirin	Subclinical	99	100	0	0	0.12	0.12
	Desacetylcephapirin	Subclinical	99	100	0	0	0.12	0.25
E. coli	Ceftiofur	Clinical	98	94.9	3.1	2	0.50	1.00
	Desfuroylceftiofur	Clinical	98	90.8	0	9.2	1.00	2.00
	Cephapirin	Clinical	98	51	29.6	19.4	8.00	64.0
	Desacetylcephapirin	Clinical	98	—	0	100	NI	NI

* Bacteria were classified as susceptible to ceftiofur at an MIC of ≤2 µg/mL, intermediate at 4 µg/mL and resistant at ≥8 µg/mL.
Bacteria were classified as susceptible to desfuroylceftiofur at the same break points as for ceftiofur.
Bacteria were classified as susceptible to cephapirin at an MIC of ≤8 µg/mL, intermediate at 16 µg/mL and resistant at ≥32 µg/mL.
Bacteria were classified as susceptible to desacetylcephapirin at the same break points as for cephapirin.

Table 2. Percentage of *Staphylococcus dysgalactiae* and *Streptococcus uberis* isolates classified as sensitive, intermediate or resistant for ceftiofur, desfuroylceftiofur, cephapirin and desacetylcephapirin.*

Bacteria	Antimicrobial	Type of mastitis	No. of isolates	Susceptible isolates (%)*	Intermediate isolates (%)	Resistant isolates (%)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
S. dysgalactiae	Ceftiofur	Clinical	47	100	0	0	0.03	0.06
		Subclinical	50	100	0	0	0.03	0.06
	Desfuroylceftiofur	Clinical	47	100	0	0	0.06	0.12
		Subclinical	50	100	0	0	0.06	0.12
	Cephapirin	Clinical	47	100	0	0	0.03	0.03
		Subclinical	50	100	0	0	0.03	0.03
	Desacetylcephapirin	Clinical	47	100	0	0	0.06	0.12
		Subclinical	50	100	0	0	0.12	0.12
S. uberis	Ceftiofur	Clinical	48	93.8	2.1	4.2	1.00	2.00
		Subclinical	48	93.8	4.2	2.1	2.00	2.00
	Desfuroylceftiofur	Clinical	48	93.8	2.1	4.2	2.00	2.00
		Subclinical	48	89.6	8.3	2.1	1.00	2.00
	Cephapirin	Clinical	48	100	0	0	0.25	0.50
		Subclinical	48	100	0	0	0.25	0.50
	Desacetylcephapirin	Clinical	48	100	0	0	0.50	1.00
		Subclinical	48	100	0	0	0.50	1.00

* Bacteria were classified as susceptible to ceftiofur at an MIC of ≤2 µg/mL, intermediate at 4 µg/mL and resistant at ≥8 µg/mL.
Bacteria were classified as susceptible to desfuroylceftiofur at the same break points as for ceftiofur.
Bacteria were classified as susceptible to cephapirin at an MIC of ≤8 µg/mL, intermediate at 16 µg/mL and resistant at ≥32 µg/mL.
Bacteria were classified as susceptible to desacetylcephapirin at the same break points as for cephapirin.

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