

Porcine and Bovine Pathogen Sensitivities Comparison of Aureomycin® Chlortetracycline and Oxytetracycline

ABSTRACT

Research studies were conducted to compare the in vitro sensitivity of various isolates of several common respiratory pathogens of swine and cattle to Aureomycin (chlortetracycline) and oxytetracycline by determining minimum inhibitory concentrations (MIC's). Different diagnostic laboratories were used in these studies. The results showed:

- A greater percentage of the porcine and bovine pathogens tested were more sensitive to Aureomycin than to oxytetracycline.
- MIC test results were not always repeatable within each laboratory, even though overall they were in close agreement between laboratories.
- Using tetracycline as the standard for sensitivity or resistance did not always accurately reflect sensitivity or resistance to Aureomycin and oxytetracycline. These studies, in tandem with sub-MIC blood and lung level studies, demonstrate that even though an in vitro test result indicates resistance, Aureomycin may still be effective against the pathogen in vivo.

EXPERIMENTAL PROCEDURES MIC's vs various pathogens

ISU study: Several porcine and bovine respiratory pathogens were isolated from animal tissue submissions by the Iowa State University (ISU) Diagnostic Laboratory.¹⁻³ Fifteen isolates of each pathogen were collected. Duplicates of each organism were sent to three other diagnostic laboratories (Kansas State University, Texas (private lab) and University of Nebraska).

The laboratories used their routine testing methods for the initial determination of the tetracycline MIC and sensitive or resistant status. Iowa State, Kansas and Nebraska labs used the full-range broth dilution microtitre plate test, and the Texas laboratory used the Kirby-Bauer plate test. For

the duplicate tests, all laboratories used procedures for a commercially prepared microtitre plate system. There were:

4 laboratories x 2 tests per isolate = 8 tests
per isolate x 15 isolates per pathogen = 120 total tests
per pathogen for Aureomycin or oxytetracycline.

MIC test results for each isolate in all four laboratories were compared to determine the repeatability of these test results within each laboratory and consistency between the laboratories.

Each isolate was classified as sensitive or resistant to Aureomycin or oxytetracycline based on a breakpoint MIC of 4 µg/mL. This breakpoint is currently used by diagnostic laboratories to classify a pathogen as sensitive or resistant to tetracycline, Aureomycin or oxytetracycline. In addition, they commonly use tetracycline as the standard for sensitivity or resistance to the entire family of "tetracycline" antimicrobials. They assume if a pathogen is sensitive or resistant to tetracycline, it is sensitive or resistant to Aureomycin and oxytetracycline.

This breakpoint of 4 µg/mL was previously established for human medicine. It was extrapolated to veterinary medicine because specific values for animals were unavailable. Consequently, this arbitrary breakpoint cannot definitively estimate in vitro resistance or sensitivity to the tetracycline family of antimicrobials for animals.

SDSU study: In an earlier study conducted at South Dakota State University (SDSU),⁴ 355 porcine and bovine respiratory pathogens were isolated from various diagnostic specimens, and the MIC's of Aureomycin and oxytetracycline vs these pathogens were compared.

TABLE 1. Tetracycline-sensitive porcine and bovine respiratory pathogens more sensitive to Aureomycin than to oxytetracycline (study with 4 laboratories^a).

Pathogen	No. isolates/ Total no. tests: Aureo. & OTC ^b	No. sensitive			Mean MIC value (µg/mL) for TC-sensitive organisms	
		TC ^c	Aureo.	OTC	Aureo.	OTC
PORCINE						
<i>Pasteurella multocida</i>	15/120	10	13	11	0.61*	0.90
<i>Bordetella bronchiseptica</i>	15/120	15	15	15	0.12*	0.31
<i>Actinobacillus pleuropneumoniae</i>	15/120	6	4	2	2.26	4.29
BOVINE						
<i>Mannheimia haemolytica</i>	15/120	6	9	6	0.40	0.50
<i>Pasteurella multocida</i>	15/120	12	14	12	0.25*	0.35
TOTAL	75/600	49	55	46		

^a Iowa State, Texas, Nebraska and Kansas State Diagnostic Laboratories
^b Oxytetracycline ^c Tetracycline
* $P < 0.01$

RESULTS

MIC's of various pathogens — Activity of Aureomycin higher compared to oxytetracycline

ISU study: Aureomycin was more active (lower MIC values) than oxytetracycline against the tetracycline sensitive isolates in these diagnostic laboratory tests ($P < 0.01$) (Table 1).

Inadequacy of tetracycline MIC's for predicting Aureomycin or oxytetracycline MIC's

As stated earlier, tetracycline is routinely used in veterinary diagnostic laboratory testing to estimate the sensitivity or resistance of pathogens to Aureomycin and oxytetracycline. Laboratories use an MIC of 4 µg/mL as the break-point:

- sensitive strain: ≤ 4 µg/mL
- resistant strain: > 4 µg/mL

The inherent error in assuming that all tetracyclines are equally active is demonstrated by the results of the ISU

FIGURE 1: Mean MIC's of all respiratory isolates tested including tetracycline resistant isolates (study with 4 laboratories).

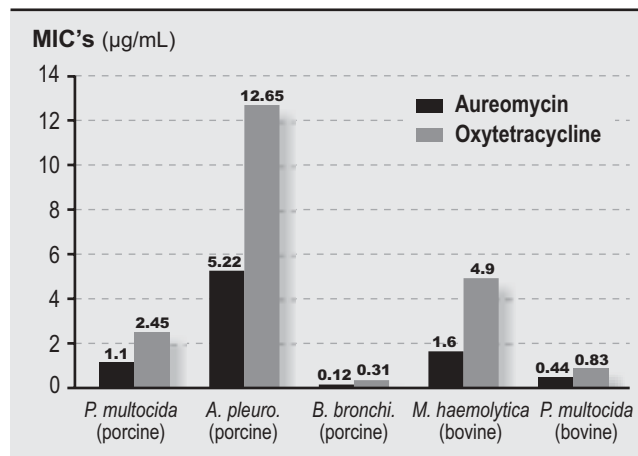
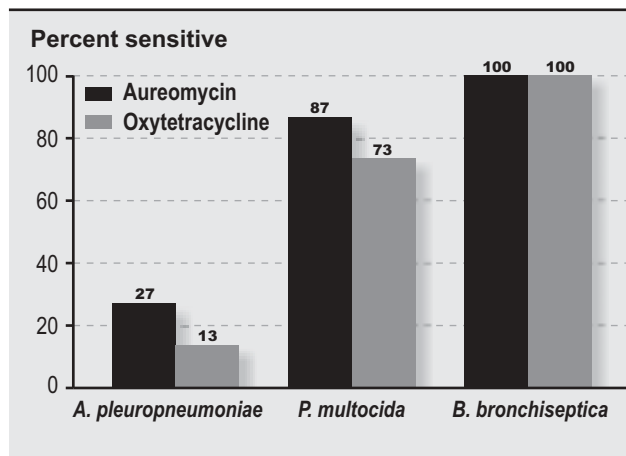


FIGURE 2: Higher percentage of porcine pathogens sensitive to Aureomycin (MIC's ≤ 4 µg/mL) than to oxytetracycline.



study (refer to Table 1). The tetracycline-sensitive pathogens were more sensitive to Aureomycin than to oxytetracycline ($P < 0.01$).

The activity of Aureomycin was greater than that of oxytetracycline ($P < 0.0001$) against all respiratory pathogens, including the tetracycline-resistant strains, in this study (Figure 1).

A higher percentage of all porcine and bovine isolates tested, except *B. bronchiseptica*, were sensitive to Aureomycin than to oxytetracycline (MIC's $\leq 4 \mu\text{g/mL}$) (Figures 2 and 3).

SDSU study: In this earlier study, many strains were equally sensitive to Aureomycin and oxytetracycline (Figures 4 and 5). However, of those that were not equally sensitive, most were more sensitive to Aureomycin than to oxytetracycline.

ISU vs SDSU studies:

Sensitivity to Aureomycin retained

Comparing the percentages of porcine and bovine respiratory pathogens sensitive to Aureomycin in the ISU study with the earlier SDSU study demonstrates that in general this sensitivity has not changed over the years (Figure 6).

DISCUSSION

Complexity of selecting an antimicrobial

Aureomycin has superior pharmacological profile

Over the years, in vitro sensitivity testing of antimicrobials against pathogens of animals, conducted by veterinary diagnostic laboratories, has helped veterinarians in selecting antimicrobials for disease control. In vitro laboratory results, however, are not necessarily predictive of in vivo efficacy.

In fact, these results may be of limited use without knowing the pharmacological profile of the medication(s). For example, an aminoglycoside such as neomycin may show in vitro activity against respiratory pathogens but is not absorbed from the gastrointestinal tract when administered orally.

Aureomycin has a superior pharmacological profile compared to oxytetracycline and tetracycline, as shown by higher blood and tissue levels, and it also has a superior microbiological profile.

FIGURE 3: Greater percentage of bovine pathogens sensitive to Aureomycin (MIC's $\leq 4 \mu\text{g/mL}$) than to oxytetracycline.

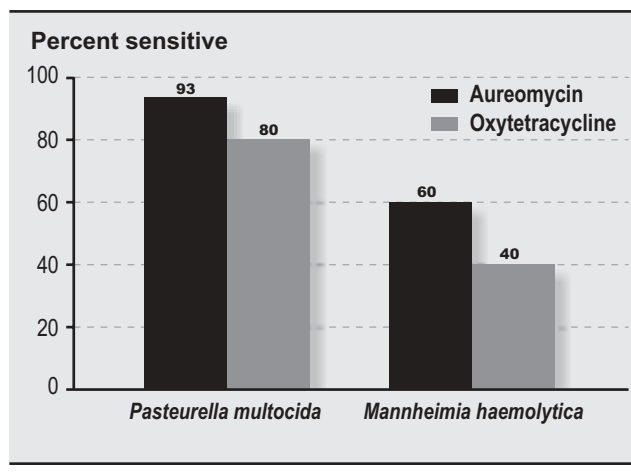


FIGURE 4: Sensitivities of swine pathogens to Aureomycin and oxytetracycline (SDSU study).

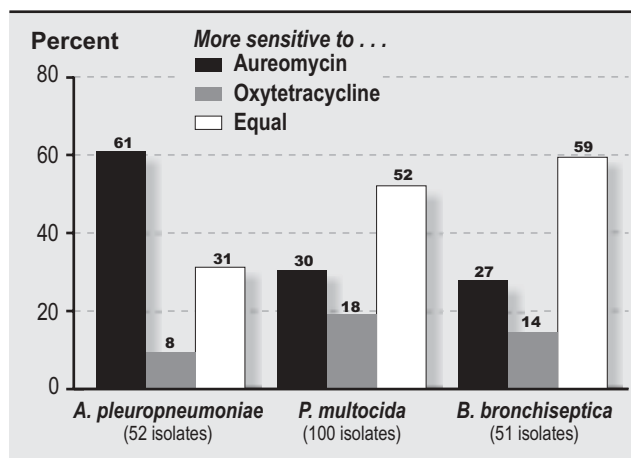


FIGURE 5: Sensitivities of cattle pathogens to Aureomycin and oxytetracycline (SDSU study).

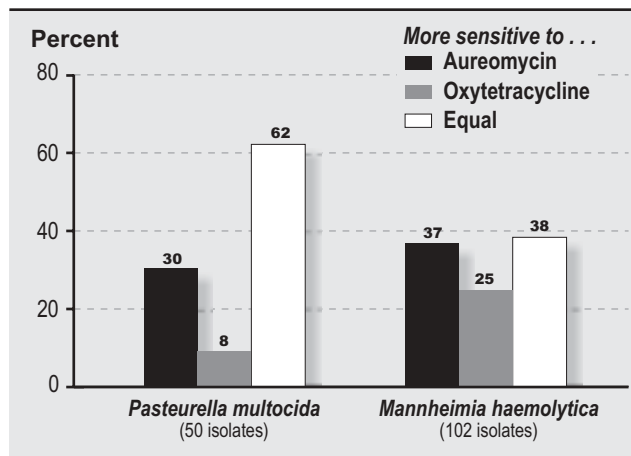
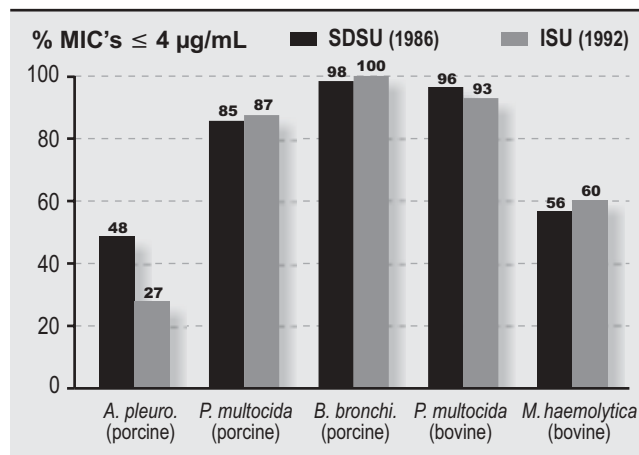


FIGURE 6: Comparison of sensitivity of various porcine and bovine pathogens to Aureomycin; ISU study with 4 laboratories vs earlier SDSU study.



Aureomycin most commonly used tetracycline

The MIC breakpoint of 4 µg/mL for the tetracyclines is taken from the human medical literature, and has little basis for use in veterinary medicine. Furthermore, Aureomycin is the most commonly used tetracycline antimicrobial in animal production. It makes sense for Aureomycin, rather than tetracycline, to be used as the standard for in vitro sensitivity testing of tetracyclines in veterinary diagnostic laboratory tests.

Variability of in vitro laboratory results

In the ISU study, MIC values in tests run by four different diagnostic laboratories were not always repeatable within each laboratory, even though overall they were in close agreement between laboratories. In vitro laboratory results may differ depending on culture medium, reagents, instruments, technician and interpretation.

Numerous factors important in selection of antimicrobial

- Animals' age, phase of production cycle (e.g., growing pig or gestating-lactating sow), genetic makeup, physiologic condition, nutritional status, and feed and water consumption.
- Nature of disease — acute or chronic, target tissues and individual characteristics of pathogen.
- Immunologic status of animals, including severity of stress which can induce immunosuppression, affecting antimicrobial efficacy.

- Characteristics of antimicrobial in vivo — spectrum and degree of activity, absorption and excretion rates, blood and target tissue (e.g., lung) levels, and sensitivity of pathogen, and cost-effectiveness.
- Veterinarian's knowledge, skill and experience.

All tetracyclines not equally active

According to the ISU four-laboratory study, sensitivity of pathogens to tetracycline, Aureomycin and oxytetracycline were not always the same. Based on the results, sensitivity to tetracycline will more likely mirror sensitivity to oxytetracycline, and sensitivity to Aureomycin may be missed. Also, both the ISU four-laboratory and SDSU studies show that a greater percentage of the pathogens tested were more sensitive to Aureomycin than to oxytetracycline.

Sub-MIC levels in target tissues indicate degree of activity

While MIC's are in vitro estimates of sensitivity or resistance, sub-MIC levels of antimicrobials in target tissues have been associated with effective in vivo disease control.^{5,6} Research results showed that Aureomycin and sulfamethazine administered in swine feed would have resulted in lung levels 13.7 and 10 times below the in vitro MIC of the *Salmonella choleraesuis* isolate used in the disease challenge model. Yet morbidity and mortality in the challenged, medicated group were significantly reduced, with resultant performance improvements.

Effects of various antimicrobials at sub-MIC levels on pathogenic bacteria have been demonstrated, including reduced multiplication rates, changes in morphology (form) and structure, and increased susceptibility to phagocytosis (destruction by white blood cells).^{5,7} In addition, these organisms have shown altered protein synthesis, which can reduce toxin production and decrease the ability to colonize in epithelial cells.

In short, if an in vitro laboratory test indicates that an isolate is resistant to Aureomycin, it means that the MIC of that isolate exceeded the arbitrary breakpoint of 4 µg/mL, which is associated with sensitivity to tetracyclines. However, Aureomycin may still be effective against that isolate in vivo due to its broad spectrum, superior absorption and tissue distribution, and high degree of antimicrobial activity.

Sub-MIC target tissue level data, referred to earlier, reflect the high degree of antimicrobial activity of Aureomycin *in vivo*. Additional studies have shown that Aureomycin achieved higher, long-lasting blood and lung tissue levels than oxytetracycline after oral administration in pigs.^{8,9} These results indicate that Aureomycin can provide a greater degree of antimicrobial activity than oxytetracycline.

LITERATURE CITED

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