



PHARMACOKINETIC / PHARMACODYNAMIC RELATIONSHIPS OF A COMBINATION OF AMOXICILLIN AND CLAVULANIC ACID AGAINST *STREPTOCOCCUS SUIS*, *PASTEURELLA MULTOCIDA* AND *ACTINOBACILLUS PLEUROPNEUMONIAE*

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Introduction:

Recently, a combination water soluble product containing amoxicillin (AMX) and the beta-lactamase inhibitor, clavulanic acid (CA) (Strenzen® – Elanco Animal Health Inc.) was approved in the European Union (EU) for the treatment of respiratory infections in pigs caused by *Streptococcus suis* (Ss), *Pasteurella multocida* (Pm) and *Actinobacillus pleuropneumoniae* (App). The purpose of this paper was to compare the pharmacokinetics (PK) of AMX with the pharmacodynamics (PD) of AMX and CA in combination against various respiratory pathogens and the clinical results in an artificial infection study.

Materials & methods:

Pharmacokinetic study (1) - The product was administered to give 10mg of AMX/kg bodyweight (bwt) and 2.5mg CA/kg bwt twice daily, via the drinking water for 5 days to two groups of 4 male and 4 female pigs of about 15 weeks of age. Blood samples were taken on the first and fifth day at 3 hourly intervals over each day. The plasma samples were assayed using LC-MS for CA and LC-MS/MS for AMX.

Pharmacodynamic studies (2) – the minimum inhibitory concentrations (MICs) of AMX/CA against 182 EU isolates of Ss, 230 isolates of Pm and 220 isolates of App, using the CLSI broth microdilution methods (6), were recorded.

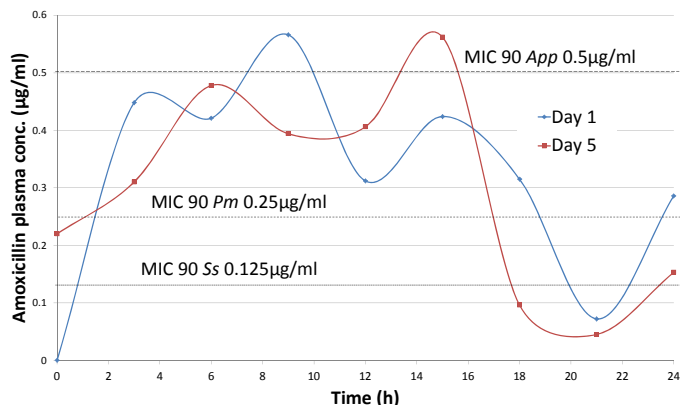
PK/PD relationships – Time greater than the MIC 50 and MIC 90 (T >MIC) was used for comparison (3).

Artificial challenge study (4) – Groups of 12 pigs were infected intranasally with an App isolate with a MIC of 0.25µg/ml at about 20kg bodyweight (bwt). One group was left untreated as controls and the other group was treated by oral gavage at a combined dose of 12.5mg/kg bwt twice daily, two hours after infection when approximately 50% of the pigs showed increases in body temperature. Treatment lasted for 5 consecutive days.

Results:

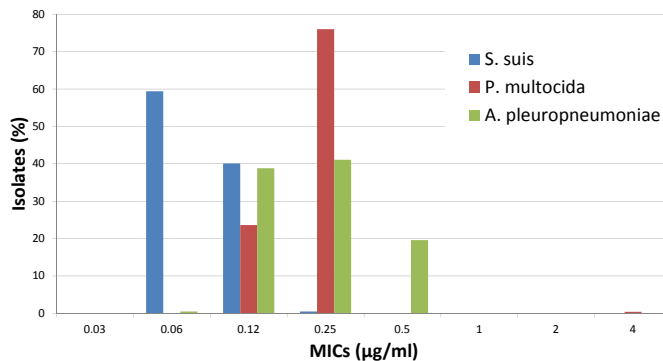
Pharmacokinetics – The mean Cmax for AMX was 0.83 and 1.06µg/ml for day 1 and 5, respectively; the Tmax was 9.8 and 9.0h respectively and the AUC 24h was 8.09 and 7.43µg.h/ml (see Figure 1).

Figure 1. Plasma PK of amoxicillin on day 1 & 5 in comparison with the MIC 90 for the systemic and respiratory bacteria (1 & 2)



Pharmacodynamics – the MIC 50, MIC 90 and MIC range for AMX/CA against Ss was ≤ 0.06, ≤ 0.125 and 0.06-0.25µg/ml, respectively; against Pm 0.25, 0.25 and 0.12 – 4.0µg/ml and against App 0.25, 0.5 and 0.06-0.5µg/ml, respectively. No resistance was reported in all the isolates tested (2) but one isolate of Pm showed reduced susceptibility to AMX/CA (see Figure 2).

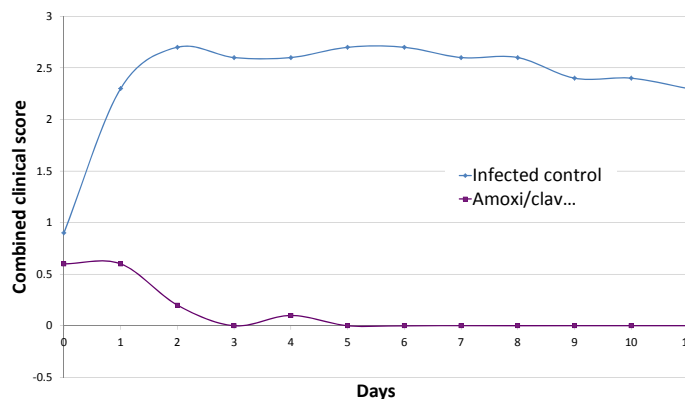
Figure 2. Susceptibility patterns AMX/CA against Ss, Pm and App (2)



PK/PD relationships – The T >MIC for Ss was 100% and 83%, respectively; for Pm was 63% and 63% and for App was 63% and 8%, respectively for the MIC 50 and MIC 90 figure.

Artificial challenge study – 69% of the untreated infected controls died within the first 2 days of challenge, whereas none of the AMX+CA treated pigs died. Clinical scores were significantly reduced (p = ≤0.001) from the first day of treatment (see Figure 3).

Figure 3. Artificial challenge study using App isolate MIC 0.25µg/ml (4)



Conclusions:

From these results, the combination of AMX+CA should have an excellent therapeutic effect against Ss and Pm and up to the MIC 50 of App (81% of the isolates) as T >MIC of 40% is considered the required minimum effective level (3). This was confirmed in the artificial challenge study using an App isolate with an MIC of 0.25µg/ml (4). AMX is very rapidly absorbed and excreted (5) when given by gavage at 20mg/kg bwt, the Cmax was 3.14µg/ml and Tmax was 1.19h. This is in marked contrast to the findings in this PK study (1) when given in the drinking water. The mean Cmax was comparatively low at 1.0µg/ml and the Tmax was exceptionally long at 9 h based on a mean of 8 figures, or the population average. The sampling at 3h intervals per day could easily have missed the individual peaks and troughs seen with gavage dosing or individual water intake and could underestimate the T >MIC for the MIC 90 of App.

References:

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