

USE OF FLUOROQUINOLONES

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COMMENTS of the
ASSOCIATION OF VETERINARY
CONSULTANTS

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EMEA Int. Parties Meeting



Association des Vétérinaires Consultants
Association of Veterinary Consultants

AVC

- ◆ VETERINARIANS
- ◆ CONSULTANTS
 - Veterinary Medicinal Products
 - ◆ Quality, Safety and Efficacy
 - Feed / Feed Additives
 - Food
- ◆ 44 EXPERTS (most from Europe)
- ◆ ETHICAL and SCIENTIFIC CODE



AVC RESPONSE

- ◆ AVC agrees with the concept that antimicrobials should be used wisely, within a rational programme, and that it is preferable and important to reserve critical antimicrobials for those conditions where their use can be justified on the grounds that only they are likely to have a positive clinical or animal welfare impact
- ◆ Quinolones and fluoroquinolones are not comparable or equal in terms of their usage in the EU or their breakpoints in different species, conditions and body compartments. Therefore, we believe it is misleading and potentially damaging to use quinolones alone as the benchmarks for decisions on fluoroquinolones, except possibly for campylobacter.
- ◆ The entire topic of breakpoints is one that deserves separate discussion.

Importance of Fluoroquinolones in food-producing animals

- ◆ They may be the only effective class of drugs
 - Colisepticaemia in turkeys
 - Colisepticaemia in broilers
 - Colisepticaemia in newborn calves
 - Colisepticaemia in piglets
 - *A. pleuropneumoniae* in pigs
 - *E. coli* mastitis
- ◆ Tissue distribution and penetration unique
- ◆ Essential for treatment of animals with life-threatening diseases

Use of Fluoroquinolones

- ◆ The influence of veterinary use on antimicrobial resistance in humans is likely to be very low
- ◆ AVC believes that farm animal use of fluoroquinolones is probably a minor relevant source of resistance in terms of impact on humans

Use of Fluoroquinolones

- ◆ Although relevant data is presented, more data is needed from individual countries and set in relation to MA for Fluoroquinolones present
- ◆ **Patent situation may be used as guide:**
 - Markets with extensive use since 15 years
 - Markets with limited use

Amount of use of FQ in non-regulated markets

- ◆ Dependent on availability of „generic/cheap“ products:
 - e.g. various Eastern European MS
 - e.g. Spain/Portugal
 - ◆ Generics available for 15 years
- ◆ Prices per unit very low (10 % of reference)
 - ◆ High use of FQs in poultry and swine
 - ◆ Broad use as preventional treatment
- ◆ High rates of resistance

Use of FQ in regulated markets

◆ E.g. Germany, UK, DK

- ➡ – FQ are **high priced** products
 - Well controlled, prescription only since launch
 - Relatively low use, mainly therapeutic/treatment
- ➡ – **Low rates of resistance**

Danmap 2004

MIC ₉₀ % sensitive	Chicken µg/ml	Cattle µg/ml	Swine µg/ml
E. Coli	0,12 88 %	0,03 100 %	0,03 96,6 %
Salm. spp	0,06 100 %	0,06 100 %	0,06* 98,1 %

Breakpoint used: 0,03 µg/ml, Including broilers and layers

*Highest MIC measured: 0,5 µg/ml

Germany

E. Coli	Chicken µg/ml	Dairy M µg/ml	Cattle µg/ml	Swine µg/ml
MIC ₉₀	0,016 #	0,06 *	0,016 #	0,016 #
% sensitive	96 %	98 %	100 %	100 %
MIC ₉₀	0,5 *	0,06 * *	16 *	0,06-0,5 *
% sensitive	~ 98 %	N=187	72,1 %	92-98 %

*Wallmann, Kroker: 3rd Conf Vet Antimicrobials, Orlando, USA, 2006;

* *Krabisch und Gangl, TU 2002;

#De Jong et al., ICAAC 2006 (Abattoirs samples)

Portugal / Spain

E. Coli	Chicken µg/ml	Calves µg/ml	Swine µg/ml
MIC ₉₀	32*	64*	16*
% sensitive	50,8 %	56,9 %	76,9 %
Spain #	8 76,5 %		0,25 98 %

Various Fluoroquinolones marketed including Generics

*Baptista et al. (2006): 11 EAVPT, Torino, 2006;
Breakpoint used: 4µg/ml

#De Jong et al., ICAAC 2006 (Abattoirs samples)

Hungary

- Fluoroquinolones since 1989, first generic licensed 1991
- ~ 25 % of antibiotics used in animal health are now **Fluoroquinolones**
- Prices reduced from 75 to 5, same time use up by 750%, 100 being Baytril
- No public data on resistance

Consequence?

Increase the price?

Can it be that simple?



Off Label Use/Illegal Use

- ◆ Care needs to be taken by over-regulating the market!

E.g. Illegal use of nitrofurans in food animals: contribution to human salmonellosis* (Portugal): 65 % of Samonella isolates from several sources (most human and poultry) with decreased susceptibility, most *S. enteritidis*

*Antunes et al. (2006) Clinical Microbiology and Infection

C. jejuni and C. coli

- ◆ AVC is critical to the *Delsol et al* (2004) study on *Campylobacter coli* described in the document, in that it was monitored for only 5 weeks after treatment and not followed through to slaughter
- ◆ AVC stresses that care needs to be taken in relating experimental studies such as Delsol et al (2004) to practical situations
- ◆ AVC disagrees with the statement that '*In the developed countries most human infections with Campylobacter and Salmonella are food borne*'
- ◆ Propose to consider *C. jejuni* and *C. coli* separately

Selection for Resistance

- ◆ AVC completely disagrees with the statement referring to '**Their potential of relatively rapid selection of resistance**' (problems only in non-regulated markets)
- ◆ In fact there is **low rate for selection**, as found in most slaughter house surveys

Problems

- ◆ No **harmonised approach** in the conditions of use of (fluoro-)quinolones in EU
- ◆ 'Antimicrobial resistance should be addressed internationally, as resistant bacteria can spread via imported food', it should be added: 'and infections can be contracted by foreign travel as highlighted in Danmap 2004; in such foreign-acquired situations, resistance to (fluoro)quinolones is frequently higher'

Problems

- ◆ The multiple MA for generic (fluoro-)quinolones (low cost) caused by low requirements for their registration
- ◆ It is not understandable why the innovator needs to carry the costs of keeping products on the market (no resistance nor environmental data requested by various MS), while the generics may potentiate the problem
- ◆ Action by legislator needed?
- ◆ Is the currently implemented EC/2004/28 the right answer?

Action Points

- ◆ More information on use by species and product would be helpful, especially for the (fluoro-)quinolones.
- ◆ More comparative human use data would also be beneficial

Proposal of AVC

- ◆ Use of (fluoro-)quinolones should be under veterinary **prescription only**, following **veterinary diagnosis**, and the products should not be available as bulk or (foreign-sourced) generics for routine on-farm use

But: After implementation of 2001/82 as amended by 2004/28, now discussion on exemption criteria for non-prescription as discussed in Brussels this week

E.g.: no vet visit, but a consultation only is necessary in some member states (weakens the vets)

Proposal of AVC

- ◆ Implementation of “prudent use guidelines” and better **penetrating** them to vets and farmers throughout the EU and globally
- ◆ Make sure that dosage is based on scientific knowledge and proof
- ◆ Limit use to *treatment* claim of animals

Different ways to approach the problem

- Reduce the occurrence of pathogens (hygiene)
- Implement strategies to reduce selection for resistance (correct dose, defined use etc.)

But: monitor via agreed test systems

Proposal

- ◆ Appropriate EU agencies and bodies should collaborate on studies to define more carefully the most appropriate **test systems, sampling strategies and breakpoints** to use for resistance determination in organisms isolated from livestock and companion animals that may be of public health significance
- ◆ Currently there are two interesting programs in place:
 - ◆ CEESA (European industry)
 - ◆ GermVet (authorities and industry in Germany)
 - Harmonising lab test systems
 - Collecting properly defined pathogens
- ◆ Useful to have that on a EU level supported by Framework 7?

THANK YOU!

Association of Veterinary Consultants

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