INVESTIGATION OF EFFECTIVENESS FOR CERTAIN TREATMENT IS A COMPLEX QUESTION – AN EXAMPLE WITH ENROFLOXACIN

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ABSTRACT

Effectiveness could be inspected by conduction of clinical trials, by reviewing in vitro susceptibility of bacteria and by performing meta-analysis or systematic review. Through meta-analysis, the researchers are able to integrate results and findings from different studies. This analytical method is of particular importance in the assessment of therapeutic efficacy when individual studies do not provide an overview over all studies on a topic. As their samples are too small, individual studies cannot provide a quantitative evaluation of the effect of treatment, nor can they test null hypothesis. Prior to meta-analysis, the traditional method was a narrative discourse on previous findings, which, however, could be misleading and subjective. Systematic reviews are exact summaries of the best evidences related to exactly specified clinical dilemmas. These reviews support the synthesis of best evidence for treatment or establishment of best medical practice.

We reviewed and evaluated the efficacy of the treatment of various infections with enrofloxacin for individual animal species. A special meta-analysis was carried out and graphically presented for the treatment of each disease (forrest plots). In most cases, we chose the odds ratio to present the effect size. By following a systematic way of reviewing, we ensured repeatability of our meta-analyses in case this would be done by other investigators. In heterogeneous meta-analyses, we calculated the total size of the effect according to a random calculation model for total effect size. Additionally the homogeneity of studies was graphically evaluated with funnel plots. In addition to clinical studies, we reviewed and combined data on bacterial in vitro susceptibility to enrofloxacin. These results were also considered in the final opinion about individual meta-analysis of efficacy of enrofloxacin. Individual studies were collected by reviewing databases available on CD ROMs or Online. We also reviewed references in different published studies and data bases on the internet. We obtained 919 articles for the studies for the first selection, for a closer review, we chose 237 healthcare studies: 110 in pigs, 67 in ruminants and 60 in poultry. In 19 meta-analyses, we reviewed and evaluated efficacy of enrofloxacin usage and bacterial in vitro susceptibility to enrofloxacin, while in 7 cases we also calculated the individual effect size (odds ratio) for a specific parameter.

The results demonstrate efficacy of enrofloxacin treatment of respiratory infections in all above mentioned domestic animals (P<0.01). Enrofloxacin is very effective in treatment of coli and salmonella infections in pigs and poultry (P<0.001) and effective in treatment of mycoplasma infections, with additional studies of colibacillosis, salmonellosis and mycoplasma infections being necessary in cattle. Meta-analysis in poultry showed efficacy of enrofloxacin treatment in infectious coryza, staphylococcosis, pasteurellosis in turkeys, and R. anatipestifer infection in ducks (P<0.001). In pigs, enrofloxacin treatment was significantly more effective in trial group than in control group for MMA syndrome, urinary tract infections and streptococcal infections (P<0.05). For Glässer's disease, the difference, in comparison to control group, was not significant (P=0.25), however, the pathogen (H. parasuis, n = 124) was 100% susceptible to enrofloxacin. In greasy pig disease, there is a high in vitro susceptibility of S. hyicus to enrofloxacin (98.3%, n = 744). Complex questions about cattle mastitis call for additional enrofloxacin studies, although in vitro results of mastitis pathogen susceptibility are good. Likewise, additional endometritis treatment studies in cattle are necessary, since the difference between trial and control group was not statistically significant (P=0.9), although the results were in favour of enrofloxacin treatment.

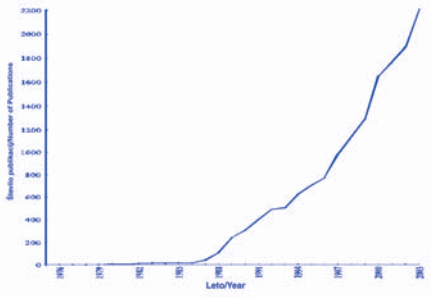
We reviewed the available studies and could assess sufficiently and insufficiently analysed parameters. Some studies revealed statistically significant results and some not. It occurred in some cases that studies that lacked significant results, due their weight, had a greater impact on the analysis than those with significant results. It was this part of our research that revealed one of the greatest difference between meta-analysis and the narrative comparison of the literature. Our findings can be considered useful for investigators, doctors of veterinary medicine in practice and for the breeders, as well as for the manufacturers of veterinary medicines and governmental authorities. Our work offers an overall survey of the problem and provides guidelines for further research of the topic.

Meta-analysis is the process of using statistical methods to review and combine the results of different, independent studies.

Combining
Detecting and investigating of differences
New cognitions (examples lidocaine, tamoxifen)

Systematic reviews are exact summaries of the best evidences related to exactly specified clinical dilemmas

Number of publications that used meta-analysis 1975 - 2003 (MEDLINE)



PROCEDURE OF META-ANALYSIS

1. Identify the problem, sources and inclusion criteria
2. Positioning of trials
3. Compilation of results and comparison with trial characteristics (analysis and explanation of results) and
4. Reporting results

WORKING GROUP
- Researchers (research field, acquainted with the problem)
- IT expert, bibliographer
- Biostatistics expert

Differences between Narrative Reviews and Meta-analysis (Systematic Reviews)

Feature	Narrative Review	Meta-analysis (Systematic Review)
Question	Often broad in scope	Often a focused question
Sources and search	Not usually specified, potentially biased	Comprehensive sources and explicit search strategy
Selection	Not usually specified, potentially biased	Criterion-based selection, uniformly applied
Appraisal	Variable	Rigorous critical appraisal
Synthesis	Often a qualitative summary	Quantitative summary
Inferences	Sometimes evidence-based	Usually evidence-based

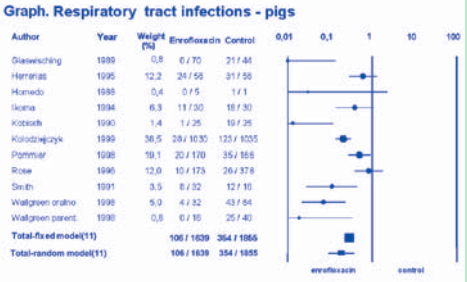
Meta-Analysis and Systematic Review for enrofloxacin

- **19 Meta-Analyses**
- **Systematic Review**
- Pigs (110 studies), Poultry (60 studies) Cattle (67 studies):
- Introduction
- Comparison with other drugs
- Statistical analysis
- **Acumulation of knowledge (literature data: for example: ecology, IQ, AIUC etc.)**

RESULTS

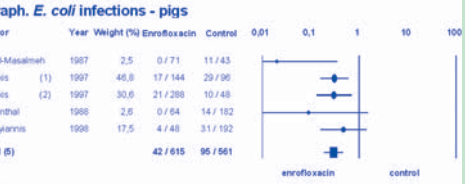
- **Graphical presentation: Mean with 95% confidence intervals (authors, year, odds ratios, total effect size)**
- **Homogeneity fixed, random model**
- **Weights: studies (●) , total (■)**
- **Funnel plots (heterogeneity, dispersion of data) and sensitivity analysis**
- ***In vitro* susceptibility to enrofloxacin**
- **19 meta-analyses (+ 7 estimations of odds ratios)**

Graph. Respiratory tract infections - pigs



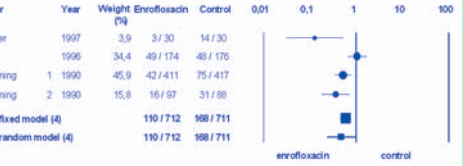
Q = 43,1, df (Q) = 10, P = 0,003

Graph. *E. coli* infections - pigs



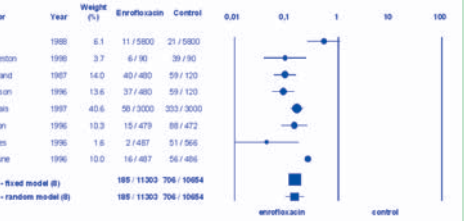
Q = 4,83, df (Q) = 4, P = 0,31

Graph. MMA Syndrome



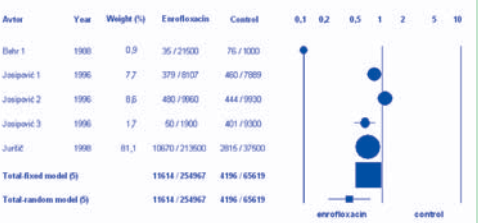
Q = 12,68; df (Q) = 3, P = 0,0054

Graph. *E.coli* infections in poultry (broilers)



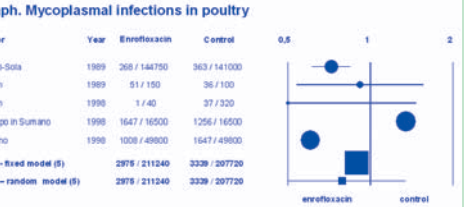
Q = 27,50 df (Q) = 7; P = 0,003

Graph. Respiratory infections in poultry



Q = 347,8; df (Q) = 4; P < 0,001

Graph. Mycoplasmal infections in poultry

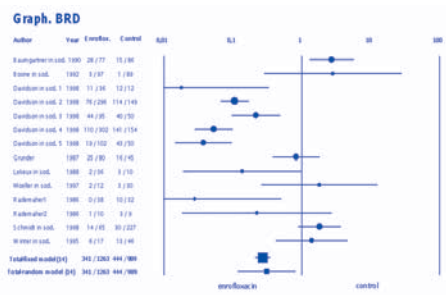


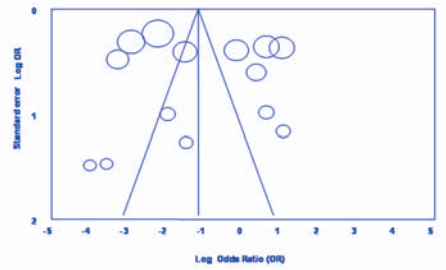
Q = 212,2; (Q) = 4; P < 0,001

Graph. Pasteurelosis (Turkeys)

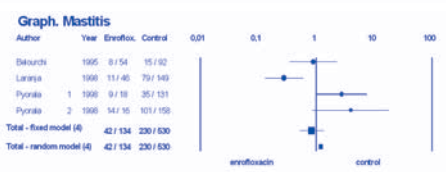
Q = 25,62; sp = df (Q) = 3; P < 0,001

Graph. BRD





Graph. Mastitis



Q = 15,4; sp = df (Q) = 3; P < 0,015

In Vitro susceptibility of mastitis pathogens to enrofloxacin

Bacteria	% resistant strains (resistant/all)
S. aureus	6,9 % (73/1059)
Streptococcus sp.	28,3 % (127/448)
Staphylococcus sp.	2,8 % (1/351)
E. coli	1,8 % (3/1695)
Coagulasa negative *Staphylococcus*	0,2 % (2/883)
S. agalactiae, S.dysgalactiae, S. uberis	10,5 % (12/114)
Nocardia asteroides	0,0 % (0/371)
Actinomyces pyogenes	0,0 % (0/20)
Corynebacterium bovis	0,0 % (0/20)

CONCLUSIONS

Investigation of effectiveness for certain treatment is a complex question – an example with enrofloxacin

1. Meta-analysis revealed that enrofloxacin is undoubtedly effective in the treatment of respiratory infections in pigs, poultry and cattle, in the treatment of *E. coli* infections, salmonellosis and mycoplasmosis in pigs and poultry, in MMA syndrome, streptococcal and urinary tract infections in pigs, in pasteurellosis in turkeys, infectious coryza, staphylococcosis in poultry, as well as in *R. anatipestifer* infections in ducks; insignificant advantage of enrofloxacin over the control drug was observed in the treatment of Glässer's disease in pigs and of endometritis in cattle, and, in mycoplasmal pneumonia in goats; whereas, to confirm high efficacy of enrofloxacin in *E. coli* infections, salmonellosis and mycoplasmosis in cattle, credible and accurate clinical trials need to be performed, which is particularly important in view of numerous contradictions associated with the treatment of mastitis with enrofloxacin.

2. The majority of tasks necessary for the investigator during the process of meta-analysis were successfully performed: descriptive survey, guidelines for further research, diagnostic survey and transfer of our findings into practice. We reviewed the available studies and could assess sufficiently and insufficiently analysed parameters. Some studies revealed statistically significant results and some not. It occurred in some cases that studies that lacked significant results, due their weight, had a greater impact on the analysis than those with significant results. It was this part of our research that revealed one of the greatest difference between meta-analysis and the narrative comparison of the literature. Additionally the homogeneity of studies was graphically evaluated with funnel plots.

3. Our findings can be considered useful for investigators, doctors of veterinary medicine in practice and for the breeders, as well as for the manufacturers of veterinary medicines and governmental authorities. Our work has a great economic impact too, since it offers an overall survey of the problem and provides guidelines for further research of the topic.