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Original Research Paper

A META-ANALYSIS AND SYSTEMATIC REVIEW OF THE EFFICACY OF ENROFLOXACIN – INFECTIONS WITH THE BACTERIUM *ESCHERICHIA COLI* IN PIGS

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Summary: A meta-analysis is a method of surveying and combining the results of several independent clinical trials. Besides quantitative integration, a meta-analysis vastly improves the potential for uncovering and studying any differences in available scientific material and provides a basis for plausible explanations of them. It can also lead to new discoveries and allows the aggregation of knowledge in the field of interest. This analytical method is of particular importance when assessing the efficacy of a therapy when the sample sizes of individual studies are too small to cover all aspects of a particular subject or provide a quantitative evaluation of the treatment's effect as well as test a 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 concise summaries of the best available evidence that address sharply defined questions; they seek to assemble and examine all the high quality evidence on any given subject.

Enrofloxacin is a fluoroquinolone chemotherapeutic that was developed exclusively for use in veterinary medicine. Shortly after administration, low concentrations have a bactericidal effect against most Gram-negative and Gram-positive bacteria and will also act against mycoplasmata.

Twenty-four studies were included in this survey, of which seven were included in a meta-analysis while others were used to build a susceptibility profile of bacteria to enrofloxacin. Eight studies dealt with economic aspects of using enrofloxacin in pig rearing. The total number of animals included in the meta-analysis was 1,296, of which 655 were from the enrofloxacin-treated test groups of the different studies and 641 from their control or alternative treatment groups. In total, there were 19,235 strains of *E. coli* examined for their susceptibility to enrofloxacin.

The results of the meta-analysis are presented graphically. The odds ratio (OR) was used as a measure of the effect size and the homogeneity and/or heterogeneity values (Q) were calculated for the graphs. Additionally, a funnel plot was used to check the dispersion of the studies included in the meta-analysis. The graphs and the calculations ($P = 0.43$) show that the studies were homogeneous.

We also combined the *in vitro* susceptibility of individual microbes to enrofloxacin and evaluated their MIC values. Each study supported the enrofloxacin treatment; although there were three results that were statistically significant ($P < 0.05$), the overall result clearly indicates the high efficacy of enrofloxacin ($P < 0.01$) in reducing mortality caused by *E. coli* infections. Of the 19,235 strains surveyed, there were only 3.4 % that were resistant and the MIC values ranged between 0.015 and 0.25 µg/ml. The studies that dealt with the economic aspects of using enrofloxacin to combat *E. coli* infections, showed that it also has important additional benefits in pig rearing, especially in regards to daily weight gain and feed conversion. Moreover, enrofloxacin reduced the level of haemolytic *E. coli* excretions and sick animals recovered faster than those in the control or alternative treatment groups did. Our results have confirmed the high efficacy of enrofloxacin usage in *E. coli* infections, which makes it economically and professionally justifiable for treating coli infections in pigs.

Key words: enrofloxacin; *E. coli;* meta-analysis; susceptibility; pigs

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Introduction

A meta-analysis is a method of surveying and combining results of several independent clinical trials. The term meta-analysis was first used by Glass in 1976, who, with his associate Mary Lee Smith, statistically compiled the results of 375 studies dealing with the efficacy of psychotherapy.

There are many definitions of the term meta-analysis. The most frequently used definition is the one by Huque: meta-analysis refers to a statistical analysis that combines or integrates the results of several independent clinical trials considered by the analyst to be combinable (1). Besides quantitative integration, a meta-analysis vastly improves the potential for uncovering and studying any differences in the available scientific material and provides a basis for plausible explanations of them. It can also lead to new discoveries.

A brief summary of the procedures involved in a meta-analysis would comprise the following logical steps:

1. the definition of the problem and the inclusion criteria for the studies;
2. positioning, classifying and coding the characteristics of individual studies and the quantitative measurement of their characteristics (scale);
3. the integration of the results and a comparison with the characteristics of the studies (analysis and explication of results); and
4. the reporting of the results. (2)

Systematic reviews are concise summaries of the best available evidence that address sharply defined questions; they seek to assemble and examine all the high quality evidence on any given subject. This includes a comprehensive search of all potentially relevant articles and the use of explicit, reproducible criteria in the selection of articles for review. When the results of primary studies are summarized but not statistically combined, the review may be called a qualitative systematic review. A quantitative systematic review, or meta-analysis, is a systematic review that uses statistical methods to combine the results of two or more studies (3).

Investigating the efficacy of certain drugs can be done in several ways: by *in vitro* susceptibility profiling of certain bacteria, by clinical trials or by using meta-analyses or systematic reviews.

Immediately after farrowing, colibacillosis diseases threaten the lives of both the farrowing sow (MMA syndrome) and the newborn piglets. *Escherichia* are considered to be part of the normal intestinal bacterial flora. Pathogenic subspecies of *Escherichia* adhere to intestinal mucous membranes with special organelles, adhesins, which they differ from. *Escherichia* subspecies produce at least one exotoxin, e.g. the one that causes diarrhoea in suckling piglets and in weaners. Other neurotoxin- and/or verotoxin-producing subspecies cause oedematous diseases in pigs. Bacteria are not usually invasive; therefore, they are effective substances that act specifically in the intestines. This contrasts with the treatment of *E. coli* infections in poultry where infections are of a systemic nature (4, 5).

Enrofloxacin is a fluoroquinolone chemotherapeutic that was developed exclusively for use in veterinary medicine. Shortly after its administration, extremely low concentrations have a bactericidal effect against most Gram-negative and Gram-positive bacteria and will also act against mycoplasmata. It acts against both bacteria in the multiplication phase and dormant microorganisms. It is effective in the presence of oxygen and, owing to this phenomenon, it does not damage beneficial anaerobic intestinal microflora.

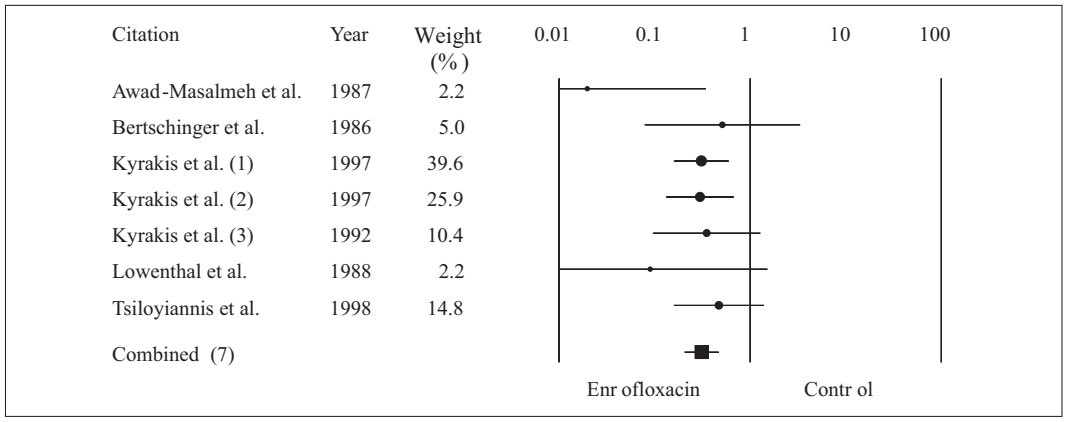
The efficacy of fluoroquinolones is related to both the maximum concentration and the time above their MIC value. *In vitro* pharmacokinetic models have shown that maximum concentrations of active substances, 8 times in excess of their MIC, have been able to reduce the number of bacteria by up to 99 % and inhibit their growth for up to 24 hours. The intensity of exposure may be quantified as the ratio between the area under the time-concentration curve (AUC) and the minimum inhibitory concentrations for the causative pathogens (MIC); a short term for this ratio is AIUC ? area under the inhibitory plasma concentration curve. For example, if in an enrofloxacin therapy the AIUC is higher than 125, the probability of a clinical and microbiological cure is above 80 %, otherwise it is only 42 % or 26 % in respect of a microbiological cure. Resistance to fluoroquinolones is also reduced to a minimum if these parameters are taken into consideration – C_{max}/MIC ratio is at least 8-10 and AUC/MIC at least 100-125 (6).

Table 1: Short survey of the studies included in the meta-analysis and the systematic review

Author, year of publication, number of animals in the study, (reference)	Meta-analysis and systematic review parameters Comparative control group
1. Lein et al., 1996; n = 86 (7)	- efficacy of enrofloxacin on the excretion of haemolytic *E. coli* - economic parameters (average daily gain, conversion, etc.) - negative control group
2. Lowenthal et al., 1988; n = 246 (8)	- clinical (intestinal bacterial infections) - mortality - gentamicin (1.0 mg/kg body weight) - trimethoprim (6.37 mg/kg body weight) and sulphadiazine (31.85 mg/kg body weight) - negative control group
3. Tsiloyiannis et al., 1998; n = 240 (9)	- mortality - economic parameters (average daily gain, conversion, feed intake) - negative control group - citric acid (1.5 %) and lactic acid (1.6 %) in feed
4. Kyrakis et al., 1997; n = 240 (10)	- mortality - economic parameters (average daily gain, conversion, feed intake) - negative control group
5. Kyrakis et al., 1997; n = 336 (11)	- mortality, clinical signs (diarrhoea) - economic parameters (average daily gain, conversion, feed intake) - negative control group
6. Kyrakis et al., 1992; n = 120 (12)	- mortality, clinical signs (diarrhoea) - economic parameters (average daily gain) - negative control group - apramycin (100 ppm)
7. Jae-Gil et al., 1992; n = 36 (13)	- economic parameters (average daily gain) - excretion of haemolytic *E. coli* - negative control group
8. Awald-Masalmeh and Willinger, 1987; n = 114 (14)	- mortality, clinical signs (diarrhoea) - economic parameters (average daily gain) - *in vitro* susceptibility testing of *E. coli* to enrofloxacin (% susceptibility) - negative control group
9. Bertschinger and Murdzinski, 1986; n = 48 (15)	- mortality, clinical signs (diarrhoea) - economic parameters (average daily gain) - ampicillin (40 mg/kg body weight) - control group (placebo)
10. Kołodziejczyk and Arh, 1999 (16)	- *in vitro* susceptibility testing of *E. coli* (% susceptibility)
11. Melin et al., 1996 (17)	- *in vitro* susceptibility testing of *E. coli* (MIC values and % susceptibility)
12. Mateu and Martín, 2000 (18)	- *in vitro* susceptibility testing of *E. coli* (% susceptibility 1997-1999)
13. Ala-Risku et al., 1997 (19)	- *in vitro* susceptibility testing of *E. coli* (% susceptibility)
14. Bole-Hribovšek and Zdovc, 2002 (20)	- *in vitro* susceptibility testing of *E. coli* (% susceptibility)
15. Bada et al., 1995 (21)	- *in vitro* susceptibility testing of *E. coli* (% susceptibility)
16. Habrun et al., 1997 (22)	- *in vitro* susceptibility testing of *E. coli* (% susceptibility)
17. Scheer et al., 1996 (23)	- *in vitro* susceptibility testing of *E. coli* (% susceptibility)
18. Salmon et al., 1995 (24)	- *in vitro* susceptibility testing of *E. coli* (MIC values)
19. Aarestrup et al., 2000 (25)	- *in vitro* susceptibility testing of *E. coli* (% susceptibility 1993-1998)
20. Trolldenier, 1996 (26)	- *in vitro* susceptibility testing of *E. coli* (% susceptibility 1991-1994)
21. Deprez et al., 1986 (27)	- *in vitro* efficacy of enrofloxacin on the excretion of haemolytic *E. coli*
22. Awald-Masalmeh et al., 1992 (28)	- *in vitro* susceptibility testing of *E. coli* (% susceptibility)
23. Belloc et al., 2002 (29)	- *in vitro* susceptibility testing of *E. coli* (% susceptibility)
24. Semjen and Wright, 1991 (30)	- *in vitro* susceptibility testing of *E. coli* (resistance development after multiple passages)

Material and methods

Twenty-four studies were included in this survey, of which seven were included in the meta-analysis while others were used to build a susceptibility profile of bacteria to enrofloxacin. All the susceptibility studies were comparative (e.g. comparisons between different antimicrobials), except for the two conducted by Aarestrup et al. and Semjen and Wright. Eight studies dealt with economic aspects of using enrofloxacin in pig rearing. The total number of animals included in the meta-analysis was 1296, of which 655 were from the enrofloxacin-treated test groups of the differ-



Graph 1: Meta-analysis of efficacy of enrofloxacin in treating *E. coli* infections in pigs (mortality)
Homogeneity testing:A Q = 5.17; df = 6; P = 0.52
(where Q = heterogeneity value (χ^2 distribution); df = degree of freedom; P = probability)

Table 2: *In vitro* susceptibility of *E. coli* to enrofloxacin

MIC range (µg/ml)	Resistant strains (% of 19,235 tested strains)
0.015 – 0.25	3.4

ent studies and 641 from their control or alternative treatment groups. In total, there were 19,235 strains of *E. coli* examined for their susceptibility to enrofloxacin.

Statistical analysis

The Comprehensive Meta-Analysis (Borenstein, 2000) computer programme was used for the statistical analysis.

Results

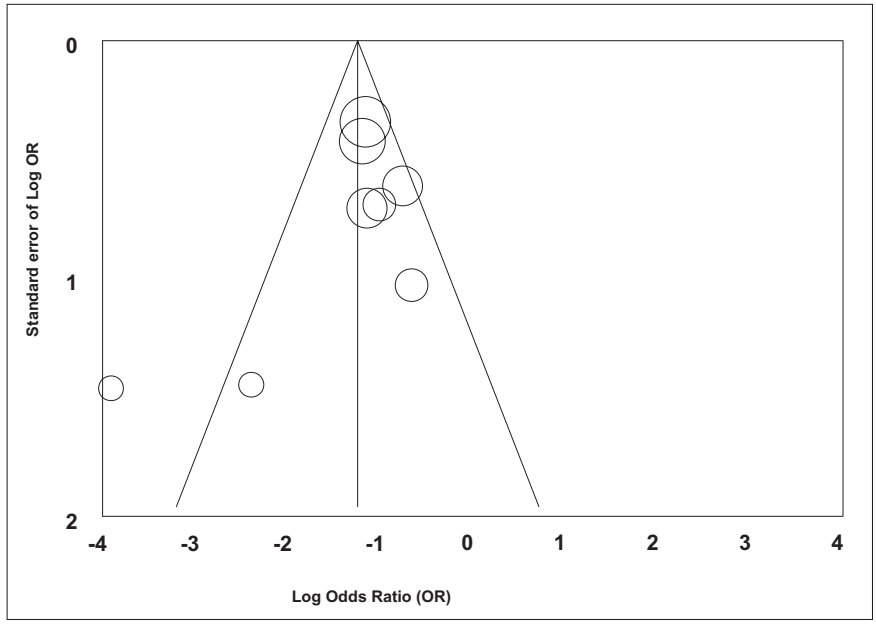
The results of meta-analyses are presented graphically. The graphs show the compiled data of individual studies (by author), the year that the study was conducted or its results published, a numerical comparison between the treatment and control groups and the mean values of effect size with 95 % confidence intervals.

The odds ratio (OR) was used as a measure of the effect size. An OR value of 1.0 means that a certain therapy has no effect, a value below 1.0 indicates that the therapy (in our case the use of enrofloxacin) is better than that of the control or alternate therapy. Values above 1.0 indicate that the control or alternate therapy was more effective. When interpreting the graph, if the mean value and the two lines either side of it, which indicate the confidence interval, do not intersect with the value of 1.0 then we speak about a statistical significance at different levels, e.g. with a 95 per cent confidence interval the P level of statistical significance equals 0.05; in 99 per cent intervals it equals 0.01, etc.

However, where a mean value, with its confidence intervals, intersects the 1.0 value line, we say that it has no statistical significance.

The homogeneity and/or heterogeneity (Q) values were calculated for the graphs. We must always form a null hypothesis that all studies pertain to the same population. The Q value is distributed to the Chi-square probability distribution with a k – 1 degree of freedom (df), where k represents the number of studies processed**.** However, statistically insignificant P values should not be considered as proof of homogeneity. Additional checks on the dispersion of the studies in the graph are obligatory. When we have evidence of heterogeneity, or a supporting calculation, we must check the graph and interpret the dispersion: do the majority of studies indicate that a treatment was effective while others indicate otherwise; does the effectiveness of the treatment vary greatly; or are there any extraordinary deviations. If a heterogeneity of $P < 0.05$ was calculated, then the total effect was always calculated using the random effects method as well.

The total effect size is always conditioned by the weight of individual studies, therefore, in a



Graph 2: Funnel plot showing standard error by effect size

meta-analysis it is referred to as the weighted total value, which, for individual studies, is represented by their mean values and confidence intervals. The weights of the individual studies are shown in the graph as full circles (•), studies with smaller weights have smaller circles and those with larger weights have larger circles. The total effect size is shown as a full square (■). Besides the graphical presentation of the meta-analysis results, a funnel graph was used to show the dispersion of the studies included in the meta-analysis. At first, funnel graphs were only used to monitor publication bias but we now know that they also indicate the heterogeneity of a study and the quality of its methodology. We also combined the *in vitro* susceptibility of individual microbes to enrofloxacin and evaluated their MIC values.

Discussion

Our survey included 24 studies, of which seven were included in a meta-analysis while others were used to build a susceptibility profile of bacteria to enrofloxacin. The studies included in the meta-analysis covered the period between 1986 and 2002.

The included studies were homogeneous, which is confirmed by the funnel graph where the only deviation (slight) was the study by Awald-Masalmeh et al. and this was probably due to its smaller sample size. As is evident from the meta-analysis, enrofloxacin is effective in the treatment of *E. coli* infections in pigs. Each study supported the enrofloxacin treatment; although there were three results that were statistically significant ($P < 0.05$) the overall result clearly indicates the high efficacy of enrofloxacin ($P < 0.01$) in reducing mortality caused by *E. coli* infections through neonatal septicaemia and diarrhoea, piglet scours, post-weaning diarrhoea and oedematous diseases.

Of the 19,235 strains surveyed, there were only 3.4 % that were resistant and the MIC values ranged between 0.015 and 0.25 µg/ml.

The studies that dealt with economically important aspects of using enrofloxacin to combat *E. coli* infections showed that it also has important additional benefits in pig rearing. In the majority of studies, groups that received enrofloxacin had statistically significantly better results than their control groups as well as better feed conversion rates and higher average daily weight gain. Moreover, enrofloxacin reduced the level of of haemolytic *E. coli* excretions and sick animals recovered faster than those in the control or alternative treatment group did.

The resistance of *E. coli* strains to enrofloxacin also is stable; however, to remain so it must be

used judiciously and in compliance with the results of scientific research, correct clinical judgement and dosage.

Our results have confirmed the high efficacy of enrofloxacin usage in the treatment of *E. coli* infections, which makes it economically justifiable and it is thus the right drug of choice in treating coli infections in pigs.

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METAANALIZA IN SISTEMATIČNI PRIKAZ UČINKOVITOSTI UPORABE ENROFLOKSACINA – OKUŽBE Z BAKTERIJO *ESCHERICHIA COLI* PRI PRAŠIČIH

L. Ščuka

Povzetek: Metaanaliza je metoda pregledovanja in kombiniranja rezultatov več neodvisnih kliničnih študij. Poleg kvantitativne integracije predstavlja tudi pomembno izboljšavo pri odkrivanju in preučevanju razlik v razpoložljivi znanstveni materiji in doseganju ali vsaj nudenju najverodostojnejših razlag ter celo pri odkrivanju novih spoznanj. Prispeva tudi h kopičenju znanja na določenem interesnem področju. Ta analitska metoda je še posebej pomembna pri ocenjevanju terapevtske učinkovitosti v primerih, ko posamezne študije ne zagotavljajo pregleda nad celotno obravnavano problematiko, po navadi imajo premajhne vzorce in zato ne morejo dati kvantitativne ocene učinka zdravljenja, in tudi ne preizkusiti ničelne hipoteze. Pred obdobjem metaanalize so pripovedno primerjali rezultate študij, kar pa je bilo lahko zavajajoče in subjektivno.

Sistematični prikazi so zgoščeni povzetki najboljših dostopnih dokazov, ki se nanašajo na jasno določena vprašanja; njihov namen je zbrati in preveriti vse visoko kakovostne dokaze o določenem specifičnem vprašanju.

Enrofloksacin je kemoterapevtik iz skupine fluorokinolonov, ki je bil razvit izključno za uporabo v veterinarski medicini. V zelo majhnih koncentracijah in hitro po dajanju deluje baktericidno na večino po Gramu negativnih in po Gramu pozitivnih bakterij, učinkuje pa tudi mikoplazmocidno.

V prikaz je bilo vključenih 24 študij, sedem od njih je bilo vključenih v samo metaanalizo, v drugih pa so opazovali profil občutljivosti bakterij za enrofloksacin. V osmih študijah so obravnavali ekonomske parametre prašičereje ob uporabi enrofloksacina. Skupno število živali iz različnih študij, vključenih v metaanalizo, je bilo 1296, od teh jih je bilo 655 razvrščenih v testne skupine, ki so prejemale enrofloksacin, ter 641 v kontrolne skupine, ki so prejemale primerjalno terapijo. Vse študije so vključevale skupno 19235 sevov *E. coli*, ki so jih preizkušali glede občutljivosti za enrofloksacin.

Rezultati metaanaliz so prikazani grafično. Kot velikost učinka smo izbrali razmerje obetov (odds ratio), izračunavali pa smo tudi vrednosti za homogenost oz. heterogenost (Q) študij. Z lijakastim grafičnim prikazom smo dodatno preverjali razpršitev študij v grafu. Iz grafov in izračunov ($P = 0.43$) je razvidna homogenost vseh vključenih študij. Pregledali smo tudi *in vitro* občutljivost posameznih mikrobov za enrofloksacin in ocenjevali vrednosti MIK.

Vse študije so govorile v prid zdravljenju z enrofloksacinom; le pri treh izmed njih so bili rezultati statistično pomembni ($P < 0.05$), skupni rezultat pa kaže na visoko učinkovitost enrofloksacina ($P < 0.01$) pri zmanjševanju smrtnosti zaradi okužb z *E. coli*. Skupni delež odpornih sevov ni presegal 3,4 % vseh v prikazu zajetih sevov in vrednost MIK se je gibala med 0,015 in 0,25 µg/ml. Študije, v katerih so raziskovali ekonomsko pomembne parametre rabe enrofloksacina pri okužbah z *E. coli*, so pokazale pomemben ugoden učinek enrofloksacina v prašičereji, še posebej na dnevno pridobivanje teže prašičev in izkoristek hrane. Enrofloksacin zmanjša tudi izločanje hemolitične *E. coli* in bolne živali si opomorejo hitreje kot tiste v kontrolni skupini, ki so vključene v primerjalno zdravljenje.

Naši rezultati potrjujejo, da je raba enrofloksacina pri zdravljenju okužb z *E. coli* zelo učinkovita, ekonomsko koristna in je zato pri okužbah s kolibakterijami pri prašičih uporaba enrofloksacin strokovno upravičena.

Ključne besede: enrofloksacin; *E. coli*; metaanaliza; občutljivost; prašiči