REPORT OF THE SCIENTIFIC COMMITTEE FOR ANIMAL NUTRITION ON THE USE OF LINCOMYCIN AND SPIRAMYCIN IN FEEDINGSTUFFS

Opinion expressed 7 October 1981

TERMS OF REFERENCE

The Scientific Committee for Animal Nutrition is requested to re-assess lincomycin and spiramycin and ascertain whether the distinguishing factors were such as to justify different decisions on their acceptability as additives in feedingstuffs.

BACKGROUND

The Scientific Committee for Animal Nutrition delivered on 8 December 1977 its opinion on the use of macrolides and related products in feedingstuffs (*). It declared itself in favour of the use of spiramycin and reserved its opinion on lincomycin, partly because of the inadequacy of the existing data on bacterial resistance. The additional documentation now available apparently necessitates a review of the conditions laid down by Community directives for the use of these products as additives in feedingstuffs (see table below) and to ensure that such use will not entail any harmful effects on human or animal health.

(*) Commission of the European Communities. Reports of the Scientific Committee for Animal Nutrition. First series (1979). Catalogue No CB-28-79-277.

Additive	Species of animal	Maximum age	Minimum content ppm (mg/kg) of complete feedingstuff	Maximum content ppm (mg/kg) of complete feedingstuff
Lincomycin (*)	Poultry, with the exception of ducks, geese and laying hens	10 weeks	2	10
Spiramycin	Turkeys	26 weeks	5	20
	Other poultry, with the exception of ducks, geese, laying hens, pigeons	16 weeks	5	20
	Pigs, calves, lambs and kids	6 months	5	20 (80)**
	Animal bred for fur	-	5	20
	Piglets *	4 months	5	50
	Calves, lambs and kids *	16 weeks	5	50

* Use authorized by derogation until 30 June 1979
** Milk feeds

OPINION OF THE COMMITTEE

The Committee examined the documentation available on lincomycin and spiramycin and was of the opinion that the data given below should be taken into consideration when replying to the Commission's question.

1. Mode of action and bacterial resistance

Lincomycin is a pyranoside. It differs chemically from erythromycin and oleandomycin, which are macrocyclic C_{14}-lactones and from spiramycin and tylosin, which are macrocyclic C_{16}-lactones.

Lincomycin differs in principle from all known antibiotics but has some similarities to the macrolides in its mode of antibiotic action (30, 32). Like the macrolides it inhibits protein synthesis of the bacterial cell as a result of similarities in the binding sites on the ribosomes. Parallel resistance to macrolides or peptolide antibiotics such as virginiamycin, which has been observed in Gram-positive cocci, is attributed to this binding analogy (31). This resistance does not extend to other antibiotics because their mechanism of action is different (15). Strains of Staphylococcus aureus showing parallel resistance to macrolides and peptolide antibiotics have occurred relatively rarely under practical conditions (13, 14, 35). When lincomycin was first introduced, the levels of resistant strains were of the order of 2-9% for staphylococci and 5-6% for streptococci (groups A and B, and Viridans) depending on the origin of the samples. Similar figures are reported for those bacilli covered by the spectrum of action of lincomycin (32). Investigations performed on man have shown that the present level of resistance to lincomycin does not deviate appreciably from the abovementioned values (8, 17, 18, 34, 36).

In Belgium, where lincomycin has been used for years both as therapeutic agent and feed additive in livestock, 12% of S. aureus strains were found to be resistant to lincomycin (34). In investigations conducted in Belgium and the Federal Republic of Germany on volunteers, no resistance to this antibiotic was shown in strains of S. aureus of the same phage-type as those isolated from hospitalized patients (34). This underlines that the transmission of genes is less common than was assumed hitherto (27, 39).

In investigations carried out in 1977, 1978 and 1979 on stock farms in the Federal Republic of Germany, pigs were fed daily a medicated feedingstuff containing 100 to 150 mg lincomycin in mixture with spectinomycin. This treatment was given either prophylactically or therapeutically against enteritis of infectious origin or mycoplasma pneumonia. Tests on pigs and piglets given this treatment showed that the levels of staphylococci in the nose-mouth cavity and the skin flora, that were resistant to lincomycin, macrolides and virginiamycin did not differ from those observed in the untreated animals (13, 14, 35).

According to other studies, colibacilli (E. coli) of the intestinal flora of the pig showed a slight sensitivity to spectinomycin used in mixture with lincomycin, up to three weeks after administration; the susceptibility of the strains to lincomycin was not affected (8, 38) and the excretion of salmonellae was not favoured (37).

The various aspects of bacterial resistance to spiramycin have been studied extensively. Recent research confirms that spiramycin (a macrocyclic C_{16}-lactone) does not have the properties of inductive resistance seen with erythromycin and oleandomycin (macrocyclic C_{14}-lactones). At the levels used in nutritional studies, spiramycin does not promote parallel resistance to macrolides or substances with a mechanism of action comparable to that of the macrolides and does not exert direct or indirect selection pressure on bacteria carrying R-plasmids (14). Spiramycin has also been shown neither to promote the colonization of the digestive tract of farm animals by salmonellae nor to modify their excretion time.

2. Toxicity and residues

Lincomycin is partially metabolised in the animal organism. Three metabolites with a much lower antibiotic activity than that of lincomycin have been detected but not identified structurally (8).

At normal levels of use of lincomycin in chicken and turkey feedingstuffs (5 to 10 ppm), residues in muscle, adipose tissues, skin, liver and kidney, on completion of treatment, are below the minimum detectable by microbiological methods (0.6 mg/kg). Test in chicken with ^{14}C-labelled molecules showed detectable residues (detection limit by radioactivity: 0.1 mg/kg) only in the liver and offal.

A series of toxicological studies has been carried out with lincomycin in laboratory animals. Most of these tests were of short duration; administration was by subcutaneous, instramuscular or intravenous injection.

The LD_{50} after oral administration is greater than 4g/kg bodyweight in the rat. Oral administration to dogs over three months of lincomycin in aqueous solution at levels of 30, 100 and 300 mg/kg bodyweight/day produced no significant clinical, haematological or histopathological effects and did not affect animal weight or feed conversion rate. Short-lived diarrhoea was observed in some rats receiving orally 600 and 1000 mg/kg bodyweight for 3 months.

In a 26 months oral feeding study using the first filial generation which was exposed in utero, rats were fed doses of 0.375, 0.75 and 1.50 mg/kg bodyweight/day of premix grade lincomycin as well as 1.5 and 100 mg/kg bodyweight/day of USP grade lincomycin. No adverse effects were noted except acute prostatities and seminal vesiculitis in male rats at the highest level of premix and USP grade lincomycin tested. The no-effect level has been estimated at 0.75 mg/kg bodyweight in the rat. From this an ADI of 0.0075 mg/kg bodyweight was determined. The results of a chronic feeding study in mice are not available.

A three-months study in dogs using oral administration revealed a significant but temporary increase in the serum glumatic-pyruvic transaminase level when lincomycin was tested at the dose-levels of 400 and 800 mg/kg bodyweight/day. A six-months study involving doses of 30, 100 and 300 mg/kg bodyweight/day revealed no clinical or haematological adverse effects and no influence on organ weights. A lymphocytic thyroiditis was observed in some animals at the dose of 300 mg/kg bodyweight. A one-year study in beagles used oral dose levels of 0.375, 0.75 and 1.5 mg/kg bodyweight of premix grade lincomycin as well as 1.5 mg and 100 mg/kg bodyweight of USP grade lincomycin. No abnormalities were noted.

A three-generation reproduction study in rats using dose levels of 0.375, 0.75 and 1.5 mg/kg bodyweight of premix grade lincomycin as well as 1.5 mg and 100 mg/kg bodyweight of USP grade lincomycin revealed no adverse effects.

A teratology study in rats using oral dose levels of 10, 30 and 100 mg/kg bodyweight on days 6 through 15 of gestation showed no teratogenic effects but there was increased embryo lethality at the 100 mg/kg bodyweight level.

Oral administration of a single 50 mg dose induces diarrhoea in the rabbit followed by death within four to eight days. The same effect has been observed in the guinea pig after subcutaneous injection of small doses of lincomycin. This was attributed to imbalance in the intestinal microbial flora.

Spiramycin is partially metabolized in the animal organism into neospiramycin and unidentified unstable polar derivatives (9).

At the normal levels of use of spiramycin in chicken and pig feedingstuffs (10-20 ppm), residue levels in the tissue, on completion of treatment, are generally below the minimum that can be determined microbiologically (limit of detection: 0.02 mg/kg). Residues of 0.02 to 0.8 mg/kg and of 0.02 to 0.06 mg/kg have been detected in the liver of chicken immediately after treatment and after a three day withdrawal period respectively. The residues were 0.18 to 0.31 mg/kg in the liver of pigs immediately after treatment and 0.17 to 0.18 mg/kg sixteen hours after administration has been stopped. The maximum residue level in the kidneys of chicken and pigs was 0.2 mg/kg immediately after treatment.

Spiramycin has been investigated in short- and long-term toxicological studies in several animal species. Oral administration to mice of a single dose of 5 mg/kg bodyweight did not cause death. A 2-year study

in rats given diets containing 1500, 3000 and 6000 mg spiramycin/kg feed revealed no adverse clinical, haematological, biochemical or histopathological effects and no carcinogenic activity. The no-effect level has been estimated at 75 mg/kg bodyweight for rats. The acceptable daily intake has been established at 0.75 mg/kg bodyweight.

Daily administration of spiramycin up to 350 mg/kg bodyweight in the feed of pregnant rats produced no teratogenic or embryotowic effects. The development of the foetuses and new-born animals was normal (40).

3. Advantages in animal husbandry

The recommended lincomycin content for poultry feedingstuffs is 2-10 g per tonne (2-10 ppm).

Fattening chickens showed average improvement of 2.7% in weight gain and 2.3% in feed conversion ratio in 31 experimental studies carried out under various stock rearing conditions (different animal strains, feed rations with different energy- and protein contents). These results have been confirmed in practice (21). The addition of lincomycin is said also to improve viability and to reduce morbidity in chickens.

The improvement obtained with spiramycin used at authorized dose levels in various animal species ranged in average from 4 to 7% in weight gain and from 2.5 to 5% in feed conversion ratio according to a number of studies. Experiments in official stations over the past 11 years in chicken and over the past 13 years in pigs have shown continued beneficial effects. It is therefore likely that the use of

spiramycin in nutritional doses favourably affects animal health without directly interfering with pathogenic bacteria; this is borne out by the fact that the product retains its full activity when used in therapeutic doses.

4. Therapeutic indications

Lincomycin is presently used for the treatment of infections due to staphylococci and to streptococci, except enterococci, especially where β-lactam antibiotics cannot be used. In addition infections caused by clostridia, corynebacteria or mycoplasma are likely to respond.

The main factors leading to the gradual restriction of the therapeutic applications of lincomycin in human medicine are as follows :

(a) Reduced absorption of the antibiotic when administered orally. It is therefore necessary to use relatively high doses with the consequent risk of causing an imbalance in the intestinal microbial flora (12, 25, 29).

(b) Lower antibacterial action on anaerobic intestinal bacteria than is shown by other antibiotics and semi-synthetic derivative of lincomycin (1, 4, 16, 22, 26, 28, 33).

(c) Fatal cases of enterocolitis occuring during therapeutic treatment as a result of imbalance in the intestinal microbial flora and possible endotoxin production (2, 3, 5, 6, 7, 10, 11, 19, 20, 23, 24).

The spectrum of antibacterial activity of spiramycin includes Gram-positive bacteria (except enterococci), neisseria and mycoplasma. Its therapeutic efficacy is limited because of its incomplete absorption and by the pH of the organic medium at the site of action. Spiramycin is suitable for use in dental medicine because of its high level of elimination in the saliva (32).

The recommended therapeutic indications are as follows. For human therapy : infections of the upper and lower respiratory tracts with Gram-positive cocci (dental infections, tonsillitis, rhinopharyngitis, otitis, bronchitis, acute lung infections, respiratory complications in eruptive diseases). In veterinary medicine : infections caused by Gram-positive cocci and mycoplasma (lung infections and infectious enteritis in cattle and pigs, mastitis, respiratory diseases in poultry).

Lincomycin and spiramycin consumption for therapeutic purposes in the Community accounts for only a very small percentage (2-3%) of all antibiotics used. Spiramycin consumption has remained relatively constant in recent years while lincomycin consumption has tended to decline.

In summary, the comparison of lincomycin with spyramycin shows :

- The two substances belong to different chemical groups but have a similar mode of antibiotic action.

- Their use in nutritional doses has no significant effect on bacterial resistance.

- Short-term and long-term toxicity studies have been conducted on both substances. A no-effect level and an acceptable daily intake have been established for each of them.

- The tissue residues of both substances are much below the acceptable limits in the conditions under which they are authorized for use as feed additives.

- When used as feed additives, both substances have shown demonstrable advantages in terms of animal husbandry.

- The therapeutic indications for the two substances in man and animals are specific. Their use is limited. Their consumption in the Community accounts for only 2-3% of all antibiotics used. There is nothing to indicate that the therapeutic efficacy of these two antibiotics is deleteriously affected by their use as additives in feedingstuffs.

In conclusion, the Committee expresses the following opinion:

1. Lincomycin

In the light of the information now available, the Committee is of the opinion that the use of this antibiotic as a feed additive is acceptable under the conditions authorized (see table p. 10).

2. Spiramycin

In the light of the information now available, the Committee confirms the favourable opinion it delivered in 1977 on the use of this antibiotic as a feed additive under the conditions authorized (see table p. 10).

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