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► **To cite this version:**

A. Anadon. STANDARD RESIDUE REGULATIONS FOR CHLORAMPHENICOL IN SPAIN. *Annales de Recherches Vétérinaires*, 1985, 16 (2), pp.149-153. <hal-00901564>

**HAL Id: hal-00901564**

**<https://hal.science/hal-00901564v1>**

Submitted on 11 May 2020

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## STANDARD RESIDUE REGULATIONS FOR CHLORAMPHENICOL IN SPAIN

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Chloramphenicol is an antibiotic widely used in veterinary medicine, but it should not be used indiscriminately because it presents several toxicological problems that are presently being studied by research workers of different countries.

Chloramphenicol possesses a wide spectrum of antimicrobial activity especially against Gram-negative bacteria, an excellent tissue distribution, and is relatively inexpensive. For these reasons chloramphenicol is extensively used in veterinary medicine. Chloramphenicol tends to accumulate in the tissues over a longer time and at a higher concentration than in serum. Research on chloramphenicol tissue residues in food-producing animals has shown that significant amounts persist in kidney, urine, and IM injection sites. Nevertheless, studies carried out about the situation of chloramphenicol after intramammary and intravenous administration in dairy cows showed only traces of chloramphenicol or of its degradation products in fluids and tissues. From these results it appears that chloramphenicol and its degradation products are rapidly eliminated after intravenous and intramammary application (Van der Lee *et al.*, 1982).

Milk residues in normal dairy cows after an IV or IM chloramphenicol injection were negligible 36 h after the last treatment. However, this may not hold true in the case of cows with mastitis.

Treatment of laying hens with chloramphenicol in drinking water provides residue levels of the antibiotic in the yolk and in the albumen. After medication ceased, chloramphenicol disappeared

from the albumen after 76 h but persisted in the yolk until at least 108 h (Sisodia and Dunlop, 1972).

Chloramphenicol can produce adverse reactions such as: allergic reactions, hematological toxicity, ecological interrelationships, bacterial resistance (plasmid-mediated resistance), and metabolic and drug interactions.

The evaluation of the nature of chloramphenicol residues, its potential mutagenicity and the establishment of a "virtually safe level" of exposure are presently receiving special consideration by the Spanish Sanitary Authorities due to its sometimes indiscriminate use in food-producing animals.

Spanish Regulatory Authorities have established the different aspects for the use of antibiotics in food-producing animals in relation to treatment, toxicity, and food hygiene.

Chloramphenicol is approved for therapeutic use in all food-producing animals and in small animals. It is commercially available in the forms of the free base, succinate, palmitate, glycinate or undecylenate ester. The drug forms mainly used in Spain are the free base, succinate and palmitate and the dosage forms are as follows: solutions for parenteral injections, oral preparations (tablets, powders, solutions) and topical preparations (sprays, ointments, tinctures).

Animal species, routes of administration and dosages of chloramphenicol currently used in Spain are listed in table 1 and the dosage forms are summarised in table 2.

Chloramphenicol is frequently used in combination with tetracycline. Different formulations include chloramphenicol and tetracycline at a ratio of 3:1 for oral solutions, 1:1 for tablets, 1:1, 2:1, 3:1 for injectable solutions, 1.4:1 for powder and 2:1 for intramammary injectable solutions, intramammary ointments and intrauterine boluses.

Chloramphenicol is also combined with various sulfonamides (sulfamethoxypyridazine, sulfaguandine, sulfisoxazole), trimethoprim, pyrimethamine, nitrofurane derivatives (furazolidine, nitrofurazone, furaltadone), vitamins (A, B1, B6, B12, C, E, K, nicotinamide) etc. ...

#### *Spanish regulations for veterinary drugs*

In Spain, the legislation on residues of veteri-

nary drugs is defined under the Order of June 13th 1983 published in the BOE or Official State Bulletin, 17 June 1983, including animal drugs or drug products and compounds used in animal production.

This Order includes the Royal Decree 163/1981, of the 23 of January, BOE of the 11 of February 1981, and the Royal Decree 794/1984 of the 30 March, BOE of the 18 April 1983, and the decree 851/1975 of the 20 March, BOE of the 23 April 1975. This order regulates the manufacturing, distribution, dispensing and inspection of controlled substances (animal drugs or drug products and compounds used in animal production). Article 15 of the order on "Authorisations and Homologations" requires from the drug manufacturer a description of analytical and phar-

Table 1. — Effective chloramphenicol doses

Animals	Route of administration	Dose
<i>CHICKEN</i> adult	IM	50 mg/bird
	Oral	100-200 mg/l of drinking water over a 4-day period or prophylactically 40-50 mg/l over a 15-10 day period
<i>SWINE</i>		
Animal less than 1 month old	IM	250 mg total
Animals of 1 month old	IM	250-450 mg total
Animals weighing 40 kg	IM	400-800 mg total
Animals weighing more than 40 kg	IM	800-1 000 mg total
prophylactic treatment	Oral	40 mg/l or drinking water over a 15-day period
<i>CATTLE</i>	IM	1 000 – 2 000 mg total
<i>HORSE</i>	IM	1 000 – 2 000 mg total
<i>SHEEP AND GOAT</i>	IM	250-1 000 mg total
Animals of 5-6 days old	IM	100 mg total, twice daily for 3-4 days
Animals weighing no more than 20 kg	IM	200 mg total, twice daily for 3-4 days
Animals weighing more than 20 kg	IM	200 mg/20 kg, twice daily for 3-4 days
<i>DOG</i>	IM	25 mg/kg
<i>CAT</i>	IM	25 mg/kg
<i>RABBIT</i>	IM	50 mg/kg
	Oral	200-400 mg/l of drinking water over a 3-4 day period, or prophylactically 50-100 mg/l over a 15-day period.

maceutical methods and pharmacologic, toxicologic and clinical studies. The manufacturer must also establish an acceptable drug withdrawal period after the last administration of the drug to a food-producing animal and must provide a satisfactory analytical method for detection of drug residues in edible animal products.

The toxicological studies involve the design of carcinogenic, mutagenic and teratogenic investigations in laboratory animals and large animals (food-producing animals) in order to evaluate the "no effect level".

In the establishment of safety factors, toxicologists must also carry out metabolism studies for the determination of total residues (active principles and their metabolites in the treated animal (relay toxicity studies) evaluating the permissible level of a residue "or no effect residue level". On the other hand the ADI is established for a drug or chemical residue to provide a guide for the maximum quantity that can be ingested daily in food without appreciable risks for the consumer. The tolerance level must also be established.

The registration of the pharmaceutical preparations of veterinary use is authorised by Article 3 of the Royal Decree 163/1981, by the Ministry of Agriculture, Fisheries and Food and of the Ministry of Health. Article 2 establishes an advisory

Commission on animal drugs or drug products which periodically meets at the Ministry of Agriculture. This Commission comprises qualified representatives of the Ministry of Agriculture, Fisheries and Food and of the Ministry of Health and it is responsible for all the dossiers and proposals about authorization, registration, convalidation or revision of animal drugs or drug products.

According to Article 3, applications and reports should be submitted to the office of the Advisory Commission on Animal drugs or drug products. This office depends on the Veterinary Services of the Ministry of Agriculture, Fisheries and Food.

In the Veterinary Service of the Ministry there also operates a Delegate Commission of the Advisory Commission which studies the dossiers beforehand and solicits additional information if necessary.

The Delegate Commission can make recommendations concerning hazard warnings for labels, first aid, availability and other restrictions of use. These recommendations are communicated to the Advisory Commission.

The manufacturers must also submit a data package to the office of the Advisory Commission if they wish to obtain approval for drug use in food-producing animals. This Advisory Commission is a counselling body, but the State Registra-

Table 2. — Chloramphenicol dosage forms

Animal	Formulation
Cattle	10 % injectable solution 10 % oral solution 50 % intrauterine spray <sup>a</sup> 4 % intrauterine bolus <sup>a</sup> 2.5 % intramammary ointment <sup>a</sup> 2.5 % intramammary injectable solution <sup>a</sup>
Sheep and Goat	10 % injectable solution 10 % oral solution
Horse	10 % injectable solution
Swine	10 % injectable solution 10 % oral solution
Dog and Cat	10 % injectable solution 0.3 % ophtalmic solution
Rabbit	5-10 % injectable solution 10 % aqueous solution
Poultry	10 % oral solution
Therapeutic control for all animal species	1-2.5-3.5-5-6-7.5-10 % spray (aerosols)
Topical preparations	5-7-10 % tincture 2 % cream, ointment or powder <sup>a</sup>

a : Chloramphenicol in combination with other active principles.

tion Authorities with whom the legal responsibility lies have agreed that new products should not be considered for registration until clearance has been obtained from the Delegate Commission. The Delegate Commission considers such things as: efficacy for the intended purpose, safety for the target animal, safety for possible unintended recipient animals, safety for important elements of the environment, compatibility with other commonly used drugs, and stability. Once the clearance certificate lists, approved claims, dosages, directions of use, limitations and precautions are issued, the office of the Advisory Commission tells the manufacturer. If the registration of the product is approved, a certificate of authorization is sent to the manufacturer. The administrative dossier (analytical and pharmaceutical reports and package labels) is returned to the manufacturer with all pages sealed as a voucher of registration and of the conditions under which the animal drug or drug products are authorized.

#### *Chloramphenicol residues*

Research on chloramphenicol tissue residues in food animals has shown that significant amounts persist in the kidney, urine and IM injection sites. Quantitative chemical and microbiological assay methods for chloramphenicol residues have demonstrated detectable tissue levels 21 days after IM injection of calves with the chloramphenicol base. In sick animals, residues can persist up to two or three times longer than in healthy animals, making emergency slaughter of chloramphenicol treated animals a liability as far as residues are concerned.

Chloramphenicol is a valuable antibiotic but unfortunately there are many varieties of dosage forms (nature of excipients) in different concentrations, and combinations with other antibiotics or other drugs, and its behaviour as an enzymatic inhibitor and its potential mutagenic properties are also unfortunate.

Careful consideration of chloramphenicol kinetics, the type of animal involved, routes of administration, type of preparation, dosages and the nature of the infection being treated, will largely avoid drug residue, intoxication and bacterial resistance problems.

The knowledge of chloramphenicol pharmacokinetics and of residue analysis has been incomplete in many instances. The determination of chloramphenicol in body fluids and tissues has been mainly performed by microbiological methods, which have the disadvantage of not being specific for a given antibiotic and of not being able to detect microbially inactive metabolites. Moreover, it is well-known that microbiological methods have high detection limits for chloramphenicol. Physicochemical methods, such as

high-performance liquid chromatography with ultraviolet or polarographic detection, have the additional advantage of being able to separate chloramphenicol and its degradation products.

The identification of the whole mosaic of residues, the studies of their bioavailability and their toxicity (mutagenicity testing: detection of gene mutation in bacteria, chromosome damage to mammalian somatic cells *in vitro*, induction *in vitro* of gene mutation in mammalian cells or a test *in vivo* in *Drosophyla melanogaster*, chromosome metaphase analysis test *in vivo* or micronucleus test, and teratogenicity and carcinogenicity testings) are also necessary for a complete evaluation of the use of chloramphenicol. These requirements should be reviewed by Regulatory Authorities.

In different countries, such as Spain, chloramphenicol, a thermostable antibiotic, has produced sanitary and technological problems derived from animal products. Effectiveness, safety and environmental impact of chloramphenicol are the concerns of Regulatory Authorities. Heavy responsibility is placed on the veterinary and the livestock producer to observe the instruction for use and the withdrawal period of a drug prior to slaughter.

In Spain, presently, there is concern about the therapeutic use of chloramphenicol. The Regulatory Authorities have restricted use in the following ways: increased withdrawal times, prohibited use in hens which are laying and they may also prohibit use in dairy cows, and indicate on package and label texts incompatibilities, contraindications and drug interactions.

#### *Spanish recommendations*

The Order of the 13th of June 1983 establishes that every new animal drug or drug products for use in veterinary medicine must have toxicological studies of the final pharmaceutical preparation and of each active drug of the preparation.

Article 3 of the Royal Decree 163/1981 of the 23rd of January rules that the animal drugs officially approved should be reexamined every five years for ratification by the Advisory Commission. Then the Advisory Commission may modify or suspend the authorization of use of any animal drug. Nevertheless, the Regulatory Authorities may also suspend at any moment the use of an animal drug for public health reasons.

The administration may consider the preparations of chloramphenicol in association with other drugs to prevent physicochemical incompatibilities, and inadequate pharmacokinetics and withdrawal times.

Initially, the Spanish Authorities try to establish in the therapeutic use of chloramphenicol a smal-

ler range of concentrations, the best (optimum) excipients in the different dosage forms, withdrawal times in relation with the excipient and routes, use of only one active drug, routes of administration (so that it is not indiscriminately used orally and IM in food-producing animals), and moreover, a restriction of its use in food-producing animals, dairy cows and laying hens to avoid risks to the consumer.

They are trying to carry out in Spain monitoring programmes of chloramphenicol mainly in serum, milk and injection sites of treated animals at farms and/or slaughterhouses for detecting chloramphenicol residues, using specific and sensitive analytical methods.

The identification of other antibiotics as alternatives responsible for some concrete indications in specific diseases must also be taken into account.

It is obvious from an international and national standpoint, that this Working Group or others should cooperate and establish regulations on the therapeutic use of chloramphenicol in line with the legislation in force in the different countries.

The Residue Group should be the focal point in the Central Office of the following investigations on chloramphenicol, referring above all to: analytical methods (establish specific methods that correct the variations of the results observed in the different countries due to the use of various analytical methods), safety of chloramphenicol, adverse effects, information interchange and distribution of bibliography on European Regulations.

*Groupe Européen d'Études des Résidus. Symposium Chloramphenicol, Fougères, France, 11 octobre 1983*

#### References

- VAN DER LEE J.J., NOUWS J.F.M., BLOEMENDAL F.W.R., 1982. Physicochemical methods for pharmacokinetics and residue analysis of chloramphenicol and degradation products in dairy cows. *J. Vet. Pharmacol. Therap.*, **5**, 161-175.
- SISODIA C.S., DUNLOP R.H., 1972. Chloramphenicol residues in tissues of broiler chickens. *Can. Vet. J.*, **13**, 263-265.