

2.1. Transfer of antibiotics to milk

Understand metabolism and pharmacokinetics

To understand the outcome of antibiotics in the body, the possibility of finding them in food (milk, eggs, honey, meat...) and secondarily the MRL definition modalities, it is necessary to know the basic notions regarding the outcome of antibiotics in the body after administration. Obviously, the outcome of an antibiotic above all depends on the administration route, as it was demonstrated many years ago (Ref. 51, Ref. 49). Whatever the administration route, the outcome of an antibiotic in the organism is related to different factors:

- Its **metabolism**: the medicine can be transformed inside the organism by different active or passive chemical processes. Into metabolites, of which some will show therapeutic and/or toxic effects and others will have none.
- Its ability to **cross the membranes**: blood vessel walls, cellular membrane... This ability is closely related on one hand to the molecule balance between hydrophilia and lipophily, and on the other hand, to the molecule size. The **equilibrium** between ionized and non-ionized forms depends on the pH of the medium and the pKa of the substance.
- Its different means of elimination: urine, faeces, saliva (with recycling), milk... (Ref. 33).

Definitions

pH: logarithmic parameter measuring at equilibrium an aqueous medium's acidity or basicity, depending on the balance between the H_3O^+ and OH^- ions resulting of the water dissociation.

pKa: logarithmic parameter describing at equilibrium the dissociation degree of a ionisable molecule in aqueous solution. In pure solution, the pH at equilibrium can be calculated from the pKa, which therefore express the strength of a base or an acid: the smaller the pKa, the stronger the acid, the higher it is, the stronger the base.

To simplify, it must be reminded that the molecules most capable of crossing the membranes are the smaller ones, more lipophilic than hydrophilic and in a non-ionized form. However, certain molecules benefit from active transport phenomena.

Once administered, the drug will progressively spread (under its different forms) into the various compartments of the organism before being metabolized then eliminated in different ways. Thus an antibiotic administered by general route will be more or less eliminated by the different routes: urine, faeces, saliva (recycling in the rumen for ruminants) and milk.

The outcome of a molecule in the body also strongly depends on the **galenic form of the medicine**. Certain "longterm action" drugs persist a long time on the injection site and at the same time in the organism. It is essential to understand that the **elimination kinetics in milk, eggs, or meat strongly varies from one medicine to another for a same antibiotic**. In any case, **the concentration drop curve progressively tends towards zero** but can go under the thresholds of the detection methods only several days and even weeks after the administration.

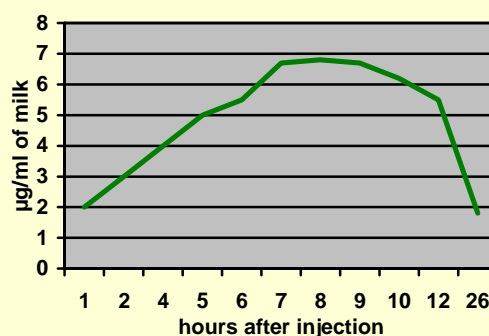
Definitions

Galenic: in honour of the Greek medical doctor (Galenus), branch of pharmacy specialized into the manufacture of medicines: forming, choice of the excipients.

Metabolites: products of the transformation of a molecule by the organism; generally under the influence of specialized enzymes.

Elimination kinetics in milk of an antibiotic injected by intramuscular route

The chart presents the elimination kinetics of tylosin (macrolide) in milk from a cow in an experimental station after intramuscular injection of 20 mg/kg. Notice that the concentration reaches a peak 8 hours after the injection. The period of appearance of the peak varies with the antibiotic. All conditions otherwise equal, it would be similar for penicillin, earlier (4 hours) for a cyclin, and even more earlier (2-3 hours) for clindamycine.



Intramammary treatments in lactation and residue persistence

The treatments administered by intramammary route to treat mastitis in lactation are submitted to two kinds of mechanisms: biological mechanisms (diffusion in the interstitial spaces, transfer to the blood...) and physical ones (mechanical elimination of the milk at each milking).

Several antibiotics with very high diffusion will rapidly pass through the different physiological barriers (cellular walls, blood vessel walls...), enter the blood circulation and will be eliminated through different ways (urine in particular) sometimes after metabolisation. They can also concentrate in the mammary tissues. On the contrary, other molecules will stay in the teat and udder cisterna and in the acini. They will be mainly eliminated with the milk on milking. In any case, the presence of residues in the milk will be evidenced during periods going from several hours to several days. In most cases, the withdrawal times are between 2 and 5 days for the antibiotic concentration in milk to be inferior to the MRL.

Dry period intramammary treatments

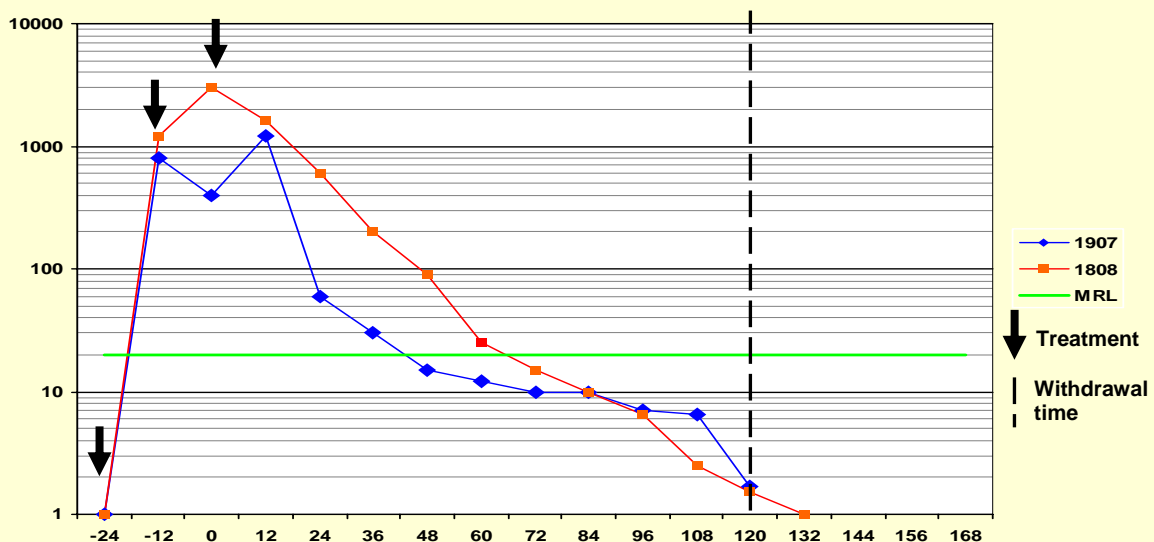
The context of the dry period treatments is very particular because they are administered after the last milking and before a period (generally two months) during which the udder, not being milked, will first involute, then rest, before being affected by the physiological transformations due to the resumption of lactation preceding the calving. The molecule nature and the galenic form have a considerable influence on the outcome of the molecules administered by the dry period treatment. Certain treatments can persist in the udder nearly 2 months (without milking) and are only finally eliminated via the first milking of colostrum and milk.

Definition

Mammary involution: mammary involution lasts three weeks after dry off. After the involution, the lactocytes present a high grade structure with a quasi-null secretory activity. The secretion volume, directly related to the lactose quantity (in high speed decrease), only represents 2% after 30 days. The pH passes from 7.0 to values around 7.6. There is a drop of the milk specific proteins and a considerable rise of the non specific proteins (immunoglobulines, lactoferrine). The length of the teat reduces and the duct provisionally expands while the keratin progressively stores up until in most cases, obstruction of the latter.

Example of an antibiotic elimination kinetics injected by intramammary route (Ref. 36)

The chart below shows that the milk from two cows (numbered 1907 and 1808) treated by three injections at a 12 hour interval contains antibiotics (in this case cefquinome) which progressively decrease. The values are inferior to the MRL after 48 hours in one case and 72 hours in the other. After the withdrawal time, the contents are not null but are set at less than 10% of the MRL.



Antibiotics persistence in the milk of small ruminants

The pharmacokinetics of several antibiotics administered by parenteral route has been studied for ewes (examples below) and has led to offer therapeutic schemes, which due to their adopted withdrawal times require great attention.

The presence of antibiotic residues in milk is a major preoccupation for the dairy ovine and caprine sectors. The screening tests used for residues in cow milk have been validated for goats (Ref. 12) and ewes (Ref. 45) and can therefore be used for small ruminants.

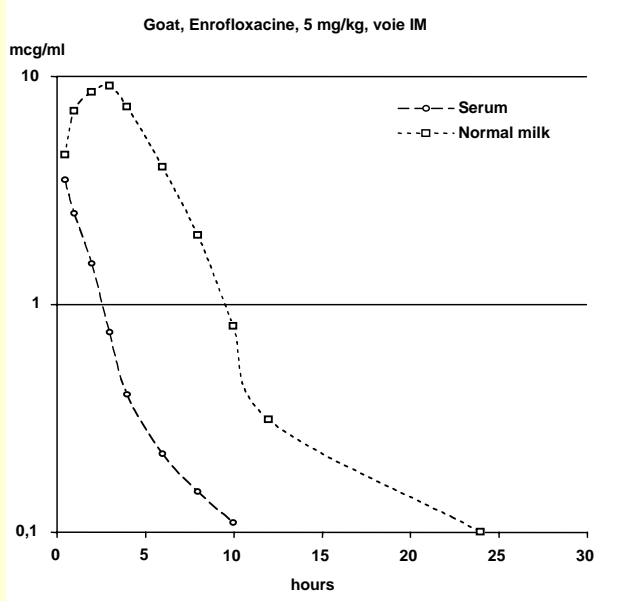
The question of residues leads to query the withdrawal time after intramammary treatment in lactation and at dry off. The data is scarce.

In lactation, the intramammary administration of 3 syringes (at a 12 hour interval) of a preparation meant for cows, containing 200mg of amoxicillin, 50mg of clavulanic acid and 10mg of prednisolone led to the detection of residues up to 136h in ewes and 112h in goats (Ref. 8, Ref. 9). In a similar study, cloxacillin residues have been detected in goat milk up to 156h after the last treatment (Ref. 27).

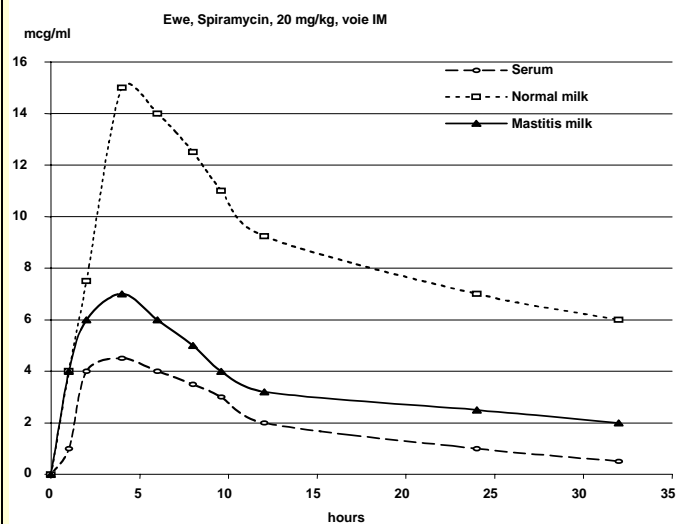
After administration at dry off of a bovine medicine, residues have been found on farrowing and up to the 3rd day in several treated ewes and up to the 7th day in several goats whose dry period had been inferior to 2 months (Ref. 42, Ref. 43). These results confirm those of Fox and al. (Ref. 23) who, after a dry period of 107 ± 33 days, found residues on the first milking only in 1 of the 34 treated goats.

In normal conditions (dry period of at least 2 months for goats and 3 to 4 months for ewes), the risk to find residues in milk at the end of the colostal period or the suckling is very low. For ewes, the milk is only delivered at the end of a period of suckling-milking of 3 to 4 weeks. However, in case of a shortened dry period, mainly goats (more than 25% of the goats could have a dry period inferior to 60 days in France) but also possibly ewes within a system of 3 lambings in 2 years (Churra breed in Spain), additional precautions are needed.

Elimination of antibiotics in ewes and goat milk after intramuscular injection



Average concentrations (micrograms/ml) of enrofloxacin in the goat serum and milk after intramuscular injection of a dose of 5 mg/kg (after Ziv and Soback, 1989) (Ref. 66).



Average concentrations (micrograms/ml) of spiramycin in serum and milk from hald udders of ewes after intramuscular injection of a dose of 20 mg/kg (after Ziv and al., 1974) (Ref. 67).