

## HEALTH ASPECTS OF THE USE OF BETA-2 ADRENERGIC DRUGS IN ANIMAL PRODUCTION

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**Summary.** - *In the zootechnical field, there is a strong need to correlate analytical results with biological effects of beta-2 adrenergic agonist drugs on animal health, food processing and human toxicology, taking into account the peculiarity of their administration (long-term treatments with doses tenfold as high as the therapeutical ones). The opportunity to use ELISA tests to readily detect illegal treatments, suspected on the basis of clinical and inspective data, can allow appropriate preventive medicine action by monitoring the food chain during its early steps (in living animals). Sanitary implications will not be limited only to serious clinical signs confirmed by analyses, but should also lead to educational programmes intended for farmers, showing them the main obvious risks in animal production associated with beta-2 agonist side-effects.*

**KEY WORDS:** beta-agonist drugs, side-effects, illegal treatments, preventive medicine.

**Riassunto** (Aspetti sanitari legati all'uso di farmaci beta-2 agonisti adrenergici nel campo delle produzioni zootecniche). - *In campo zootecnico, è indispensabile mettere in luce una correlazione fra i risultati delle analisi e gli effetti biologici dei farmaci beta-2 agonisti adrenergici sulla salute animale, sulla lavorazione degli alimenti e sul piano della tossicologia umana, prendendo in considerazione la peculiarità della loro somministrazione (trattamenti a lungo termine con dosi dieci volte superiori a quelle terapeutiche). La possibilità di utilizzare i test ELISA per scoprire in breve tempo i casi di trattamento illegale, sospettati sulla scorta dei risultati clinici ed ispettivi, può permettere l'attuazione di utili interventi di medicina preventiva attraverso il monitoraggio delle prime fasi della catena alimentare (nell'animale in vita). Le implicazioni sanitarie non dovranno limitarsi soltanto alle gravi manifestazioni cliniche, ma dovranno anche portare all'attuazione di programmi di educazione desti-*

*nati agli allevatori, mostrando a questi ultimi gli evidenti rischi per la produzione zootecnica dovuti agli effetti collaterali dei farmaci beta-agonisti.*

**PAROLE CHIAVE:** farmaci beta-agonisti, effetti collaterali, trattamenti illegali, medicina preventiva.

Until few years ago, veterinary drugs were administered to production animals (cattle, swine, poultry, fish, etc.) for prophylactic and therapeutical purposes, or as growth-promoters (auxinic drugs) in order to select the appropriate microbial gut flora capable of inducing maximum feed conversion into metabolic energy. Nowadays, pharmacological treatment can directly influence the animal's intermediate metabolism so as to obtain final products (milk, meat, eggs) with modified composition in proteins, lipids, and sugars. Molecules such as Clenbuterol, Mabuterol, Cimaterol, Salbutamol, Ractopamine, Isoxsuprine can be illegally given to farm animals as "repartitioning agents" to improve weight gain and to lower the amount of adipose tissue. These drugs are frequently used in human and veterinary clinical medicine to treat obstructive bronchial diseases (pneumonia, asthma) for their selective action on beta-2 adrenergic receptors present all along the respiratory tree. The influence of such drugs on metabolism was first noted as a side-effect of long-term treatments in asthmatic patients whose adipose tissues were significantly reduced. In the adipose tissue, digestive tract and smooth muscles, in fact, beta-3 adrenergic receptors (also called "metabolic") are found which can partially cross-react with Clenbuterol and its analogues during long-term treatments, despite the differences in their molecular structures compared with beta-2 receptors. This is the reason why very high doses (tenfold as the therapeutical ones) of beta-2 adrenergic agonist drugs are

used in the zootechnical field in order to exploit this metabolic side-effect [1]. At present, no beta-3 agonist drugs are available on the market for metabolic purposes.

While the first risk factor for animal and human health is the high dosage, the second one is the period of drug administration which usually lasts over 30 days in the finishing period, very close to the slaughtering age. At this time, the animal shows a slowing down in protein synthesis with a marked increase of adipose tissues. This trend can be effectively countered by pharmaceutical treatment. A short withdrawal time is allowed, usually no more than five days, because, as the drug action decreases, a massive lipogenesis takes place as a "rebound effect" in the animal's body, which renders the metabolic performances useless. This time cannot be sufficient for the complete elimination of the drug from the body.

These reasons have already led to poisoning in consumers who ate calf liver. Typical beta adrenergic effects such as headache, vertigo, feeling of revulsion, heart failure were clinically observed, and the presence of Clenbuterol was confirmed in the food and in the patients' urines by gas chromatography-mass spectrometry analysis [2, 3].

Zootechnical treatments, however, represent a major risk factor for farmers who, handling for long periods black market products containing extremely concentrated beta-2 agonist drugs, may be exposed to a continuous intake of drug molecules by inhalation, ingestion, or by absorption through the skin.

While zootechnical advantages are well documented in the scientific literature, other undesirable side-effects on animal health and on food processing are currently understated. The veterinarian can readily notice these side-effects both after clinical diagnosis and after inspection of the carcasse at slaughter. It should be stressed that the administration of other drugs is often needed to limit and to mask the incidence of these toxicological effects on animal production, with resulting increased presence of xenobiotic residues in the animal's body and in the foods produced.

Major pharmacological, often toxicological, side-effects involve the central nervous system (CNS), and target organs are the heart, small arteries, the uterus and the liver. Central effects are due to the stimulation of adrenergic and dopaminergic receptors in the hypothalamus, that play an important role in the secretion of pituitary hormones-releasing factors and in the control of such biological functions as hunger. Calves under treatment exhibit increased secretion of bovine growth hormone and cortisol, hypoestrogenism, and decreased food intake, with resulting severe stress.

The CNS-derived decrease in appetite, supported by the bitter taste of the drugs, is the main adverse effect from the zootechnical point of view. In order to counteract this effect and maintain weight gain, anti-anorexic drugs, such as short-acting benzodiazepines, are administered with the feed, out of any therapeutical purpose.

With regard to target organs, the heart is often involved in overstimulation, due to the cross-reactivity of the drug with beta-1 receptors. In piglets and calves the failure in the heart conduction tissue may be the cause of instant death. The vasodilator effect on arterioles can lead to foot-pad lesions. The above clinical symptoms, besides compromising livestock performances, always need differential diagnosis from infectious diseases, such as foot-and-mouth disease, that would call for severe prophylactic measures involving both the farm and its products.

The drug-induced lipolysis results in a triglycerid overload in the liver, and the altered metabolism can lead to ketosis, with adverse consequences on animal health and productions.

The clinical effects of beta-2 agonist drugs on the animal's health are closely consistent with the findings at slaughter inspection. Liver steatosis, lowered amount of adipose tissue, muscular hypertrophy especially in the hind part of the carcasse may be suggestive of a suspect illegal zootechnical treatment. Histological examination will reveal morphological and functional changes in the thyroid, prostate, Bartolino glands, and the appearance of a third protein band in the muscular fibres [4].

Meat processing can be adversely affected by "dark cutting" phenomena, which occur when a stressed animal is slaughtered. The muscles cannot reach a pH value of 6 or less, at which microbial growth is inhibited: an insufficient glycolysis takes place due to a shortage of carbohydrates in the fibres. Moreover, beta-2 agonist drugs may render lysosomal vesicles stabler; as a result, a delay occurs in the softening process and the meat becomes hard to the cut and has an altered taste [5].

There are several reasons for discouraging the zootechnical use of beta-2 agonist drugs. A closer connection between obvious clinical and inspective findings and pharmacological and toxicological knowledge can be a helpful tool for veterinarians taking action as health officers. Educational programmes addressed to farmers, showing them the side-effects of these drugs on their productions, constitute the main task of preventive medicine, in order to limit the consumer's exposure to the risk of introducing residues from meat. Farmers must have not only zootechnical information on, but also scientific knowledge of the advantages of long-term treatments with these drugs, with due consideration to the health problems involved, economic cost of the drugs and the risk of legal prosecution.

From an analytical point of view, real-time analyses are strongly needed to correlate causes and effects. Enzyme Linked ImmunoSorbent Assays (ELISA), easy and quick tests, can readily provide early qualitative information on negative and positive (true and false) samples at the farm and at slaughter. The possibility to test biological fluids

such as plasma and urine in the living animal will greatly assist in preventing the occurrence of xenobiotic residues in meat products. In fact, the efficacy of veterinary control is increased when it is carried out during the first steps of the food chain. When positive results are seen in living animals (in the farm or at pre-slaughter time), the respect of the proper withdrawal time can recover the soundness of animal production and its commercial value. In addition, the analytical laboratory will have time enough to confirm ELISA results and to identify the drug involved [6].

The presence on the black market of a large number of drugs makes the identification of the compound difficult for the analyst. Clinical and inspective data provided by veterinarians can restrict the field to one class of molecules having the same biological activity and will help the laboratory in the chemical characterization of the drug.

Submitted on invitation.

Accepted on 10 July 1992.

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