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Scientific substantiation of the use of iron-containing drugs in veterinary medicine

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Abstract. The relevance of this study is conditioned by the need to summarise current knowledge about the use of iron-containing drugs in veterinary medicine and their scientific substantiation. The purpose of this study was to analyse the results of the latest experimental data presented in

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the literature on the pharmacological and toxicological properties of iron-containing drugs and the specific features of their use in veterinary medicine. The study employed the method of literature analysis with the formulation of relevant substantiated conclusions and their generalisation or comparison. Iron-containing medicines are particularly relevant in modern veterinary medicine for the prevention of iron deficiency anaemia in piglets. The use of iron dextran preparations is a scientifically sound and necessary preventive measure in modern pig production. Furthermore, the study covered new approaches to the development of effective antianaemic drugs for animals of other species, including calves. The study also covered the controversial issues of the use of iron-containing drugs in pregnant females for the prevention of iron deficiency in animals born from them. The analysis of the literature data presented in this study shows a prominent degree of scientific interest in the study of pharmacological and toxicological properties of iron in high valences (specifically, ferrous iron in clathrochelate form) with a view to their use in medicine. The conducted literature review suggests the multidirectional use of iron-containing drugs in various dosage forms in veterinary medicine. The study identified the key trends in the pharmaceutical market of iron-containing drugs registered in Ukraine. In recent years, there has been a growing body of scientifically based evidence indicating the effectiveness of iron-dextran complex in combination with micro- and macronutrients and vitamins. Currently, the use of iron-containing drugs in the world's veterinary practice, considering their scientifically and experimentally proven pharmacological properties, is extremely promising. The materials of this study are of practical value for expanding the possibilities of using new forms of iron in veterinary medicine

Keywords: iron; iron deficiency; anaemia; piglets; calves; prevention

Introduction

Iron is one of the most abundant metals in nature. It is well known that as a chemical element, it can change its valence. At present, iron in low valence forms, i.e., the second and third, is well-researched. The properties of high-valent iron are being actively investigated in Ukraine and worldwide (Derkach, 2023; Plutenko, 2024).

In a living organism, the biological role of iron correlates with the physiological role of iron-containing compounds that ensure the body's vital functions. Thus, the trace element iron is a necessary structural part of haemoglobin, iron-containing and iron-dependent enzymes that affect physiological and biochemical processes in the body and cell functioning. It is natural that a lack or excess of this trace element provokes the development of pathological conditions, and with a prolonged imbalance in its content, diseases occur that can have fatal consequences. M. Morales & X. Xue (2021) prove the correlation between iron levels in the body and cell proliferation in cancer.

According to recent publications, hepsidin plays a crucial role in iron metabolism in animals as a humoral factor, with an increase in the trace element's content stimulating hepsidin synthesis in the liver, which reduces iron absorption in the intestine and its transport into the bloodstream. Conversely, a decrease in iron absorption in the intestine leads to inhibition of hepcidin synthesis and, as a result, restoration of iron absorption. This hormone, which is a 25-amino acid peptide, affects the absorption and release of iron from macrophages during recycling from red blood cells. Hepsidin can also block iron transport in the placenta,

epithelium, and other tissues (Nemeth & Ganz, 2021). Under anaemic and hypoxic conditions, hepsidin gene expression decreases, while iron absorption from macrophages and the intestine increases (Vydyborets & Borysenko, 2019). According to J.H. Joachim & K.J. Mehta (2022), hepcidin, as a hormone that maintains systemic iron homeostasis, is involved in the development of hepatocellular carcinoma, one of the most common causes of death in cancer.

In veterinary medicine, the use of iron-containing products is particularly relevant in pig farming. This ~~is~~ primarily due to the risk of iron deficiency anaemia in piglets. Animals of this species have a biological predisposition to develop iron deficiency during the suckling period. First of all, this is conditioned by the fact that of all farm animals, they are born the most immature; their growth is comparatively quite intensive, which precedes the development of erythrocytopoiesis in their body. Inhibition of erythrocytopoiesis in the spleen and liver occurs against the background of activation of the erythropoietic capacity of the bone marrow. The consequence is that during this period, the piglet's body does not sufficiently ensure the production of red blood cells and the synthesis of haemoglobin (Derkach, 2023). According to M. Todorov *et al*. (2023), the complex use of iron-containing and tonic preparations in the case of rehabilitation and treatment measures in piglets is more effective than the conventional scheme used on farms for the treatment of weakened and anaemic piglets.

However, iron deficiency also develops in young animals of other species, and in adult animals it is a symptom of certain diseases or poisoning (Paslawski *et al*., 2021). According to the latest data, haemotransfusion is effective in the treatment of anaemia in cats (Malyuk *et al*., 2022). The development of new or improvement of current preventive measures against the occurrence and development of iron deficiency in animals of different species stays relevant. Moreover, new properties of iron in high valence forms are being investigated with a view to their application in medicine.

The purpose of this study was to analyse the literature data on the findings of modern scientific research on the pharmacological and toxicological properties of iron-containing medicines and promising areas of their use in veterinary medicine, as well as their range in the pharmaceutical market of veterinary medicines in Ukraine. The study was conducted using widely recognised scientific methods, including search, observation, analysis, comparison, systematisation, and comparison with the findings of other studies, description, and a systematic approach. The search for and processing of scientific information was carried out through a literature review, which helped to identify key trends and gaps in existing knowledge. Observations of facts and phenomena were an essential component of obtaining concrete data and formulating assumptions. The analysis and comparison of the findings with the results of other studies helped to identify trends, confirmation or contradiction of the findings. Systematisation and structuring of information was important for the logical presentation of data. The description and systematic approach helped to put the research findings in context, contributing to the field and facilitating further research.

Historical background on the use of anti-anaemic drugs in veterinary medicine

As noted by H. Saito (2014), the trace element iron is important for the animal body, while its metabolism, according to recent data, is regulated primarily by the hormone hepsidin (Starzyński *et al*., 2013; Machalová Šišková *et al*., 2016; Sangkhae & Nemeth, 2017). We share the opinion of researchers who believe that in

veterinary medicine, iron deficiency poses the greatest risks to newborn piglets.

Iron deficiency anaemia is a separate nosological disease of suckling pigs. In animals of this species, it develops from 5-7 days of life, and a month after the birth of piglets, it manifests itself to the maximum. The main symptoms of this disease are a decrease in the number of red blood cells and/or a decrease in the content of haemoglobin per unit volume of blood; metabolic disorders, hypoxia, growth retardation, decreased resistance to other diseases, and a high mortality rate (Antonyak, 2002; Levchenko *et al.*, 2015).

According to primary sources, the first attempts to prevent anaemia in piglets were based on feeding newborn piglets red clay and watering them with solutions of iron and copper sulphates. With the development of pharmaceuticals in the 20th century, preventive measures were associated with the use (first enteral and later parenteral) of anti-anaemic drugs containing low-valent iron.

Thus, to prevent iron deficiency anaemia, it was recommended to use salts of iron, manganese, copper, and cobalt; licks with ferrous fumarate; chalk-based iron-containing briquettes; highly dispersed paste, granular feed with ferric glycerophosphate in piglet feeding (Ulyzko & Todorov, 2014). Among other options available were foal blood, protein extract of ruminant liver and spleen using the Filatov method. Generally, it was believed that the introduction of proteins, which can be sourced from vegetable or animal proteins (soy protein, albumin, gelatin, casein, etc.), has a positive effect. Liver products and immunostimulants were offered as anti-anaemic drugs. Subsequently, organic/inorganic and complex iron-containing compounds were widely used: ferrous sulphate (II) preparations for oral administration, ferrous dextran (III) preparations for enteral and parenteral administration. In general, from the 1930s to the present day, anti-anaemic iron-containing drugs are generally divided into those used orally (monocompounds of iron salts, their combinations with cobalt and copper salts, vitamins (Svoboda & Pistkova, 2018), and those used parenterally (complex iron-containing compounds of iron with dextran, trace elements, vitamins).

As the range of iron-containing products has expanded, researchers have tried to develop classifications based on various criteria. Thus, according to one classification, this pharmacological group includes iron (II) medicinal products; iron (III) medicinal products; inorganic medicinal products; organic medicinal products. Therewith, inorganic compounds are represented by iron (II) sulphate and iron (III) chloride, while organic compounds are iron (II) gluconate, fumarate, xylitol, sorbitol, and iron (II) dextran, dextrin, and iron (III) ferroprotein (Troshin & Nechaeva, 2006).

According to the literature, researchers have investigated the use of iron-containing drugs in various dosage forms and with different routes of administration, including aerosolisation; oral administration in the form of powder (Grushanska, 2005), pastes (Ulyzko & Todorov, 2014), etc. Many journals indicate that they used to treat the sow's udder with a solution of ferrous sulphate (together with copper sulphate and cobalt chloride).

Use of iron-containing anti-anaemic drugs in suckling piglets

The conducted literature analysis suggests that currently the simplest and most effective way to prevent anaemia and treat animals with anaemia is to use iron-containing drugs in the neonatal period. However, the disadvantages of the injection route of administration are that this method involves non-physiological intake of iron in the animal's body, and high doses of the trace element are unsafe, as iron is a

heavy metal with the ability to accumulate and pro-oxidant properties (Boldt, 1999) and blocks phagocytic mononuclear cells in the form of haemosiderin (Levchenko *et al*., 2015).

Notably, the method of oral administration of iron-containing medicines is natural. The use of iron in feed additives is considered a significant advantage for suckling piglets in terms of prevention of iron deficiency anaemia (Maes *et al*., 2011; Starzyński *et al*., 2013). R. Antileo *et al*. (2016) investigated the anti-anaemic efficacy of non-heme (NHI) and heme (HI) iron microparticles to develop a new oral iron supplement. It was found that iron deficiency anaemia in piglets can be prevented by administering an oral encapsulated NHI/HI supplement in three doses.

However, the authors of the present study share the opinion of scientists who believe that iron absorption is inhibited by inflammation and this method of treating anaemic animals is ineffective in case of metabolic disorders in their bodies. It is also well-known that inorganic iron-containing substances have poor absorption properties, which can result in dyspeptic conditions. T. Tuomainen *et al*. (1999) proved that, compared with the use of non-ionised iron-containing combination preparations, oral use of ferrous sulphate increases sensitivity to oxidation of plasma lipoproteins.

The study of the toxicological and pharmacological properties of new iron-containing antianaemic drugs stays relevant worldwide (Lipinski *et al*., 2010; Geisser & Burckhardt, 2011; Cui *et al*., 2018). Comparative studies of the efficacy of iron-dextran medicines in the prevention of anaemia and the treatment of patients with this pathology are relevant. Such medicinal products in a dose of 150-200 mg of iron per injection are recommended for intramuscular administration to piglets on the days 3-5 after birth (if necessary, repeated on the days 7-10). The advantage of using iron dextran compared to iron salts is that it creates an iron depot in the body of newborn animals and minimises the risk of anaemia. The researchers found that the absolute weight gain in piglets treated with Bioferon during the first month of life was 880 g higher, and in piglets treated with Suiferovit – 1,134 g compared to the control. At weaning, the average weight of piglets was 1.81 kg and 2.66 kg higher, respectively. Researchers attribute this to the fact that in the first case, Suiferovit contains trace elements and vitamins (Prokopenko & Martynov, 2012).

Many researchers believe that iron-dextran preparations should be combined with trace elements (zinc, copper, cobalt) and vitamins (groups B, C), which will help stimulate haemocytopoiesis, as iron is absorbed by only 60-70% when administered parenterally. J.D. Cook & M.B. Reddy (2001) found that the use of ascorbic acid promotes haemocytopoiesis, as iron absorption increases by 2.9-3.5 times. Some scientists emphasised the pro-oxidant capacity of iron ions in high concentrations, which was considered a disadvantage of iron-dextran preparations. Therefore, combinations with cyanobalamin, tocopherol, and selenium were recommended. Therewith, developers of new iron-containing drugs have tried to reduce the iron content in complex anti-anaemic drugs (Vered, 2006; Danchuk *et al*., 2017).

T.S. Tokarchuk & V.V. Danchuk (2017) found that intramuscular injection of a complex of zinc, iron, and germanium citrates twice together with vitamin E supplementation increased piglet body weight by 6.8%. The use of 2.5 mL of this combination of trace element citrates increased the haemoglobin concentration by 18.0% and 15.5%, respectively, and increased the number of red blood cells in piglets' blood on day 35 of life. V.B. Todoryuk (2012) noted that the use of an iron-containing micronutrient composition (synergistic essential polynuclear complexes that exhibit a

biocoordination effect) in piglets of the experimental group led to an increase in haemoglobin concentration by 18% on day 8, by 20% on day 14, and by 17% on 32, while the number of red blood cells increased by 8% on days 8 and 14, and by 4% on day 32 compared to the control. Therewith, an increase in haematocrit by 6-8% was found throughout the experiment. Erythrocyte parameters were increased compared to the control: MCH by 11-15%, MCV/MCHC by 5-9%. The use of additional amounts of trace elements contributed to their accumulation in the piglets' body, specifically, on day 32 of life, the level of iron in the animals' blood increased by 53%.

V.S. Bityutskyi (2007) proposed the development of complex preparations containing iron in the form of cluster compounds stabilised by the carbohydrate component of micelles. The latter is an analogue of ferritin and a source of a non-toxic and easily accessible form of the trace element. Apart from the prosthetic groups of antioxidant enzymes, such medicines include chelated complexes of copper, zinc, and selenium. It was found that the administration of polymetal and polymetal-selenium to suckling piglets prevented iron deficiency anaemia in animals, as evidenced by positive changes in common diagnostic markers of iron deficiency in the experimental groups compared to the control. Thus, according to the findings of research by many authors, it was proved that a reliable anti-anaemic effect in suckling piglets was observed when iron was combined with other trace elements, vitamins, and antioxidants.

In previous studies by I. Derkach (2023), a comprehensive solution to this scientific and practical problem was presented, which makes provision for the investigation of the anti-anaemic activity of iron in valence IV. S. Tomyn *et al*. (2017) first reported clathrochelate iron compounds in valence IV. The physicochemical properties of these compounds were actively studied: the high stability of iron (IV) clathrochelate was found to be primarily conditioned by the fact that metal ions in this compound are "packed" in an organic matrix, from which the metal is released gradually *in vivo* as the substance biodegrades. It was predicted that the use of medicinal products based on iron (IV) clathrochelate would minimise the undesirable effects associated with the toxicity of aquariums and aquacomplexes of low-valent iron. Preclinical studies have established that iron (IV) in clathrochelate form corresponds to Hazard Class III according to the classification of chemicals by hazard and to Toxicity Class IV as a low-toxic substance. The studied tetravalent iron exhibited weakly expressed cumulative properties, and no irritant or allergenic effects were observed. Clinical studies of iron (IV) clathrochelate and its use in newborn piglets have shown an anti-anaemic effect, which is confirmed by high levels of haemoglobin, haematocrit, and red blood cell count (Derkach, 2023).

Many publications are devoted to the study of the effectiveness of nanocompounds in medicine. The use of iron nanocompounds is also promising in veterinary medicine. Such drugs in low doses have a pronounced pharmacological effect. Ukrainian researchers have conducted a range of studies of the combination of iron nanopreparation and brovapherone-100. It was found that the iron content in the blood plasma of suckling piglets increased during 20 days of life compared to piglets that were administered these drugs separately. It was also proved that piglets from the experimental groups were more active and competitive than those from the higher lactation groups. The use of iron nanochelates contributed to a dose-dependent decrease in cortisol concentration, an increase in T3 and insulin concentration in piglets' blood, which increased stress tolerance,

productivity, and resistance of animals. It was found that the combined administration of iron nanopreparation and iron dextran reduced the prooxidant effect, while increasing the activity of catalase and glutathione peroxidase (Danchuk *et al*., 2017). Thus, despite the long history of research on piglet iron deficiency anaemia, the development of drugs for its prevention and treatment of sick animals, this issue is still relevant today.

Use of iron-containing anti-anaemic drugs in sows

The issue of using iron-containing preparations in pregnant sows to prevent anaemia in piglets born from them is currently under debate. Some scientists believed that the administration of iron-containing medicines to pregnant and lactating animals would ensure reliable iron reserves in the liver and blood of suckling piglets, while others believed that such preventive measures would not have a reliable preventive effect.

L.Ya. Bozhik (2009) noted that feeding sows with ferrous methionate in doses of 0.7 mg/kg body weight for 30 days before farrowing and 1.4 mg/kg before weaning would prevent the development of anaemia in piglets and have a positive effect on the physiological state of the sow's body and increase the count of red blood cells and haemoglobin content in their blood by 12.2% and 32.4%, respectively, compared to the control. Therewith, an increase in the count of T- and B-lymphocytes and immunoglobulin content was observed by 12.4%, 16.7%, and 19.9%, respectively; in sow colostrum, the level of total protein increased by 17.0% and immunoglobulins by 20.0%.

S. Bhattarai *et al*. (2019) investigated the relationship between haemoglobin levels in sows and piglets during farrowing, as well as the correlation between sow haemoglobin levels and the probability of foetal death. The researchers found that the average haemoglobin content in the blood of sows and piglets was 106.9 ± 12.2 g/L and 124.4 ± 19.9 g/L, respectively. There is also a positive correlation between these indicators ($P = 0.058$). On the other hand, the probability of dead piglets is negatively related to sow haemoglobin content ($P = 0.021$). The findings obtained by the researchers suggest that the haemoglobin content in the blood of newborn piglets can be increased and stillbirth rates reduced as a result of increasing the haemoglobin level in the blood of sows.

The results obtained by the researchers when using a solution of iron (IV) clathrochelate to farrowing sows 14 and 7 days before farrowing are of great significance. Studies have not observed any stillbirths or iron deficiency anaemia during the critical period of piglet rearing for the development of iron deficiency. The pharmacokinetic properties of iron (IV) clathrochelate administered to gestating sows were characterised by the ability of iron to penetrate the placenta and be excreted in colostrum. The above suggests the antianaemic activity of iron (IV) clathrochelate, and therefore it was proposed for the prevention of iron deficiency anaemia in piglets in production conditions: intramuscular injection of 10% solution of ferrous clathrochelate (IV) to pregnant sows at a dose of 10 mL 14 and 7 days before expected farrowing, which will ensure transplacental iron intake into the foetus; intramuscular injection of a 10% solution of iron (IV) clathrochelate at a dose of 10 mL and cyanocobalamin at a dose of 500 µg in the form of a solution 14 and 7 days before expected farrowing to stimulate erythropoietic function in pregnant sows and piglets born from them (Derkach, 2023). Thus, the opinion of researchers who consider the prevention of iron deficiency anaemia in piglets, which involves the use of iron-containing drugs in farrowing sows, to be effective, is relevant.

Use of iron-containing anti-anaemic drugs in calves

It is well-known that iron deficiency develops in young ruminants and other species, while in adult animals it is a symptom of various pathologies. Therefore, there are many reports in the literature on the effectiveness of various iron-containing drugs for the prevention of anaemia in other species of animals or the treatment of already anaemic animals.

According to V.M. Sokolyuk *et al*. (1995), it was proved that 30% of calves under 3 days of age suffer from anaemia, 35.4% – at 10 days of age, and 33.6% of these animals – at 20-40 days of age. The results of the clinical examination and laboratory analysis of blood serum for bilirubin and trace elements showed that at 1-3 days of age, calves had hypoplastic nutritional deficiency anaemia, which the researchers attributed to unsatisfactory feeding of dry cows. In older calves, myelotoxic anaemia was also observed, which was explained by the toxic effect on the bone marrow of products of impaired metabolism in diarrhoea syndrome. Calf anaemia was characterised by a marked decrease in haemoglobin content compared with changes in the number of red blood cells. Therefore, according to various classifications of anaemia, these animals showed hypochromic and microcytic anaemia. The hemoglobin content in the blood of sick 10-day-old calves was 77 ± 1.2 g/L (105 ± 1.2 g/L in healthy animals), the number of red blood cells, respectively, was 6.1 ± 0.1 T/L compared to 6.5 ± 0.15 T/L in healthy animals. The researchers pointed out that the largest number of calves with anaemia was observed in the last months of the year, in winter and early spring, while in summer the number of such cases decreased by 2-4 times. Thus, a critical decrease in the intensity of hemocytopoiesis occurred in the autumn-winter and spring periods. Therefore, it was in the autumn-winter and spring seasons that the use of drugs to stimulate blood formation in calves was recommended.

Whole milk is known to contain low levels of iron, and therefore studies of iron deficiency anaemia in dairy calves fed whole milk are relevant. J. Allan *et al*. (2020) evaluated the effect of iron supplementation on calf growth rate and blood haemoglobin levels. It was found that iron caused an average increase in growth rate by 78 g/day (standard deviation 18 g/day) in calves of the experimental groups compared to the control. There was also a considerable increase in haemoglobin levels in the blood of calves aged 6 weeks, with haemoglobin levels in animals not receiving iron decreasing by an average of 12.1 g/L. In contrast, calves with higher growth rates in the first 6 weeks were also more likely to have low haemoglobin levels. There were differences in animal growth rates and haemoglobin levels on each farm. However, generally, on all farms, the level of iron in the body of calves affected their daily weight gain during the first 6 weeks. The researchers suggested that the magnitude of the effect depended on the farm, as there was a marked difference between the variations in animal growth rates across farms. The researchers proposed iron injections that led to a considerable increase in haemoglobin levels after 6 weeks, which prevented its decline during the first 6 weeks of life. The use of systemic iron supplements has been shown to have a positive effect. Therefore, considering the current industry recommendations to feed larger volumes of milk over a longer period of time, the researchers suggested systemic iron supplementation for calves fed whole milk. In the future, it was planned to establish a link between early iron deficiency and long-term growth rates of calves, as well as to investigate the relationship with their morbidity before weaning.

J. Joerling & K. Doll (2019) found no direct correlation between serum ferritin and serum

iron. Comparing calves' dairy diets, it was found that reduced levels of ferritin in the blood serum of calves were observed more often in those animals fed milk replacer compared to calves fed whole milk. The findings obtained by the researchers suggest that the determination of haemoglobin and serum iron content is limitedly suitable for the diagnosis of iron deficiency in calves. Serum ferritin was considered more informative, as serum iron levels are subject to physiological fluctuations, while iron deficiency can be caused by inflammation or neoplastic diseases.

V.I. Levchenko *et al*. (2015) investigated the effect of ferrolife on haemocytopoiesis in calves and piglets. They found that double administration of the drug in a dose of 4-5 mL to sick calves increased the haemoglobin content by 20.8%, iron concentration – by 23.5%, red blood cell count – by 31.4% and haematocrit value – by 8.6%; no negative effect on the albumin synthesising function of the liver was observed.

According to the results of studies by many researchers, it was proved that the iron contained in milk replacer meets only the basic needs of this trace element for erythrocytopoiesis. R. Kupczyński *et al*. (2017) established the effect of feeding a protein-iron complex on productivity and iron metabolism, haematological parameters, antioxidant and immune status within 35 days after calf birth. The preparation of the complex involved the enzymatic hydrolysis of milk casein and the addition of ferric chloride to the hydrolysate and lyophilisate. Therewith, experimental groups of calves were created that received low and high doses of iron as part of a protein-iron complex (10 g/day and 20 g/day, respectively) and a control group. Dietary supplements containing a lower concentration of iron had a significant positive effect on the metabolism of the trace element, while a higher dose of concentrate led to an increase in total iron binding capacity, transferrin saturation and a decrease in unsaturated iron binding capacity, which indicated iron overload. Furthermore, treatment with lower doses of iron noticeably increased antioxidant parameters, mainly the overall antioxidant status of the body and the activity of blood glutathione peroxidase. At higher doses of iron in the protein-iron complex, a lower overall antioxidant status was observed. Concentrations of IgG, IgM, insulin, glucose, TNFα, and IGF-1 stayed unchanged in any of the groups after supplementation. The researchers stressed that in practice, the use of protein-iron complex concentrate requires accommodating for the iron content of milk substitutes and other feeds. Only a lower dose of the protein-iron complex had a positive effect on the immune and antioxidant status of the body. The authors plan to focus further research on the investigation of iron concentration in the liver, as well as the relationship between hepsidin-ferroportin and cytotoxicity after adding a protein-iron complex to calf diets.

A. Budny-Walczak *et al*. (2023) studied the effect of protein-iron complex on productivity and iron metabolism, haematological and biochemical parameters when fed whole milk until weaning. The Polish Holstein cattle were divided into a control group, where they were fed whole milk, and an experimental group, where calves received an iron supplement in milk at a dose of 16 g/day. To determine the production performance, calves were weighed at 7 and 42 days of life, and changes in such production parameters as average weight gain, feed conversion rate and growth rate were analysed. Blood was also taken from the jugular vein on days 7, 14, 28, and 42 of life. It was found that the average daily body weight gain, growth intensity and feed conversion rate were the highest in calves of the experimental group. The addition of a protein-iron complex had a substantial effect on iron metabolism in the experimental group of animals.

Doctors described the latest drugs containing the iron complex trimaltol (international non-proprietary name: ferrimaltol), which was developed, synthesised, and tested *in vitro* and *in vivo* in 1980-1981 after the discovery of a new class of alpha-keto-hydroxy-heteroaromatic iron chelators. According to the findings of relevant studies, it was established that natural and synthetic lipophilic chelators, including maltol, formed stable iron complexes and transferred it across cell membranes, as well as contributed to an increase in the intensity of iron absorption in animals (Kontoghiorghes *et al*., 2021). Although the risks of developing iron deficiency anaemia in animals of other species at a young age are much lower compared to suckling pigs, their study is also relevant, and the scheme of preventive measures and treatment of sick animals needs to be improved considering modern world developments in medicine.

Iron-containing drugs in obstetric and gynaecological veterinary practice

Considering the significance of iron for all living things, apart from the use of iron-containing products for the prevention of anaemia, other areas of application of iron-containing products for various pathologies in animals, including obstetric and gynaecological veterinary practice, are being investigated.

V.Y. Stefanyk *et al*. (2017) proved that the effectiveness of intrauterine administration of suppositories containing iron nanoparticles after calving and aftermath of litter stimulated antioxidant functions in the body of cows, contributed to a decrease in the content of lipid peroxidation products. I.B. Kobylukh *et al*. (2017) found that after the application of suppositories with iron nanoparticles to cows (intrauterine after the afterbirth), the content of immunoglobulins of class A (3.9 times), immunoglobulins of class M (2.8 times) in the blood serum significantly increased, while the content of immunoglobulins of class G decreased (4 times). The duration of the service period was reduced by 14 days ($P < 0.05$), and the insemination index decreased by 0.2 units compared to the control.

C.M. Oliveira *et al*. (2012) proposed new methods for studying the placental transition using iron and other nutrients necessary for the survival and maintenance of the embryonic foetus until birth. According to the classification of placental types among animals (cattle, small ruminants, dogs, and cats), iron transfer across the placenta can occur by transferrin-associated absorption through the outer surface of the trophoblast in direct contact with the mother's circulating blood; erythrocyte uptake by the chorionic epithelium in direct contact with a pool of blood extracted from haemotophages; absorption by the chorionic epithelium in direct contact with iron-rich secretions from the endometrial glands and absorption by blood extracts on the surface of the mother and foetus with subsequent phagocytosis of erythrocytes by trophoblast cells. The function of erythrophagocytosis observed after extravasation of blood into the maternal-foetal interface has not been determined in several species. The researchers suggested that iron is transferred to the foetus through trophoblastic erythrophagocytosis in the haemophageal region of the placenta, as well as in the glands of the endometrium.

Thus, the literature presents the findings of studies confirming the effectiveness of iron-containing preparations for obstetric and gynaecological pathologies. However, this issue needs to be investigated more extensively to develop new drugs in relevant dosage forms, register them on the pharmaceutical market, and introduce them into veterinary practice.

Analysis of the pharmaceutical market of iron-containing drugs registered in Ukraine

Currently, colloidal solutions of ferric hydroxides in low-molecular-weight glucose polymers (dextrans) are particularly effective in iron deficiency. In modern veterinary practice, they are administered to newborn animals (mainly piglets and calves) in the first days of life to prevent iron deficiency anaemia and ensure the creation of iron depots in the liver of young animals, as well as to fur-bearing animals when they are fed fish, etc.

Many publications cover the research on the pharmaceutical market for iron-containing drugs. Thus, previous publications have analysed the Ukrainian pharmaceutical market of anti-anaemic drugs for pigs in recent years (Derkach, 2023). In Ukraine, in 2017, the market was represented by 13 medicinal products in the group QB03A Anti-anaemic agents. Ukrainian pharmaceutical manufacturers (O.L.KAR-AgroZooVet-Service, Farmaton, Brovapharma, Research and Experimental Production of the Institute of Epizootology, Biopharm and Vetsintez) provided 38% of the iron preparations (ATC-vet classification). At the same time, 62% of foreign pharmaceutical products in this group are represented by pharmaceutical companies from Estonia, Denmark, South Korea, Poland, France, and the Czech Republic. The medicines contained a dextran complex of ferrous hydroxide, which in some products was combined with vitamins, macro- and microelements. Moreover, the Ukrainian pharmaceutical market offers iron-containing feed additives, ready-made feeds and premixes for animals and poultry of various species in various forms.

In 2017-2022, the modern pharmaceutical market of veterinary drugs in Ukraine was sufficiently supplied with anti-anaemic drugs for pigs, but mostly imported drugs (Fig. 1).

The share of Ukrainian drugs in this group was higher in 2020, but in 2022 the share of imported drugs prevailed again (Table 1).

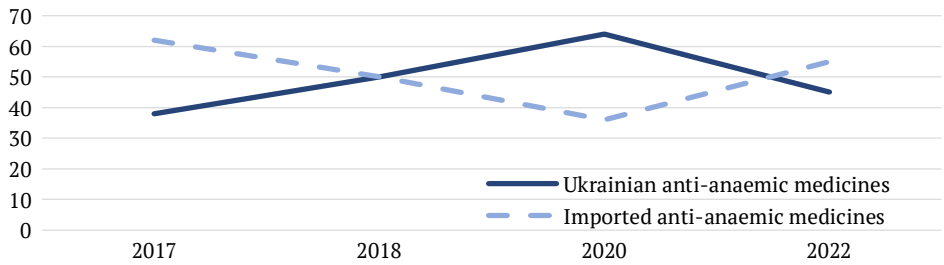

Figure 1. Trends in the domestic pharmaceutical market of anti-anaemic iron-containing drugs for pigs, 2017-2022

***Sourse**: I. Derkach (2023)*

Table 1. Iron-containing drugs registered in Ukraine as of 01.01.2022

Drug name	Registration date	Registration valid until	Registration procedure	Manufacturer	Country of manufacture
Ferrum +	04.03.2021	03.03.2026	re-registration	Biotestlab	Ukraine
Brovaferan-100	24.12.2020	23.12.2025	re-registration	Brovapharma	
Ferrovet +B12®	26.11.2019	25.11.2024	re-registration	Vet-synthesis	
Ferofort	12.04.2017	11.04.2022	registration	Fortis-pharma	
Bioferon Forte	26.11.2019	25.11.2024	registration	Biopharm	

Table 1. Continued

Drug name	Registration date	Registration valid until	Registration procedure	Manufacturer	Country of manufacture
Ferro 2000	07.07.2020	16.12.2023	changes	Dopharma France	France
Gafervit	07.07.2020	06.07.2025	re-registration	Bioveta, a.s	Czech Republic
Ferribion 10%	15.07.2019	14.07.2024	re-registration		
Intrafer-100 V12	07.07.2020	06.07.2025	re-registration	Interchem Verken "De Adelaar" Esti AS	Estonia
Intrafer-200 V12	04.03.2019	03.03.2024	re-registration		
Uniferon	28.02.2018	27.02.2023	re-registration	Pharmacosmos A/S	Denmark

***Source**: I. Derkach et al. (2023)*

According to the analysis of the pharmaceutical market of iron-containing drugs, according to official data provided in the State Register of Veterinary Drugs, it was found that this group is currently represented by 11 anti-anaemic drugs out of 1,394 items registered in Ukraine as of 1 January 2024 (Official website of the State Service of Ukraine on Food Safety and Consumer Protection of People, n.d.). All medicinal products are solutions of trivalent iron in combination with dextran for injection. Of these, 5 drugs (45%) are of Ukrainian origin (manufacturers: Vetsintez LLC, JSC Biopharm LLC, Biotestlab LLC, German-Ukrainian Production Company Brovapharma LLC). Biopharm Pharmaceutical Company offers 2 iron-containing products: Bioferon and Bioferon Forte. The first preparation is a 10% solution of iron dextran, containing excipients phenol and purified water. 1 mL of Biopheron Forte contains 7.5% of the active ingredient ferrodextrin, as well as copper chloride, cobalt chloride, cyanocobalamin, phenol, and highly purified water. These medicinal products are intended for the treatment of animals with anaemia and for the prevention of iron deficiency anaemia in sows, piglets, calves, and lambs.

Ferrovet+B_{12} (Ukraine) contains iron (III) hydroxide complex with low molecular weight dextran, which stimulates the hematopoietic system, increases haemoglobin levels, increases the number of red blood cells, replenishes iron deficiency, and increases animal productivity, and cyanocobalamin, which stimulates hematopoiesis, activates creatine synthesis, lipid metabolism, methionine biosynthesis, and metabolic processes necessary for DNA synthesis. The half-life of iron from blood plasma is 5 hours. Therewith, small amounts of iron are excreted in the urine, while dextran is metabolised and excreted by the kidneys. The drug is intended for the prevention and treatment of iron deficiency anaemia in calves, foals, sows, lambs, puppies, and piglets. If necessary, the injection of the drug in an analogous dose is repeated in 10-12 days.

Brovapheran 100 (Ukraine) is a complex compound of ferric hydroxide and low-molecular-weight dextran. Its pharmacological effect is based on increasing the level of iron and haemoglobin, increasing the number of red blood cells in the body, stimulating the haematopoietic system and improving the safety of young livestock. The medicine is used for the treatment and prevention of iron deficiency anaemia in animals, especially piglets and calves. 1 mL of Ferrum+ (Ukraine) contains 100.0 mg of ferrous iron (in a complex with low molecular weight dextran), 5.0 µg of cyanocobalamin, 200.0 µg of folic acid; excipients: phenol and water for injection. The drug is recommended for the treatment of piglets, sows, calves, lambs, goats, dogs, fur-bearing animals with iron deficiency anaemia and for the prevention of the disease in case of blood loss and haemorrhagic diathesis.

According to the product leaflets, the contraindications were listed by Ukrainian manufacturers as follows: do not use in animals with

insufficient vitamin E and/or selenium in their bodies; animals with diarrhoea; in combination with tetracyclines; do not mix with other veterinary drugs, and do not use in animals with hypersensitivity to the drug's components. Among the warnings for use, it was noted that allergic reactions may occur, and in case of overdose, peripheral vascular collapse, which may result in depression, slowing/acceleration of the pulse, hypotension, cyanosis of the mucous membranes, ataxia, and coma. Cases of no symptoms of toxicity within 12-48 hours after administration of the drug were described, but later, pulmonary edema, vascular and motor collapse, cyanosis, acute liver failure, etc. suddenly developed. In case of an overdose, it is recommended to use the antidote Deferoxamine, which forms water-soluble chelated compounds with iron that are rapidly excreted by the kidneys. In rare cases, animals may die, specifically in breeds that are genetically sensitive to iron-containing drugs. There may be slight pigmentation of the tissues in the injection site, slight swelling that disappears in 2-3 days. Antacids slow down the absorption of iron. Some manufacturers indicated that after the first withdrawal from the vial, the drug should be used within 14 days (subject to aseptic withdrawal and storage in a dark place at 5-25°C), while others indicated that after opening the vial, the drug should be used within 24 hours and that it should not be frozen.

The medicines Intrafer-100 B_{12}, Intrafer-200 B_{12} (Estonia), Feribion 10% (Czech Republic), Ferro 2000 (France), and Uniferon (Denmark) contain a complex compound of iron (III) hydroxide and cyanobalamin. These drugs are prescribed intramuscularly and subcutaneously for the prevention and treatment of calves and piglets (Ferro 2000 and Uniferon were recommended only for pigs, including piglets) with iron deficiency anaemia. Hafervit injectable (Czech Republic) contains ferrous dextran, porcine serum immunoglobulin, thiamine hydrochloride, riboflavin, pyridoxine hydrochloride, nicotinamide, calcium pantothenate, copper chloride, and cobalt chloride anhydrous. It is prescribed only for pigs.

According to the manufacturers' official instructions for use, iron in combination with low-molecular-weight dextran is a low-toxic anti-anaemic drug that reliably increases haemoglobin levels. After parenteral administration, iron accumulates in the tissues and is gradually released from the dextran complex, binding to proteins. Up to 60% of iron dextran is absorbed 3 days after administration, and up to 90% within 1-3 weeks.

Conclusions

Iron-containing medicines are particularly relevant in veterinary medicine for the prevention of iron deficiency anaemia in suckling piglets. To stimulate erythrocytopoiesis in the hematopoietic organs, animals of this species are administered iron-containing compounds on the days 3-5 after birth, the most commonly used of which are iron-dextran preparations worldwide. There are a range of advantages and disadvantages regarding the methods and forms of their application, but in the system of preventive measures for pig health, such prevention is generally accepted. The review analyses the various possibilities of using iron-containing drugs in veterinary medicine and describes new approaches to this with due regard for the development of modern medicine and pharmaceuticals. The study analysed the pharmaceutical market of iron-containing veterinary drugs registered in Ukraine in recent years. Notably, the share of relevant Ukrainian medicines is lower than that of imported pharmaceutical products, which should be a motivational task for Ukrainian producers. There is a general trend towards the combination of iron dextran with vitamins (especially

cyanobalamin), macro- and microelements in modern anti-anaemic iron-containing drugs. Ukrainian scientists have paid great attention to the study of the prooxidant effect of these drugs and the effect of selenium on lipid peroxidation and the antioxidant system in general. The literature provides data on the use of iron-containing compounds in pregnant females to provide microelements to piglets after farrowing. Some scientists proved that the formation of a reserve of the trace element in the liver/blood of newborn piglets and in colostrum/milk of sows can be achieved by using iron-containing preparations during pregnancy and lactation, although others have refuted this. For this reason, this prevention scheme has not been widely used in veterinary medicine. At the same time, the authors have already proved that in production conditions for the prevention of iron deficiency anaemia in piglets, intramuscular injection of ferrous clathrochelate (IV) solution to farrowing sows 14 and 7 days before the expected farrowing has a reliable preventive effect (provided transplacental intake of iron into the foetus) and intramuscular injection of 10% solution of ferrous clathrochelate (IV) and cyanocobalamin 14 and 7 days before expected farrowing (stimulated erythrocytopoiesis in farrowing sows and piglets born from them).

The findings presented in this study are significant for clarifying the possibilities of using new iron-containing drugs in veterinary medicine. For instance, this is the case with iron-containing medicinal substances in which the trace element has high valence forms. Only their physicochemical properties are well-studied, and the issues of pharmacokinetics and pharmacodynamics require further in-depth research and development of a new scheme for the effective prevention of iron deficiency in animals, which we consider to be promising areas for further research in the context of the subject under study.

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Conflict of Interest

None.

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Наукове обґрунтування застосування залізовмісних препаратів у ветеринарній медицині

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Анотація. Актуальність дослідження зумовлена необхідністю узагальнення сучасних уявлень про застосування залізовмісних лікарських засобів у ветеринарній медицині та їх наукового обґрунтування. Мета дослідження – провести аналіз результатів останніх експериментальних даних, представлених у літературі щодо фармако-токсикологічних властивостей залізовмісних препаратів та особливостей їх використання у ветеринарній медицині. Під час дослідження використано метод аналізу літературних джерел з формулюванням відповідних обґрунтованих висновків та їх узагальнення чи порівняння. Особливо актуальними залізовмісні лікарські засоби у сучасній ветеринарній медицині є за профілактики залізодефіцитної анемії у поросят. Застосування залізодекстанових препаратів є науково обґрунтованим і необхідним превентивних заходом у сучасному свинарстві. Крім того, у статті розкриваються нові підходи до розробки ефективних антианемічних препаратів тваринам інших видів, зокрема телятам. Розкрито дискусійні питання щодо застосування залізовмісних препаратів вагітним самкам з метою

профілактики залізодефіциту у народжених від них тварин. Аналіз літературних даних, представлений у статті, засвідчує високий ступінь наукового інтересу до вивчення фармако-токсикологічних властивостей заліза у високих валентностях (зокрема заліза чотирьохвалентного у клатрохелатній формі) з метою їх застосування у медицині. Наведений огляд літературних джерел засвідчує про багатовекторність застосовування у ветеринарній медицині залізовмісних лікарських речовин у різних лікарських формах. Встановлено основні тенденції на фармацевтичному ринку залізовмісних препаратів, зареєстрованих в Україні. Упродовж останніх років зростає кількість науково обґрунтованих доказів, які вказують на ефективність залізодекстранового комплексу в комбінації з мікро- та макроелементами і вітамінами. Нині у світовій ветеринарній практиці застосування залізовмісних препаратів із врахуванням їх науково обґрунтованих та експериментально доведених фармакологічних властивостей є надзвичайно перспективним. Матеріали статті становлять практичну цінність для розширення можливостей застосування нових форм заліза у ветеринарній медицині

Ключові слова: залізо; залізодефіцит; анемія; поросята; телята; профілактика