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Alfacalcidol (1-Alpha-Hydroxycholecalciferol) and Its Efficacy in Broiler Nutrition

Review Article

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ABSTRACT

Alfacalcidol (1-alpha-hydroxycholecalciferol) is a synthetic analog of vitamin D. This medicine has been considered as a precursor for calcitriol (1, 25-dihydroxyvitamin D_3) which alters to calcitriol after hydroxylation. Alfacalcidol is one of the most effective compounds that enter the body and can be converted to an active form and be effective in conditions that the body is challenged with vitamin D insufficiency or hypocalcemia. The clinical benefits of alfacalcidol are relevant to stimulating the absorption of calcium and phosphorus, improving muscle functions, and improving bone mineralization. Several studies have been conducted regarding the supplementation of alfacalcidol in broiler chickens diet. In summary, results of some studies revealed that the effectiveness of alfacalcidol significantly decreases with the increase in dietary calcium level. This vitamin D metabolite not only acts by hydrolyzing phytate molecules in a phytase-like manner, but also enhances the utilization of phytate phosphorus in other procedures. Also, results of a research trial showed that the best results regarding performance criteria and bone tissue formation in broiler chickens eventuated when 5 µg of alfacalcidol and 1500 IU of cholecalciferol/kg of diet were supplemented to diet.

KEY WORDS alfacalcidol, broiler chickens, cholecalciferol, phytase, phytate phosphorus.

INTRODUCTION

Alfacalcidol (1-alpha-hydroxycholecalciferol) is a synthetic vitamin D analog that was introduced in the early 1970s. Alfacalcidol is metabolized by hydroxylation in the liver to calcitriol the biologically active form of vitamin D. The alfacalcidol can be effective in the situations where the body is challenged with vitamin D insufficiency or hypocalcemia. Alfacalcidol is one of the most effective compounds that after entering the body has become an active form and can be effective in situations where the body is challenged with vitamin D insufficiency or hypocalcemia. The clinical benefits of alfacalcidol are relevant to stimulating the absorption of calcium and phosphorus, improving muscle functions, and improving bone mineralization. The compounds which have been consumed in the poultry industries as a source of vitamin D include cholecalciferol and to a lesser extent 25-hydroxycholecalciferol. As a vitamin D analog, alfacalcidol may become a feed additive in the hereinafter (Ghasemi *et al.* 2019; Landy *et al.* 2021; Shams *et al.* 2022). Since it is feasible to mass produce alfacalcidol, the accessibility of this compound for inclusion in boiler is much enhanced. Decisions on the use of alfacalcidol as a substitution for cholecalciferol or in combination of cholecalciferol may become a actuality. Thus, understanding of the biological function of cholecalciferol and alfacalcidol in metabolism is required for the ability to understand the efficiency of this compound in broiler diets.

Chemical structure

One-alpha-hydroxycholecalciferol is a member of fat-soluble secosteroids in charge of enhancing intestinal absorption of calcium, magnesium, and phosphate, and numerous biological effects in which the hydrogen at the 1-alpha position is replaced by a hydroxyl group (Figure 1). The chemical formula of this substance is C27 H44 O2 and it has a molecular weight of 400.643 g/mol. This composition is colorless, sensitive to temperature, light and air, and it must be stored at 2–8 ˚C under nitrogen (Sweetman, 2002). Also, contingent on temperature and time, there is a possibility of modifiable isomerization to the pre-alfacalcidol in the liquid mixture. This compound is soluble in water, alcohol and fatty acids.

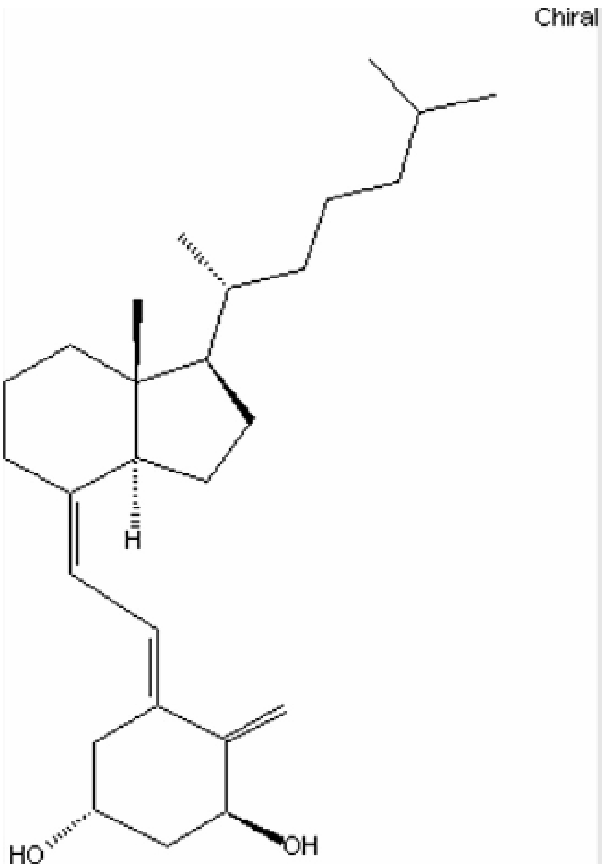

Figure 1 Chemical structure of 1-alpha-hydroxycholecalciferol

Calcidiol and alfacalcidol

The binding capacity of alfacalcidol to natural receptors of calcitriol is almost twice that of ergocalciferol. However, the binding capacity of this metabolite of vitamin D to the natural receptors of calcitriol is 500 times lower than that of calcitriol. However, this metabolite is considered a suitable substitute for calcitriol. This form of vitamin D must be hydroxylated by 25-hydroxylase in the liver afore it becomes metabolically active. This procedure is done quickly and is not adjustable, so the time required for effectiveness is comparable to calcitriol (Skelly *et al.* 2012).

Pharmacokinetics

Alfacalcidol, similar to other vitamin D metabolites, is well absorbed from the digestive system, since this compound is soluble in fats; its absorption is accelerated by the existence of bile salts. As it is easily attached to the alpha globulins of the blood and then quickly distributed in the body, it is hydroxylated and finally turns into calcitriol. Little intact alfacalcidol that is not converted to calcitriol, undergoes 24-hydroxylation and oxidative cleavage of the side chain before excretion in the bile. The main places for metabolism of alfacalcidol are the liver and kidneys. The main sites for long-time storage of vitamin D and its metabolites consist of adipose tissue and muscle. Excretion of alfacalcidol and other metabolites of vitamin D occur mainly in bile and feces, and only a small amount of it is excreted through urine (Holick *et al.* 1977). Regarding the bioavailability of this substance, it can be mentioned that this metabolite of vitamin D is 100% bioavailable (Dollery, 1999).

Targets-pharmacodynamics

Alfacalcidol, similar to other vitamin D metabolites, binds with great affinity (Kd=10-8M) to unique nuclear-cytosol receptors on different textures. Although, it's physiological function is the consequence of its quick biological conversion (hydroxylation) to calcitriol, which binds to these receptors and causes the synthesis of mRNA and protein. These results in the transfer of calcium and phosphorus in clinically important objective textures such as the small intestine bone and muscle (Joffe *et al.* 1994).

Therapeutics

Alfacalcidol have been consumed orally (capsule, drops) or intravenous injection in the prevention and treatment of physiological conditions caused by vitamin D insufficiency, such as rickets (Muraki *et al.* 1983), osteoporosis Nishii (2003) and hypocalcemia related to disorders including hypoparathyroidism (Halabe *et al.* 1994) and decreased parathyroid hormone levels in secondary hyperparathyroidism.

Supplementation of alfacalcidol causes a dose-dependent enhance in calcium and phosphorus absorption, eversion of myopathy, and improvement of bone tissue formation. In cases of severe kidney failure, where symptoms of vitamin D deficiency are observed, alfacalcidol (or calcitriol) should be used, because cholecalciferol needs hydroxylation to become its active form by the kidneys. Since vitamin D metabolites may be the cause of hypercalcemia, plasma calcium levels should be regularly monitored (Akiba *et al.* 1998).

Adverse effects

Extra consumption of vitamin D induces hypercalcemia and related complications, such as hypercalciuria, aberrant calcification, and kidney and cardiovascular failure. Clinical sign of excessive use of this metabolite include anorexia, vomiting, diarrhea, polyuria, sweating, headache, thirst and dizziness. Hypercalciuria, hypercalcemia, and hyperphosphatemia are among the early symptoms of poisoning. Renal failure and premature death have been reported due to the combined effects of hypercalcemia and uremia. Chronic overuse of this substance induces extensive texture calcification, especially in the kidney, blood vessels, heart, lungs, and skin (Vervloet, 2014).

Clinical research

Pre-clinical research

Generally, cholecalciferol has been consumed as a commercial source of vitamin D in poultry feed. It is well known that cholecalciferol is converted into 25-hydroxycholecalciferol under the influence of 25-hydroxylase in the liver. The 25-hydroxycholecalciferol is converted into calcitriol in the kidney under the influence of 1-alpha hydroxylase thereafter. Nowadays, the consumption of synthetic compound 25-hydroxycholecalciferol in poultry feed has been authorized. Soares *et al.* (1995) evaluated the supplementation of 25-hydroxycholecalciferol in poultry feed, and the results indicated that the biological activity of 25-hydroxycholecalciferol is almost twice that of cholecalciferol. Dollery (1999) reported that the use of 0.3 and 0.9 mg alfacalcidol/kg/d in rats and rabbits caused a decrease in body weight of babies' mouse at birth, although the growth of embryonic and fetal stem cells was not affected by the consumption of this metabolite.

Supplementation of alfacalcidol in broiler diet as a substitute for cholecalciferol

Since the use of calcitriol in poultry feed is not cost-effective and the production of alfacalcidol is cost-effective, thus the use of alfacalcidol as a substitute for calcitriol is under investigation (Biehl *et al.* 1998). Haussler *et al.* (1973) investigated the possibility of substituting alfacalcidol instead of cholecalciferol in the feed of broiler chickens; the results indicated that this metabolite is a suitable substitute for cholecalciferol. Boris *et al.* (1977) stated that the efficiency of alfacalcidol in bone mineralization is comparable to calcitriol. Landy *et al.* (2014) investigated the possibility of using 5 µg of alfacalcidol/kg of broiler diet as a substitute for cholecalciferol; the results showed that the addition of 5 µg alfacalcidol/kg of diet compared to 5000 IU cholecalciferol/kg of diet improved performance-related parameters and improved some parameters related to tibia, although it simultaneously increased the incidence and severity of tibia dyschondroplasia. Edwards *et al.* (2002) stated that the activity of alfacalcidol is eight times as effective as cholecalciferol.

Supplementation of alfacalcidol in broiler diet on growth performance

Landy *et al.* (2015) reported that supplementation of alfacalcidol to the Ca and P sufficient diet had not any marked effect on growth performance and parameters related to tibia, which showed that alfacalcidol could not promote performance criteria and parameters related to tibia of broilers when broilers fed Ca and P adequate diet and cholecalciferol provided at optimum level. Unfortunately, most researchers investigated efficacy of alfacalcidol in Ca-P adequate diet and there has been dearth of information on the efficacy of alfacalcidol on performance criteria when Ca and P provided adequate. Warren *et al.* (2020) reported that using alfacalcidol in Ca adequate diet my decrease the growth due to Ca toxicity or antagonism, and its efficacy must be investigated when inadequate levels of Ca are provided. Diaz (2018) reported that alfacalcidol can improve performance criteria by increasing digestibility of Ca and there is a quadratic relationship between dietary Ca inclusion, increased Ca digestibility and growth of the birds. Han *et al.* (2009) stated that addition of 5 µg alfacalcidol/kg in combination of 5 µg cholecalciferol/kg had negative effects on growth performance indices of broiler chickens, which showed that alfacalcidol, could not increase performance criteria of broiler chickens when basal diet contained sufficient levels of cholecalciferol. Han *et al.* (2012a) stated that supplementation of alfacalcidol in Ca-P deficient diet could improve growth performance and meat color of broiler chickens. It seems that alfacalcidol can improve growth performance of broiler chickens in Ca-P deficient diet due to more digestibility and absorption of Ca.

Supplementation of alfacalcidol and phytase in broiler diets

The hydrolysis of phytate phosphorus (PP) by poultry and other non-ruminants is limited because they do not have the microflora required for significant hydrolysis of the phytate molecule. Enhancing public pressure to decrease phosphorus excretion through poultry manure has increased researches to enhance the availability of PP. One of these methods is addition of phytase enzyme to the feed to enhance the hydrolysis of phytate molecule (Nelson *et al.* 1971; Simons *et al.* 1990). In this regard a variety of hydroxylated analogs of vitamin D, including calcitriol (the hormonal form of vitamin D), and its synthetic analog, alfacalcidol, have also been evaluated (Edwards, 1993; Biehl *et al.* 1995; Mitchell and Edwards, 1996; Biehl and Baker, 1997). Several studies have shown that calcitriol or alfacalcidol promote PP retention additively and synergistically with phytase enzyme (Edwards, 1993; Mitchell and Edwards, 1996; Biehl and Baker, 1997).

Snow *et al.* (2004) evaluated the effects of using alfacalcidol alone or in combination with phytase during starter period in broiler chickens fed a basal diet containing 1.3 g PP/kg of diet; the findings showed the affirmative effects among alfacalcidol and phytase. Similarly, Driver *et al.* (2005) reported that alfacalcidol and phytase synergistically cause phosphorus retention. Kheiri *et al.* (2019) evaluated the effects of using 500 FTU of phytase alone, 5 µg alfacalcidol/kg of diet alone or using combination of them in Japanese quail, showed that using both of these compounds increases the percentage of tibia ash compared to other groups. The results show that this metabolite of vitamin D does not only act by hydrolyzing phytate molecules similar to phytase, but also increases the use of phytate phosphorus by other mechanisms. The mechanism of hydrolysis and absorption of phosphorus when using these analogs is still under investigation.

The effectiveness of alfacalcidol and its relevance with calcium level in broiler diet

Several studies have shown that the supplementation of alfacalcidol to phosphorus-deficient diet improves performance criteria and bone ash in broiler chickens (Edwards, 1993; Biehl and Baker, 1997; Snow *et al.* 2004). Research on the use of 25-hydroxycholecalciferol has shown that diets containing 25-hydroxycholecalciferol increase the retention of PP at a less content of calcium in the diet (Ledwaba and Roberson, 2003). Edwards *et al.* (2002) stated that alfacalcidol improved performance related parameters of broiler chickens (1-16 days old) when dietary non-phytate phosphorus levels did not reach 0.3%, however it enhanced tibia ash. Additional studies showed that the inclusion of 5 µg of alfacalcidol/kg of diet and 1000 FTU phytase/kg of diet improved growth and bone ash in broilers fed diets deficient in calcium and phosphorus (Driver *et al.* 2005). Han *et al.* (2012b) in an experiment investigated the effectiveness of alfacalcidol in phosphorus-deficient diets with different levels of calcium. The results showed that alfacalcidol negatively responds to the dietary calcium level.

Supplementation of alfacalcidol alone or in combination with cholecalciferol

Landy and Toghyani (2014) investigated the efficiency of using 5 µg alfacalcidol/kg of diet as a substitute for cholecalciferol; the results showed that alfacalcidol as a substitute for cholecalciferol can promote performance criteria and parameters related to tibia in broilers, although the findings were not statistically significant. Han *et al.* (2009) stated that inclusion of alfacalcidol to the diet of broiler chickens that contained adequate levels of cholecalciferol had a negative effect on performance criteria. Edwards *et al.* (2002) stated that the inclusion of alfacalcidol to a basal diet that does not contain cholecalciferol can improve the daily weight gain of broiler chickens. Furthermore, Landy *et al.* (2015) stated that addition of 5000 IU cholecalciferol/kg of diet to inadequate calcium-phosphorus diets containing 500 FTU phytase and 5 µg of alfacalcidol/kg reduced Tibia ash, calcium and phosphorus. In another study conducted by Landy and Toghiani (2017), the results showed that supplementation of alfacalcidol to a diet that did not contain cholecalciferol increased bone ash in broilers, although it had no effect on the incidence and severity of tibial dyschondroplasia. According to the relevant reports in this regard, in another study, Kheiri and Landy (2019) evaluated the effects of using 5 µg of alfacalcidol/kg of diet alone or in combination with different levels of cholecalciferol in inadequate calcium-phosphorus diets, the results showed that the best results regarding to performance criteria and bone mineralization obtained in broiler chickens fed diets containing 5 µg of alfacalcidol and 1500 IU cholecalciferol/kg of diet.

CONCLUSION

In conclusion, it seems that the effectiveness of alfacalcidol decreases with the increase in dietary calcium level. This vitamin D metabolite not only acts by hydrolyzing phytate molecules in a similar way to phytase, but also enhances the utilization of phytate phosphorus in other procedure. Furthermore, the results of an experiment indicated that the best results regarding to growth performance and bone mineralization in broiler chickens obtained when 5 µg of alfacalcidol and 1500 IU of cholecalciferol/kg of diet were supplemented to diet containing 500 FTU phytase/kg.

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