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The Roles of Ionophores in Ruminant Animalsnutrition: A Review

*[1]Babandi, B., [2]Ashiru, R M., [3]Baba.M.,[4]Gumel, I.A.,[5]Umar, Z.[6]Baso, M.U.,[7]Mustapha, Y[1]Ubayi K.M and [8]Sariyyu. S

[1]*Department of Animal Health and Production Binyaminu Usman polytechnic, Hadejia P.M.B 103*
[2]*Department of Animal Science Kano University of Science and Technology, WudilP.M.B 3244*
[3]*Department of Animal Science BayeroUniversty, Kano P.M.B 3011*
[4]*Department of Animal Science Federal University, Dutse Jigawa State P.M.B 7156*
[5]Department of BiologyJigawa State College of Education Gumel P.M.B 1002
[6]*Department of Agric Education Federal College of Education, Katsina P.M.B 2041*
[7]*Department of Regulatory Affairs, Nigerian Institute of Animal Science plot 1882, KabusaOkanjeDistric, Abuja*
[8]*Department of Animal Health and Production Audu Bako College of Agriculture Danbatta, Kano State*

Abstract
The review examines the role of ionophores to improve performance in ruminants, this will enable the design of specific dietary programs to improve ruminant animals' nutrition, health and productivity. Ionophores have been used in the animal industry of most nations for various reasons. Available literatures have attested to the importance of ionophores in manipulating rumen ecology to favour non harmful microorganisms as against the harmful ones. In addition, inclusion of ionophores in the diets of ruminant animals dictates the type and amount of volatile fatty acids that result from fermentation activities, for instance ionophores have been found to enhance the production of propionic acid as against acetic acid. Ionophores also have positive impact on the environment through reduction in methane emission that exacerbate global warming.The key areas reviewed in this article points to some positive effects of feeding ionophoreson animal productivity such as weight gain, milk and meat production, control of methane emissionand control of some rumen digestive disorders. Other positive attributes of ionophores include enhanced energy and protein metabolism, reduce proteolysis and improvement in reproductive performances. However, the use of ionophores for improvements in utilization must not interfere with the health of the animal and should not be continuous but progress in feeding with ionophores that leads to better fermentation in the rumen, digestion in the gastrointestinal tract and metabolism should be given utmost attention. In conclusion ionophores could be used to improve animal production efficiency and mitigate the effect of methane on the environment.

Key words: ionophores, rumen fermentation, methane emission

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I. Introduction

The ever-increasing human population and attendant increase in the demand for animal protein for human consumption necessitated the need for nutritionist to explore the possibilities of manipulating rumen environment in order to improve feed conversion efficiency and by extension, animal productivity. Efforts are ongoing to find a sole feed supplement that can improve the rate of gain and efficiency of productions as well as reproduction, to prevent certain diseases or preserve feeds,to specifically modify the micro flora of the host by altering the rumen flora to aid digestion and can also be beneficial for production (Azzaz*et al.*, 2012). Thus, some antibiotics can improve the efficiency of production of healthy animals receiving optimal nutritional diets. These compounds are classified as ionophores antibiotics, or probiotics (Hossam *et al.,* 2015). Several strategies have been used to achieve rumen ecology manipulation using some dietary additives or supplements including buffers, hormones, enzymes, synthetics amino acids, essential oils and microbial feed supplements (Azzaz*et al.*, 2013, 2015a; Murad and Azzaz, 2013; Morsy*et al*., 2012;Kholif*et al*., 2012). In the mid-1970s a number of active compounds were discovered that when fed, can improve ruminant production efficiency. Ionophores were introduced originally in poultry production as an anticoccidial agent in 1971. Since the mid 1970's ionophores have been extensively used to manipulate rumen fermentation, to improve the efficiency of feed utilization, and to increase weight gain of growing cattle (Igneacio*et al.,* 2005). They have since been used in feed for ruminants to improve the efficiency of feed conversion, for the regulation of ruminal fermentation end products and to control metabolic diseases (MCGuffey*et al*., 2001). Ionophores reduced rumen ammonia and reduced luminal break down of dietary protein in dairy cattle fed with Monensin(Ali Haimoud*et al*., 1995). Ionophores improved energetics of rumen fermentation caused by Monensinas illustrated by the work of Rogers and Davis (1982). Ionophores are also feed additives used in cattle diets to increase feed efficiency and body weight gain, they are also compoundsthat alter rumen fermentation patterns. Ionophores can be fed to any class of cattle and can be used in any segment of beef cattle industry. The objective of the paper is to review the role of ionophores in ruminant nutrition, this will enable the design of specific dietary programs to improve ruminant animals' nutrition, health and productivity.

DEFINITION OF IONOPHORES

An ionophore is a chemical species that reversibly binds ions (Bakker *et al*., 1997). Ionophore means "ion carrier" as these compounds catalyze ion transport across hydrophobic membranes such as liquid polymeric membranes (carrier-based ion selective electrodes) or lipid bilayers found in the living cells or synthetic vesicles (Bakker *et al*., 1997). They are small hydrophobic molecules that dissolve in the lipid bilayer and increase the permeability of certain ions (Hossam *et al.,* 2015). Furthermore, according to Azzaz*et al.* (2015b) ionophores are organic compounds mainly from streptomyces species that facilitate selective transportation of ions across the outer cell membrane.Hossam *et al.* (2015) also reported that ionophores act by interrupting transmembrane movement and intercellular equilibrium of ions in certain classes of bacteria and protozoa that inhabit the gastrointestinal tract. Ionophores are highly lipophilic substances capable of interacting stoichiometrically with metal ions, thereby serving as a carrier by which these ions can be transported across a bimolecular lipid membrane (Hossam *et al.,* 2015; McGuffey *et al.,* 2001). Ionophores also are toxic to many bacteria, protozoa, fungi and higher organisms and thus fit the classical definition of antibiotics (Pressman, 1976).However, ionophores are growth promoters used in animal feed to improve cattle productivity, improving the microbial fermentation in the rumen, decrease of the bacterial population reduce the production of methane and acetate, causing it to generate more metabolizable energy per kilogram of food consumed.

TYPES OF IONOPHORES USED FOR RUMINANT ANIMALS

Hossam *et al.* (2015) stated that there are two types of ionophores used for cattle viz;Laso-locida and Monessen. These ionophores are produced by various strains of Streptomyces and include Monensin (Rumensin^{TM}), Lasa-locid (Bouatec^{TM}), Laid lomycin propionate (Catalyst^{TM}), Salinomycin and Narasin. Monensin is polyether anti-biotic which is orally fed as a sodium salt and considered the most widely used preparation of the different kinds of ionophores (Yang *et al*., 2007).Bergen and Bates (1984) reported that benefits derived by ruminants from the biological actions of ionophores are classified into three areas of effects as follows:

i. Increased efficiency of energy metabolism of rumen bacteria and /or the animal
ii. Improved nitrogen metabolism of rumen bacteria and/or the animal
iii. Retardation of digestive disorders resulting from abnormal rumen fermentation.

Each action provides nutritional and metabolic advantages to the ionophores-supplemented animal over a non-supplemented animal (Hossam *et al.,* 2015). The animal transforms these into increased production or improved efficiency.

IMPORTANCE OF IONOPHORES IN RUMINANT NUTRITION

The nutritional advantages of ionophores supplementation in ruminant nutrition cannot be over emphasized, among which includes aiding in increased animal production and or improved efficiency. Economic benefits derived from feeding animal with ionophores include but not limited to improved feed efficiency, increased weight gain and reduction in morbidity and mortality rate (Van Navel and Demeyer, 1988). In addition, MCGuffey*et al.* (2001) reported that cows fed Monensin had higher average milk yield (1.3Kg- 1day^{-1}), higher milk protein yield (26g day^{-1}), lower milk fat and protein percentage while, milk fat yield and dry matter intake were not different for control and Monensin fed cows. Also, Symanowski*et al.* (1999) observed improvement in milk production efficiency by 3.6%, for Monensin premix treated cows while, MCGuffey and Giner-chavex (1998) reported that Monensin premix supplemented cows showed enhancement in milk production efficiency by 7.0%. Ionophores also help to reduce the amount of excreta and gaseous emissions from animals, thus, a positive effect on the environment occurs when ionophores are fed. Other important effects of ionophores supplementation include increasing the concentration of propionate, lowering the concentration of acetate, increased ruminal pH, lowering lactate and methane production, increase feed intake, slowing down passage in the gastrointestinal tract, increases dry matter digestibility, increases protein digestibility, decreases ruminal deamination, decreases ruminal proteolysis, decreases ruminal ammonia, raises a protein sparing effect, can be used with other growth promoters (Bergen and Bates, 1984).

Ionophores such as Monensinare antimicrobials used in commercial beef and dairy cattle diets in Canada to modulate feed intake, control bloat and improve feed efficiency. Monensin causes a change in the bacterial species in the rumen resulting in an increased proportion of propionate. At times, Monensinmay also cause a decrease in the numbers of rumen protozoa in the rumen, which provide a habitat for the rumen methanogens (Guan*et al*., 2006). Furthermore, decreases in methane (CH_4) production of up to 10% is possible with Monensin, depending upon the dose but the reduction in CH_4 is not always sustained over time. This limits the usefulness of Monensinas a long-term solution to CH_4 abatement (Derek and Goodwin, 1977). Ionophores have also been used to positively affect reproductive process in beef cow herds. The post-partum interval can be decreased in cows gaining body weight and body condition score as a result of improved nutritional status associated with ionophores supplementation. However, the change in cow body weight and condition score during the supplementation period strongly influenced overall post-partum interval response (Sprott*et al.*, 1988).

INFLUENCE OF IONOPHORES ON RUMEN FERMENTATION

Ruminant bacteria maintain high intercellular potassium and low intracellular sodium concentrations (Chow and Russell, 1992) and conversely, the ruminal environment contain high sodium and low potassium concentrations. Thus, ruminal bacteria rely heavily upon ion gradients (both K^+ and Na^+ gradients) to take up nutrients and to establish a proton motive force (PMF) (Rossen, 1986; Dawson and Boling, 1987; Van Kessel and Russell, 1992). Ruminal pH is somewhat acidic due to volatile fatty acids (VFA) concentrations; however intracellular pH of many ruminal bacteria is near neutral, thus creating an inwardly directed proton gradient (Russell and Strobel, 1989). Monensin is a metal/proton antiporter that can exchange H^+ for either Na^+ or K^+ (Pressman, 1976; Russell and Strobel, 1989). Once inserted in the membrane, Monensinexchanges intracellular potassium ions for extracellular protons (Russell and Strobel, 1987). However, because the potassium gradient is greater than the sodium gradient, protons accumulate inside the bacterium (Chow *et al.*, 1994). The bacterium reacts to this cytoplasmic acidification by activating a reversible adenosine triphosphate phase (ATP-phase) to pump these protons out of the cell (Booth, 1985).Additionally, other ATP – utilizing primary pumps for Na^+ removal and K^+ uptake is activated to re-establish ion gradients; resulting in the uncoupling of ATP hydrolysis for growth, thereby decreasing intracellular ATP pools, leading to cellular death (Russell and Strobel, 1987; Russell and Strobel, 1989).

EFFECT OF IONOSPHORES ON ANIMAL PRODUCTIVITY

Weight Gain

Management practices to improve growth performance of ruminants include manipulating feed so that the rate of digestion is not too rapid, which could result in digestive problems, nor too slowwhich could result in poor feed efficiency rates (Hatfield *et al*., 1997). Rumen metabolic modifiers (ionophores) have been shown to have positive effect on live weight gains, feed conversion and a resultant decrease in carcass fatness. The metabolic modifiers are thus, mainly developed to improve the efficiency and profitability of meat production and subsequently to improve carcass composition (Dikeman, 2007). Carboxylic polyether ionophores antibiotic, produced by various strains of Streptomyces species, are compounds of these rumen metabolic modifiers and include products such as Monensin, Lasalacideand Salinomycine(Bergent and Bates, 1984).Nagaraja (1995) reported that the overall effectiveness of these compounds seems to be similar, although they may vary, depending on the dietary inclusion level, diet composition and various inherent animal factors. The economic benefits derived from feeding ionophores include feed efficiency, increased weight gain and a reduction in morbidity and mortality rate (Van nevel and Demeyer,1988). However, reviews of numerous grazing trials using steers and heifers indicated that supplementation with 155 mg/day of Monensinresults in an improvement in average daily gain of 0.18 lb./day or a 1.3 5% increase compared to non-supplemented control cattle (Kunkle *et al*., 2000).

Milk Production

Milk production could be altered as a result of ruminal fermentation, since energy balance is improved, which enhances milk production and efficiency in ruminant animals. The magnitude of these effects appears to be determined by several factors, many of which are poorly understood. The response in milk production appears to be independent of the stage of lactation in which the supplementation of ionophores was initiated. However, the type of diet fed and body condition of cows may affect the milk production responses to ionophores. For instance, supplementing diet that contain more than 50% forage with Monensinincreased milk production more than providing Monensinin diet that contain less than 50%forage (Hossam *et al.,* 2015) likewise Monensinhad no significant effect on milk production of cow classified as fat. Ionophores may slightly depress milk fat and milk protein percentages, however, because of increase in milk production efficiency of milk production is improved(Hossam *et al.,* 2015). The improved efficiency of milk production by cow fed ionophores has been attributed to the increase in availability of energy from feeds caused by the ionophores effects on ruminal fermentation (increased propionate and decreased methane)(Hossam *et al.,* 2015). Other factors that could potentially contribute to improved efficiency are the ionophores induced reduction in ruminal protein degradation as well as decreased ketosis caused by increased propionate production in the ionophores –

fed dairy cows (Igneacio*et al*., 2005). Davis and Brown (1970) proposed that factors produced in the rumen with milk fat – depressing diets were linked to the reduction in milk fat. Such diets were typically low in fiber and resulted in a decreased molar proportion of acetate and an increased molar proportion of propionate in rumen VFA. These dietary effects on rumen acetate and propionate are mimicked by ionophores in the trials summarized above generally tended to show some reduction of milk fat percentage. However, studies have linked reduced milk fat percentage to the production of trans-octadecenoic acids by ruminal micro-organisms during biohydrogenation of unsaturated fatty acids (Grinari*et al.*, 1998). The authors further reported that dietary unsaturated fatty acids and a low fiber diet interacted to produce a dramatic reduction in milk fat.

Meat Production

Results of previous studies Zinn (1980 and 1987); Montgomery *et al*. (2003) showed no effect of ionophores supplementation on carcass characteristics. Beermann (1995) concluded that effects of ionophores on dressing percentage and carcass composition are too small to be of economic importance. Even though all ionophores are fermentation products, it is important that they should be viewed as decrease chemical entities with their own distinct properties rather than as a uniform group with uniform effect in order to obtain maximum benefits (Wessels, 1993). The subsequent lack of literature regarding the effect of dietary ionophore inclusion on production performance and carcass composition of intensively fed lamb is one shortcoming that needs to be addressed, since it hinders the decision-making process of producers and feed manufactures.

INFLUENCE OF IONOPHORES ON THE CONTROL OF METHANE EMISSION IN RUMINANT NUTRITION

Changes in fermentation associated with ionophore feeding have resulted in an increased production of propionate and decreased production of methane, lactic acid and froth formation in the rumen. A decreased degradation of protein and de-amination of amino acids in the rumen has also been recorded (Bergen and Bates, 1984). Due to these changes in rumen fermentation, the efficiency of energy and nitrogen metabolism is improved, and the presence of ruminal disorders reduced. Ionophores (especially Salinomycin) have also exhibited effectiveness in the treatment of coccidial infections in poultry and cattle (Zinn, 1986). Ionophores inhibit methanogenesis by lowering the availability of hydrogen and formate, these primary substrates are sensitive to ionophores, whereas methanogens are more resistant (Chen and Wolin, 1979). Additional evidence for this mechanism is that, in the presence of Monensin, methane production by mixed cultures of rumen microbes can be increased by adding hydrogen gas (Van Nevel and Demeyer, 1977). Bacteria that reduce succinate to propionate are resistant to ionophores, so propionate production increases, the hydrogen produced are colonized by methanogens (Russell and Strobel, 1989). Similarly, rumen fungi, which also produce hydrogen, are sensitive to Monensin*in vitro* (Marounek and Hodrova, 1989). Furthermore, an important source of methane emissions is from enteric fermentation in farm animals. This is responsible for 27% of human methane emissions (Hossam *et al.*, 2015). Animals like cows, sheep and goats are examples of ruminant animals and during their normal digestion process they produce large amounts of methane. Enteric fermentation occurs because of microorganisms in the stomach of these animals, which creates methane as a by-product that is either exhaled by the animal or released via flatus.

Humans raised these animals for food, their emissions are considered human-related. The meat that we eat everyday contributes significantly to total methane emissions because of this, livestock farming creates 90 million tons of methane annually (Torrent and Johnson, 1994).Livestock related emissions have grown mainly because of the large growth of livestock populations worldwide over the last fifty years. Global livestock production has increased substantially since the 1960s with beef production more than doubling during this time (Hossam *et al.,* 2015).

CONTROL OF RUMEN DIGESTIVE DISORDERS BY IONOPHORES

Certain animal conditions, for instance, bloat and acidosis are caused by or related to disturbances in ruminal fermentation. These conditions are reduced when ionophores are fed because of a specific effect on a particular bacterial species, changes in eating behavior or changes in end products of fermentation (Hossam *et al.,* 2015).

Bloat: Bloat result from excess production of stable foam in the rumen (Bartley *et al*., 1983). Feeding of Monensin(40 mg kgG1) reduced the incidence of bloat to 4.2% over the following 36 days. On the other hand, removal of Monensinfrom the diet caused incidence of bloat to increase to 24.3% for the next36 days. During the feeding of Monensin, viscosity of rumen fluid from bloat-susceptible steersdecreased to values similar to normal steers (Bartley *et al*., 1983). Similar effects of Monensinon viscosity of rumen fluid were noted in sheep (Usagawa, 1992)

Acidosis: Ionophores have the potential to ameliorate the disease of acidosis by two distinct mechanisms.

The first mechanism is through ionophore effects on lactic acid producing strains of bacteriasuch as *Streptococcus bovis.* Dennis *et al*. (1981) reported that Lasalocidand Monensininhibit manyof the major strains of rumen bacteria that produce lactic acid. They also reported that the majorstrains of lactate fermenting bacteria were resistant to ionophores. Colony counts of *S. bovis*and *Lactobacillus* (lactate producing gram positive bacteria) were reduced in rumen fluid taken from cattle infused intraruminally with glucose and ionophore. Conversely, colony counts of lactate utilizing bacteria (gram negative) were unaffected by presence of ionophore(Hossam *et al.,* 2015).

The second mechanism is that ionophores may impact acidosis through changes in eatingdynamics of cattle fed ionophore containing diets. Ionophores change the eating behavior of cattle

and this may cause a reduction in digestive conditions, including acidosis and death (Black and McQuilken, 1980; Cooper *et al*., 1999).

II. Conclusion

The use of ionophores in ruminant nutrition is required for optimum production in modern production systems. The inclusion of ionophores in ruminant diet, as can be seen from the review has wide ranging implications in ruminant animal production.The key areas reviewed in this article points to some positive effects of feeding ionophores on animal productivity such as weight gain, milk and meat production, control of methane emission and control of some rumen digestive disorders. Other positive attributes of ionophores include enhanced energy and protein metabolism, reduce proteolysis and improvement in reproductive performances.Feeding costs approximately 70% in livestock production inputs therefore, both optimal digestion and metabolism are important for efficient and economic production system. However, the use of ionophores for improvements in utilization must not interfere with the health of the animal and should not be continuous butprogress in feeding with ionophores that leads to better fermentation in the rumen, digestion in the gastrointestinal tract and metabolism should be given utmost attention.In conclusion ionophores could be used to improve animal production efficiency and mitigate the effect of methane on the environment.

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