NOVATEUR PUBLICATIONS
JournalNX- A Multidisciplinary Peer Reviewed Journal
ISSN No: 2581 - 4230
VOLUME 8, ISSUE 8, Aug. -2022

EFFECTS OF PAPAVERINE AND "VETVITTELS" LLC COMMERCIAL DIETARY SUPPLEMENTS ON BLOOD GLUCOSE AND BODY WEIGHT IN OBESE DOGS

D. Adamchuk
VetVittles LLC, 2220 Avenue X Brooklyn, NY, 11235 USA, Clinical Specialty Pharmacist,
Clinical Assistant professor Arnold & Marie Schwartz College of Pharmacy

M. Kuziev
Samarkand State University, Faculty of Biology,
Samarkand, Uzbekistan, PhD

B. Zaripov
National University of Uzbekistan named after Mirzo Ulugbek,
Tashkent, Uzbekistan, DSc, professor

B. A. Niyazmetov
National University of Uzbekistan named after Mirzo Ulugbek, Tashkent, Uzbekistan, PhD

Corresponding Author: B. A. Niyazmetov
National University of Uzbekistan named after Mirzo Ulugbek, Tashkent, Uzbekistan

Abstract
Our experiments showed that papaverine inhibits sugar absorption in vivo as well as in vitro. The inhibitory effect of papaverine on glucose absorption was demonstrated in experiments on three species – rats, guinea pigs and dogs and it can be observed in different types of cells (enterocytes and cardiocytes). It blocks the absorption of sugar both in healthy and diabetic animals. Oral administration of papaverine significantly reduced blood sugar level but after an hour blood sugar level showed tendency to come back to the initial levels that were characteristic for these diabetic dogs. Dietary supplement D-28 has proven to be quite effective in reducing body weight in dogs. For a month, dogs with initial overweight lost on average more than 2 kg (12.8±0.4), that is a very good result for their size.

Keywords: papaverine, sugar, absorption, small intestine, blood glucose level, dietary supplements

Introduction

Papaverine (from lat. papaver "poppy") is an opium alkaloid, an isoquinoline derivative, a drug of antispasmodic and hypotensive action. Isolated from opium and studied in 1848 by Georg Merck (1825-1873). G. Merck was the son of Emmanuel Merck (Merck, 1794-1855), the founder of Merck Corp., the largest German chemical and pharmaceutical company. Georg Merck was a student of the famous German chemists Justus Liebig and August Hofmann [1, 2].

According to its purpose, Papaverine refers to antispasmodics of widespread use. Once in the body, the drug is able not only to relieve spasm of smooth muscles, but also to relax the vessels, allowing them to expand, and also to relieve spasm from the respiratory system, for example, from the bronchi. As a result, it improves blood circulation and tissues receive more oxygen. Special doses of the drug can

reduce cardiac excitability and affect the central nervous system. It is an inhibitor of the enzyme phosphodiesterase and causes intracellular accumulation of cyclic 3, 5-adenosine monophosphate, which leads to impaired contractility of smooth muscles and their relaxation in spastic conditions [2, 3, 4].

Glucose, along with fatty acids and ketone bodies, is an essential source of energy. The level of glucose in the blood is maintained at a constant 4-6 mM (0.8-1.0 g/l) due to the fine regulation of the processes of its intake and consumption. Glucose comes from the intestines (through the food digestion), liver and kidneys. In this case, the liver performs the function of "glucostat": in the phase of resorption, glucose enters the liver from the blood and accumulates in the form of glycogen. In case of glucose deficiency (postresorption phase, starvation), the liver, on the contrary, supplies glucose, which is formed due to the processes of glycogenolysis and gluconeogenesis [7, 8].

Diabetes mellitus is one of the most common endocrine disorders in dogs. Mostly middle-aged and elderly dogs (7-10 years old) are ill. There is a gender bias. Diabetes mellitus is predominantly recorded in unsterilized females. In this case, it occurs under the influence of contrainsular hormones: progesterone and somatotropic hormone. After the end of oestrus, the concentration of progesterone in the blood of dogs increases. High concentrations of progesterone in the blood stimulate the process of secretion of somatotropic hormone by mammary gland tissue, which is typical for dogs. Both progesterone and growth hormone, being contrainsular hormones, increase tissue resistance to the action of insulin. That is, there will be a relative insufficiency of insulin. Under the current conditions, beta cells responsible for the synthesis and secretion of insulin are forced to be in a state of hyperfunction to ensure normal glucose concentration by increasing the concentration of insulin in the blood. In the past it was shown that papaverine inhibits glucose transport in rat's small intestine in vitro [5, 6]. This effect was never verified in vivo. We conducted such study on dogs by measuring blood sugar level.

MATERIALS AND METHODS

Mix-breed, medium size (average 12-15 kg), 2-5 years old, castrated dogs were tested in the morning after a night without access to food. One group of animals included five healthy dogs. The second group included four dogs that were previously diagnosed as diabetic. At the morning experiment, diabetic dogs did not get their regular insulin injection.

Scheme of the experiment was the same in both groups. Blood glucose level was measured by glucose meter "Advocate".

Blood sugar measuring were executed before the breakfast (150 g of dry EN "Purina" food). Then blood testing was performed 30 minutes after breakfast followed by oral adminstration of papaverine ("MR Papaverini hydrochloridum" 2% sterile solution). Three doses were tested - 0.5 ml, 1.5 ml or 3 ml, and after that we measured blood sugar level every 30 minutes.

RESULTS AND DISCUSSIONS

As seen on Fig. 1, the initial blood sugar level was normal at all animals and it was between 80 and 90 mg. Soon after the breakfast, it raised 25-35 %. Just after oral injection of 0.5 ml of papaverine solution, blood sugar level reduced and reached initial level in an hour. After two hours a slight increase of blood glucose level was registered (Fig. 1).

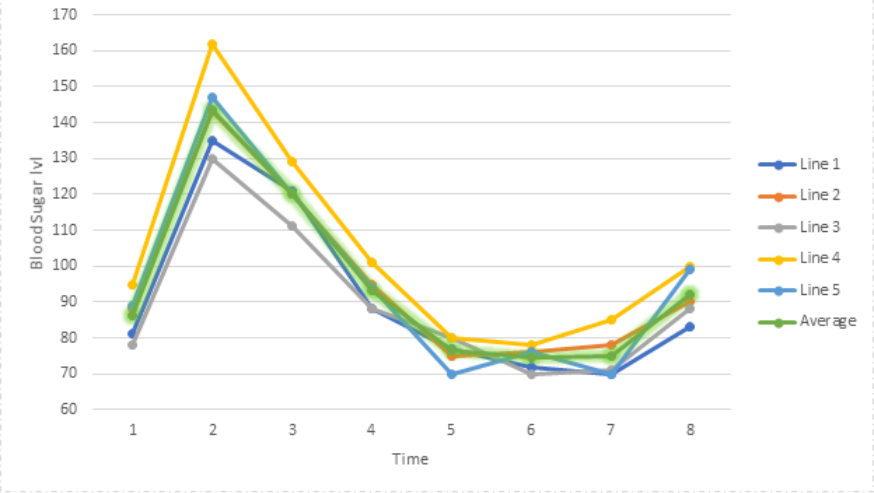

Figure 1: Effect of oral injection of 0.5 ml solution of 2% papaverine on blood sugar level of healthy dogs.
1 – control; 2 – 30 min after breakfast; 3 – 30 min after oral injection of papaverine; 4, 5, 6, 7 and 8 – blood sugar level measured in 30 min intervals.

Then we verified the effect of higher (1.5 ml versus 0.5 ml) dosages of papaverine under the same conditions as above on the next day on the same group of dogs. The 1.5 ml dose of papaverine solution caused deeper reduction of blood sugar level after the breakfast and this effect lasted somewhat longer but at the end of testing time, it comes to almost initial level (Fig. 2).

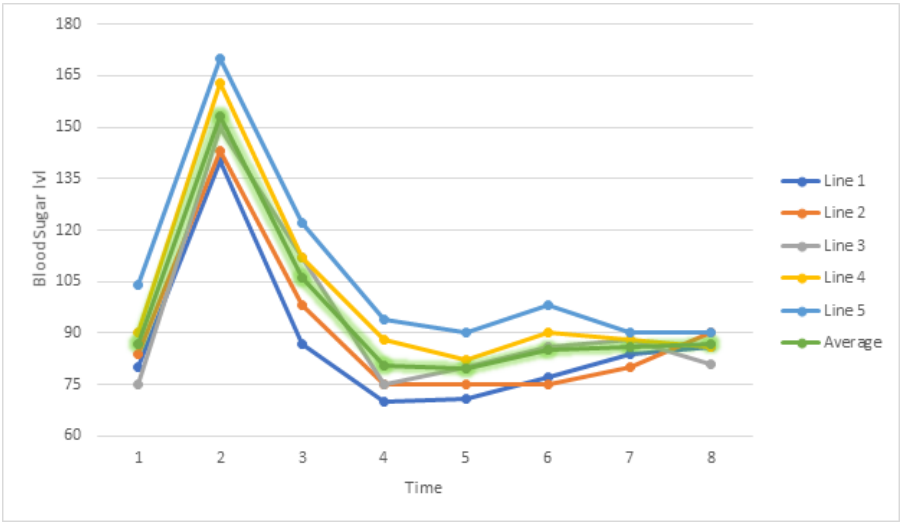

Figure 2: Effect of oral administration of 1.5 ml solution of 2% papaverine on blood sugar level.
1 – control; 2 – 30 min after breakfast; 3 – 30 min after oral administration of papaverine; 4, 5, 6, 7 and 8 – blood sugar level measured in 30 min intervals.

Additional increase of papaverine dose demonstrates no additional inhibitory effect on glucose input (**Fig.** 3).

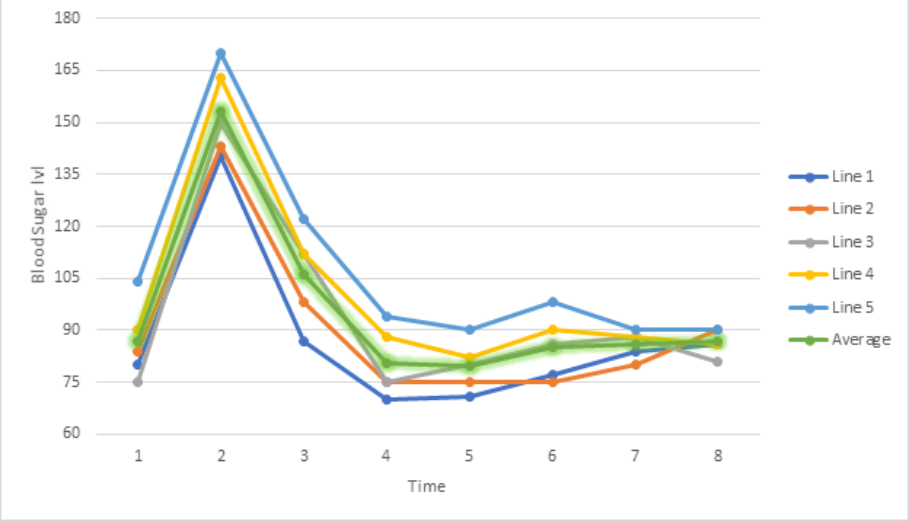

Fig. 3: Effect of oral administration of maximal dosage (3 ml) solution of 2% papaverine on blood sugar level.
1 – control; 2 – 30 min after breakfast; 3 – 30 min after oral administration of papaverine; 4, 5, 6, 7 and 8 – blood sugar level measured in 30 min intervals.

In a separate experiment, we tested the papaverine effect on blood sugar level without breakfast. It appears that without food no significant changes in blood sugar level could be observed (**Fig.** 4).

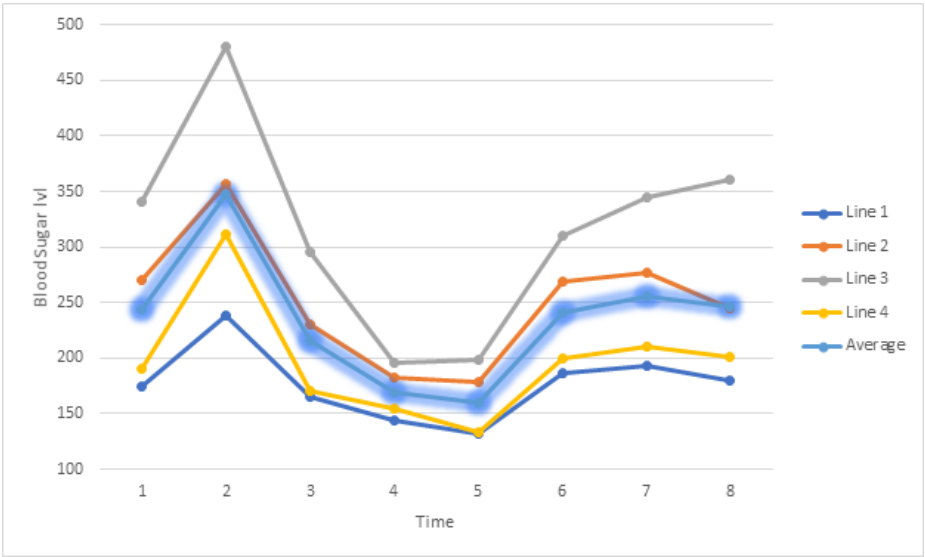

Fig. 4: Effect of oral administration of 1.5 ml solution of 2% papaverine on blood sugar level in dogs with diabetes.
1 – control; 2 – 30 min after breakfast; 3 – 30 min after oral injection of papaverine; 4, 5, 6, 7 and 8 – blood sugar level measured in 30 min intervals.

As we can see from this data dogs with diabetes had significantly elevated initial level of blood sugar while fasting. The increase of blood sugar level after the breakfast was significantly higher than in healthy animals. Oral administration of papaverine significantly reduced blood sugar level but after an hour blood sugar level showed tendency to come back to the initial levels that were characteristic for these diabetic dogs.

Our experiments showed that papaverine inhibits sugar absorption in vivo as well as in vitro. The inhibitory effect of papaverine on glucose absorption was demonstrated in experiments on three species – rats, guinea pigs and dogs and it can be observed in different types of cells (enterocytes and cardiocytes). It blocks the absorption of sugar both in healthy and diabetic animals.

On an empty stomach, effect of papaverine in diabetic animals is undetectable, which means that inhibition occurs only during absorption of external sugar and elevated level of blood sugar in diabetic animals is supported by glucose coming from internal storages. There is no tradition in veterinary medicine to distinguish diabetes 1 and 2 types in dogs [4].

On our recommendation, VetVittels LLC has made several overweight dog supplements that we have tested on dogs with these problems. In total, four recipes were tested, differing in the proportion of medicinal herbs included in them. The exact recipe for the composition of nutritional supplements is the know-how of VetVittels LLC and can only be published after obtaining a patent.

Terms. The experimental animals were kept in normal household conditions and received a normal diet with normal physical activity. Pet owners received D-28, D-29, and D-30 nutritional supplements with instructions to give the animals a teaspoon twice daily.

The exact composition of D-28, the most potent supplement, is VetVittels know-how, but its main ingredients were papaverine and extracts of hibiscus, fenugreek, and ginseng, which were carried in coconut oil, providing a comfortable texture and appealing taste to dogs.

D-29 and D-30 supplements lacked papaverine, and D-30 supplements also lacked ginseng. The observation of the animals lasted a month during which the weight of the animals and the degree of rise in the level of blood glucose after a trial breakfast were monitored weekly.

Table 1 Effect of D-28 Dietary Supplement on Body Weight in Overweight Dogs (n=4)

One week from start of observation	0	1	2	3	4
Weight, in kg	11.5±0.5	11.3±0.6	10.9±0.5	10.5±0.5	10.2±0.4
Weight, in% of the initial	100	98.1	94.5	91.2	88.7

From the data in Table 1, it can be seen that the D-28 dietary supplement for weight loss in dogs was quite effective. Over the course of a month, dogs with initial overweight lost an average of more than 2 kg, which is a very good result for their size.

The food supplement D-29 turned out to be practically ineffective (Table 2) - after a month of its use, the weight of the animals decreased by only 3%, which is unreliable.

Table 2 Effect of D-29 Dietary Supplement on Body Weight in Overweight Dogs (n=5)

One week from start of observation	0	1	2	3	4
Weight, in kg	13.2±0.5	13.3±0.6	12.9±0.5	13.0±0.5	12.8±0.4
Weight, in% of the initial	100	101	98	98	97

Dietary supplement D-30 had some positive effect on weight loss in dogs, but was inferior in effectiveness to dietary supplement D-28 - the reduction in body weight in this case was 6% compared to 11% when using dietary supplement D-28 (Table 3).

Table 3 Effect of D-30 Dietary Supplementation on Body Weight in Overweight Dogs (n=4)

One week from start of observation	0	1	2	3	4
Weight, in kg	10.5± 0.5	10.3±0.6	10.2±0.5	9.6±0.5	9.9±0.4
Weight, in% of the initial	100	98	97	91	94

CONCLUSION

It also should be noted that there is a definite limit in the amount of papaverine needed for complete inhibition of sugar absorption. Oral administration of 0.5 ml of papaverine solution caused significant reduction in glucose absorption and this effect became even more significant when the amount of inhibitor was tripled to 1.5 ml, but an additional increase in dose to 3 ml had no effect.

Therefore, it looks like papaverine after an additional research can be added to the list of pharmaceuticals that prevents sugar absorption in intestine for blood sugar control and/or weight loss. Dietary supplement D-28 has proven to be quite effective in reducing body weight in dogs. For a month, dogs with initial overweight lost on average more than 2 kg (12.8±0.4), that is a very good result for their size.

ACKNOWLEDGEMENT

The authors are grateful to DSc B.Z. Zaripov and E. Gurman for their advices and comments on an earlier version of the manuscript.

REFERENCES

1. Y. Dang et al. Papaverine inhibits lipopolysaccharide-induced microglial activation by suppressing NF-κB signaling pathway / Drug Des Devel Ther. 2016; 10: 851–859. Published online 2016 Feb 26. doi: 10.2147/DDDT.S97380
2. K. M. Hocking et al. Papaverine Prevents Vasospasm by Regulation of Myosin Light Chain Phosphorylation and Actin Polymerization in Human Saphenous Vein / PLoS One. 2016; 11(5): e0154460. Published online 2016 May 2. doi: 10.1371/journal.pone.0154460
3. Ahmadzadeh. Papaverine increases human serum albumin glycation / Biol Phys. 2014 Jan; 40(1): 97–107. Published online 2014 Jan 12. doi: 10.1007/s10867-013-9337-5
4. E.G. Gurman, E.A. Bagirova. The papaverine effect on the monosaccharides and glycine transport in the small intestine in vitro. Physiol. J. 1989, v 35, # 2, pp. 24-40
5. S. J. Bircbard & R. G. Sberding. Sauders Manual of small Animal Practice.1994.
6. Papaverine and its derivatives radiosensitize solid tumors by inhibiting mitochondrial metabolism / Proc Natl Acad Sci U S A. 2018 Oct 16; 115(42): 10756–10761. Published online 2018 Sep 10. doi: 10.1073/pnas.1808945115
7. M. Aggarwal, G. P. Leser, R. A. Lamb. Repurposing Papaverine as an Antiviral Agent against Influenza Viruses and Paramyxoviruses / J Virol. 2020 Mar; 94(6): e01888-19. Prepublished online 2020 Jan 2. Published online 2020 Feb 28. doi: 10.1128/JVI.01888-19
8. Gaber et al. Novel Papaverine Metal Complexes with Potential Anticancer Activities / Molecules. 2020 Nov; 25(22): 5447. Published online 2020 Nov 20. doi: 10.3390/molecules25225447.