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PAPAVERINE EFFECTS ON SUGAR ABSORPTION IN DOGS IN VIVO

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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 (1), guinea pigs (2) and dogs (3) 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.

KEYWORDS: papaverine, sugar, absorption, small intestine, blood glucose level.

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]

Papaverine has no narcotic properties, but has long been used as a smooth muscle relaxant for the treatment of vasospasm and erectile dysfunction. Its vascular effects were thought to be related to its activity as an inhibitor of phosphodiesterase 10A. Fibrosis at the injection site is a side effect associated with prolonged use of the drug.[5,6]

One study found that papaverine has an "off-target" effect that inhibits mitochondrial complex I in all cell lines. Papaverine in vivo increases the oxygenation of the tumor model within 30 minutes.

In the research, it was found that papaverine reduces tumor hypoxia and enhances response to radiation therapy. Papaverine, or one of its derivatives, appears to be ideal candidates for radiosensitization. Scientists believe that the additional benefit of papaverine in combination with stereotactic radiation therapy (SRT) will be useful in malignant neoplasms.[3]

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 a condition in which dogs are unable to effectively absorb sugar (glucose) and control blood sugar levels. The insulin that the pancreas produces is important in regulating the absorption and content of glucose in the blood. Insufficient insulin production is

deadly.

In the past it was shown that papaverine inhibits glucose transport in rat's small intestine in vitro.[4,5] 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).

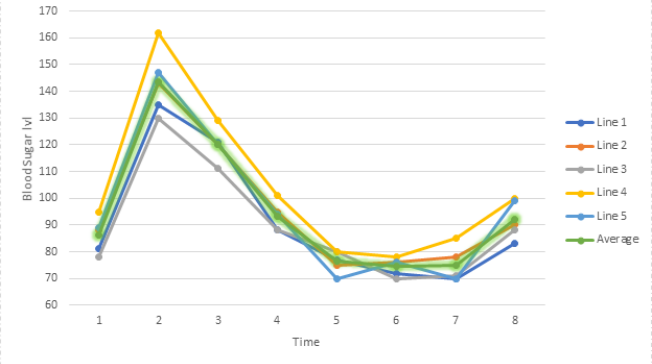

Figure 1: Effect of oral injection of 0.5 ml solution of 2% papaverine on blood sugar level of healthy dogs.
1 – control; 2 – 30 min after breakfast; 3 – 30 min after oral injection of papaverine; 4, 5, 6, 7 and 8 – blood sugar level measured in 30 min intervals.

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).

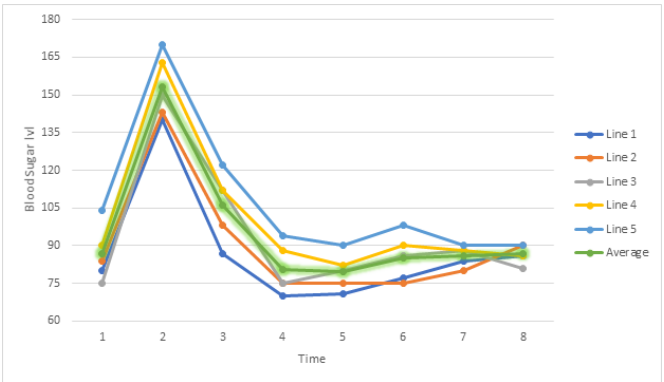

Figure 2: Effect of oral administration of 1.5 ml solution of 2% papaverine on blood sugar level.
1 – control; 2 – 30 min after breakfast; 3 – 30 min after oral administration of papaverine; 4, 5, 6, 7 and 8 – blood sugar level measured in 30 min intervals.

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

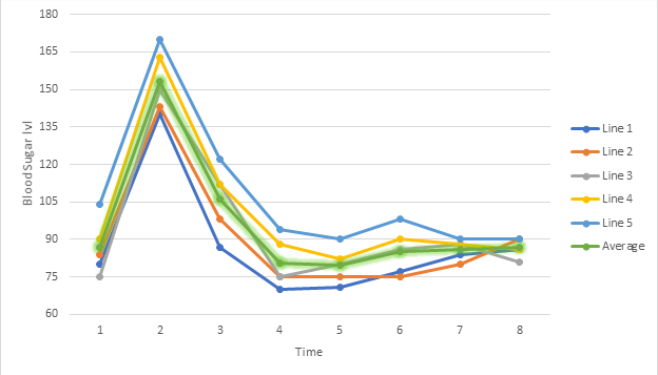

Fig. 3: Effect of oral administration of maximal dosage (3 ml) solution of 2% papaverine on blood sugar level.
1 – control; 2 – 30 min after breakfast; 3 – 30 min after oral administration of papaverine; 4, 5, 6, 7 and 8 – blood sugar level measured in 30 min intervals.

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).

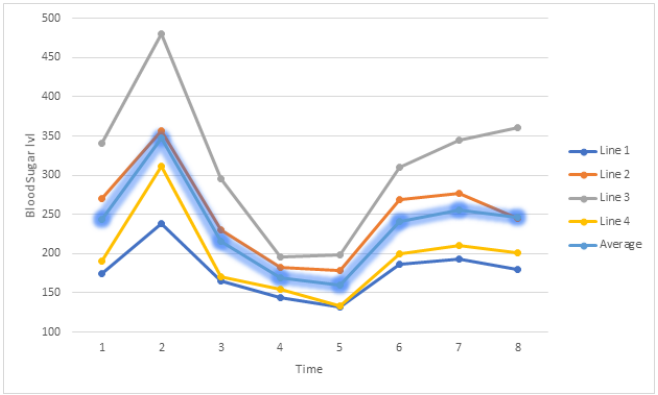

Fig. 4: Effect of oral administration of 1.5 ml solution of 2% papaverine on blood sugar level in dogs with diabetes.
1 – control; 2 – 30 min after breakfast; 3 – 30 min after oral injection of papaverine; 4, 5, 6, 7 and 8 – blood sugar level measured in 30 min intervals.

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]

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.

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