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The Pharmacodynamic Interactions of Sodium Stibogluconate (SSG) and Paromomycin (PM) on Various Isolated Tissues Preparations

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Abstract: In this study, sodium stibogluconate and paromomycin were investigated for their effects on isolated perfused rabbit heart, rabbit aortic strip and isolated intestine and rat uterus. When sodium stibogluconate was added to the isolated perfused rabbit heart it produced a slight increase in the force of heart contraction, where as paromomycin effect. The combination of 2 drugs increased the force of contraction slightly; this may be due to the effect of sodium stibogluconate. Both drugs have neither stimulatory nor inhibitory effect on the rabbit aortic strip and prior administration of each these drugs did not antagonize the stimulatory effect of noradrenaline in this organ, suggesting that they have no alpha antagonistic property. Both drugs either separately or in combination produce no effect on the rat uterus preparation wether in contracting or non contracting state. Similarly, the 2 drugs didn't relax the contractile rat uterus. Similarly, the 2 drugs produced no effects on the isolated rabbit intestine.

Key words: Sodium stibogluconate, paromomycin, pharmacodynamic, isolated tissues preparations, rabbit, drugs

INTRODUCTION

Chemotherapy constitutes the main tool for the control of leishmaniasis, but it is usually slow, expensive and toxic (Ponte-Sucre, 2003). The pentavalent antimony carbohydrate complexes sodium stibogluconate (Pentostam®) and meglumine antimoniate (Glucantime®) are the mainstay drugs against all forms of leishmania infections (Haimeur and Marc, 1988). The antimoniates were empirically developed >80 years ago and their mechanism of action has remained elusive. When these drugs are ineffective, or can not be prescribed, treatment with amphotericin B, pentamidine, Ambisome or paromomycin is indicated (Ponte-Sucre, 2003).

Pentavalent antimonial compounds are widely used for the treatment of visceral, mucosal and complicated cutaneous leishmaniasis. However, the cost, toxicity and long duration of treatment with antimonial drugs, together with the emergence of resistant strains, has led to a search for alternative drugs (Scott *et al*., 1992).

In general, high dose regimens of sodium stibogluconate are fairly well tolerated; toxic reactions are usually reversible and most subside despite continued therapy. Effects most commonly noted include: Pain at the injection site after intramuscular administration; chemical pancreatitis in nearly all patients; elevation of serum hepatic transaminase levels. Bone-marrow suppression is usually manifested by decreased red-cell, white-cell and platelet counts in the blood. Muscle and joint pain; weakness and malaise; headache; nausea and abdominal pain and skin rashes have also been reported. Changes in the electrocardiogram that include T-waves flattening and inversion and prolongation of the QT interval found in patients with systemic disease are uncommon in other forms of leishmaniasis. Reversible polyneuropathy has been reported. Hemolytic anemia and renal damage are rare manifestations of antimonial toxicity, as are shock and sudden death (James and Leslie, 2001).

In recent years, in Bihar state in the north east of India infections with visceral leishamaniasis have become increasingly unresponsive to first line treatment with pentavalent antimony compounds. While, a daily dose of 20 mg kg^{-1} sodium stibogluconate for 20-40 days was efficacious in the 1980s, up to 25% unresponsiveness is

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now reported even with high doses and longer administration (Jha *et al*., 1998). In Sudan cases of antimony-resistant visceral leishmaniasis have been reported from Eastern Sudan (Khalil *et al*., 2000).

Paromomycin is an aminoglycoside antibiotic identical to aminosidine. An injectable formulation of 500 mg of paromomycin sulphate had until recently been on the market in several countries for over 35 years for the treatment of bacterial and parasitic infections (Thakur *et al*., 2000). Aminosidine was first shown to have antileishmanial activity in the 1960s and it has been shown to act synergistically with antimony drugs (Jha *et al*., 1998).

Paromomycin was isolated from cultures of *Streptomyces rimosus*, is structurally related to neomycin and shares most of the antibacterial properties of other antibiotics in this class. Paromomycin acts directly on amoebae and also has antibacterial activity against normal and pathogenic micro-organisms in the gastrointestinal tract. Besides, its role in the treatment of amoebiasis, Paromomycin may have some value in treating other protozoal infections. For example, it has been found to be effective in some cases of visceral and cutaneous leishmaniasis and it has undergone limited controlled clinical trials for the treatment of cryptosporidiosis in AIDS patients. Other clinical uses of paromomycin include the experimental therapy of amebiasis and giardiasis in pregnancy and the treatment of infections with *D. fragilis*. Paromomycin is also effective in the treatment of infections with various tape worms (James and Leslie, 2001).

Most patients who received aminosidine combined with antimony compounds and the combinations were found to be highly efficacious and well tolerated (Jha *et al*., 1998).

In North American literature, aminosidine has been reported to be both ototoxic and nephrotoxic when given parenterally to animals and humans. Worldwide experience with the injectable compound has not revealed a higher incidence of these adverse effects than incidences of the adverse effects of either gentamicin or kanamycin (Kanyok *et al*., 1997).

One of the factors that can alter the response to drugs is the concurrent administration of other drugs. There are several mechanisms by which drugs may interact, but most can be categorized as pharmacokinetic, pharmacodynamic, or combined interactions. Knowledge of the mechanism by which a given drug interaction occurs is often clinically useful, since the mechanism may influence both, the time course and the methods of circumventing the interaction (Philip, 2001). Drug-drug interactions occur when one therapeutic agent either alters the concentration (pharmacokinetics interactions) or the biological effect of another agent (pharmacodynamic interactions). Pharmacokinetic drug-drug interactions can occur at the level of absorption, distribution, or clearance of the affected agent (Sorin and Laurinan, 2006).

However, research and development in leishmania has been neglected, because the disease mainly affects the poor sector (Philippe *et al*., 2002).

Objectives: To study the effect of Paromomycin and sodium stibogluconate and their interaction on some isolated animal tissues.

MATERIALS AND METHODS

The effects of Sodium Stibogluconate (SSG), Paromomycin (PM) and SSG + PM were studied in isolated perfused rabbit heart, rabbit aortic strip and isolated intestine and rat uterus, using Harvard universal oscillograph, Harvard research tissue bath, isometric transducer (Harvard) and isotonic transducer (Harvard).

Animals: Wister albino rats and rabbit (local strain) were used.

Isolated rabbit heart: The isolated heart was set up based on the method of Langendorff. The Rabbit was sacrificed and the thorax was opened immediately and the heart was exposed and removed as rapidly as possible and plunged into ice cold solution, then it was attached to a transducer (Kitchen, 1984a). The experiment demonstrates the effects of drugs on heart force and rate of contraction.

Rabbit aortic strip preparation: The preparation is based on the method. The rabbit was exsanguinated. The chest was opened and the aorta was dissected out, transferred to a Petri dish containing aerated Ringer's solution and then it was cut spirally, so as to produce a continuous strip then it was attached to a transducer (Kitchen, 1984a).

The rat uterus: The rat was killed by dislocating the neck and then it was exsanguinated. The abdomen was opened and the 2 uterine horns were exposed by pulling the intestine a side. The tissue was transferred to an isolated organ bath and then attached to the transducer (Kitchen, 1984c).

Rabbit intestine: The rabbit was exsanguinated. The abdomen was opened and the jejunum was isolated. A part of the jejunum was mounted in an organ bath and attached to the transducer (Kitchen, 1984b).

RESULTS AND DISCUSSION

Isolated perfused rabbit heart: When added sodium stibogluconate in a dose of 16 μg mL^{-1} to the isolated perfused rabbit heart it produced a slight increase in the

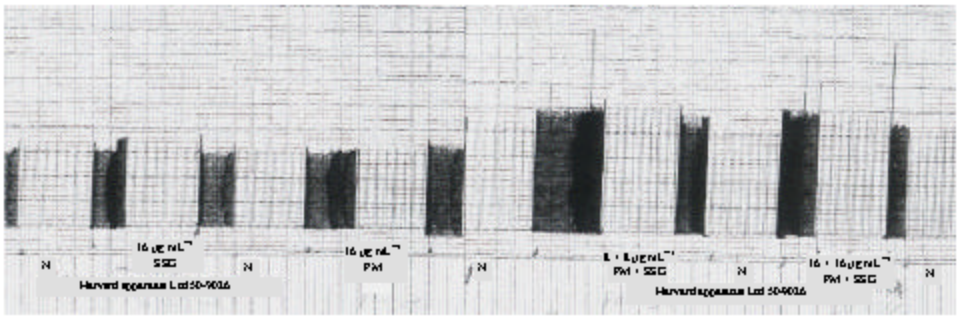

Fig. 1: Responses of the isolated perfused rabbit heart to sodium stibogluconate, paromomycin and the combination of the 2 drugs

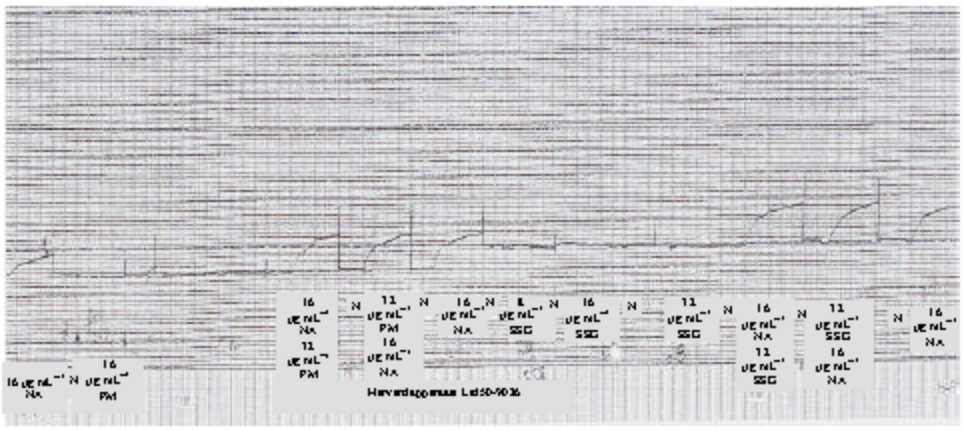

Fig. 2: Responses of the isolated rabbit aortic strip to sodium stibogluconate and paromomycin

force of heart contraction; where as Paromomycin in a dose of 16 μg mL^{-1} produced no effect. The combination of sodium stibogluconate (16 μg mL^{-1}) and paromomycin (16 μg mL^{-1}) increased the force of contraction slightly.

Isolated rabbit aortic strip: Both sodium stibogluconate and paromomycin when added in a dose of 32 μg mL^{-1} has neither stimulatory nor inhibitory effect on the rabbit aortic strip. Prior administration of each these drugs did not antagonize the stimulatory effect of noradrenaline (16 μg mL^{-1}) thus, they has no alpha antagonistic property.

Isolated rat uterus: Sodium stibogluconate and paromomycin in a dose of 16 μg mL^{-1} has no effect on the isolated non contracting rat uterus. Similarly, they didn't relax the contractile rat uterus.

Isolated rabbit intestine: Sodium stibogluconate and paromomycin when added in a dose of 32 μg mL^{-1} they produced no effects on the isolated rabbit intestine.

The pharmacodynamics effect and interactions of paromomycin and sodium stibogluconate was investigated in isolated perfused rabbit heart, rabbit aortic strip and intestine as well as isolated rat uterus. When sodium stibogluconate was added in a dose of 16 μg mL^{-1} to the isolated perfused rabbit heart it produced a slight increase in the force of heart contraction; where as paromomycin in a dose of 16 μg mL^{-1} produced no effect. The combination of 2 drugs at the same concentration increased the force of contraction slightly; this may be due to the effect of sodium stibogluconate and that paromomycin has no effect on the response (Fig. 1). Both drugs when added in a dose up to 32 μg mL^{-1} have neither stimulatory nor inhibitory effect on the rabbit aortic strip. Prior administration of each these drugs did not antagonize the stimulatory effect of noradrenaline (16 μg mL^{-1}) in this organ, suggesting that they have no alpha antagonistic property (Fig. 2).

Both drugs in a dose of 16 μg mL^{-1} either separately or in combination produce no effect on the rat uterus preparation wether in contracting or non contracting state. Similarly, the 2 drugs didn't relax the contractile rat

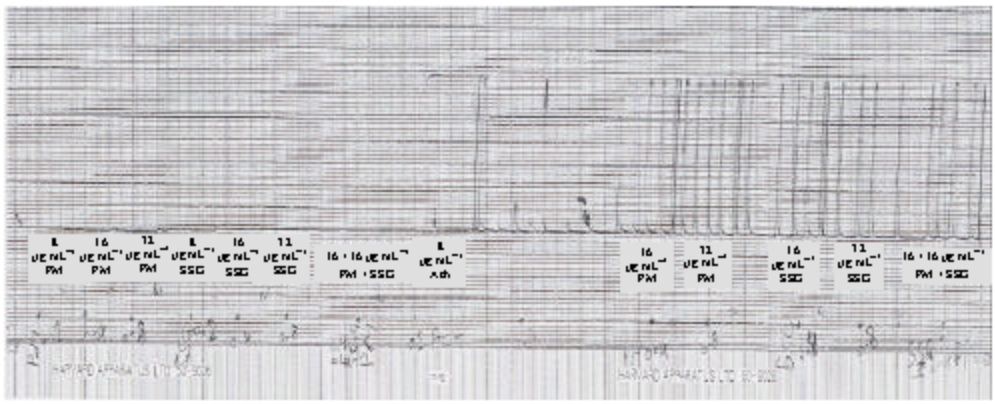

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Fig. 3: Responses of the isolated rat uterus to sodium stibogluconate and paromomycin

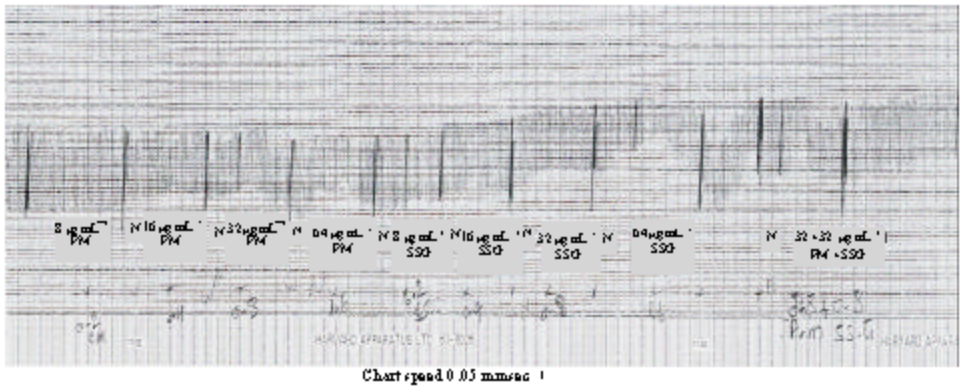

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Fig. 4: Responses of the isolated rabbit intestine to sodium stibogluconate, paromomycin and the combination of the 2 drugs

uterus (Fig. 3). Similarly, the 2 drugs when added in a dose of 32 μg mL^{-1} produced no effects on the isolated rabbit intestine (Fig. 4).

CONCLUSION

Thus, these results showed that these drugs have no significant effects on various isolated animal tissues except the effect of sodium stibogluconate on the isolated perfused rabbit heart that produced a very slight increase in the force of heart contraction and there fore it should be used with caution in patients with heart problems. Also these results indicated that the 2 drugs have no synergistic effect on various isolated animals tissue when they were added together.

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