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Intragastric administration of radioactive tablet under the influence of anesthesia for gastro retentive study in New Zealand White rabbit

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Abstract

The purpose of this study was to evaluate the effect of dissociative anesthesia in the oral administration of radiolabelled gastro-retentive Metformin tablet in New Zealand White rabbits. The radiolabelled tablet formulation was administered to the rabbit by oral route. In this pilot experiment, it was observed that maximum activity was retained in the oral cavity as compared to gastric area. Hence, to address this problem modification with oral gavaging was done. Intragastric administration of radiolabelled Metformin drug formulation under effect of dissociative anesthesia resulted in 92.6% retention of radioactive tablet in the gastric region with minimal esophageal contamination. Therefore, it was possible to carry out further experiments in these animals with successful administration of tablet followed by sequential scintigraphy imaging at different time intervals. Significant retention was observed up to 6 hrs. Judicious use of dissociative anesthesia helps to attempt the practical problems for oral administration of a tablet in laboratory animals. The procedure can be useful for further pre-clinical testing of newer drug formulations in tablet form.

Key words: Intragastric dosing, Tablet, Anesthesia, Scintigraphy imaging, Rabbit

Introduction

Laboratory animals are used in biomedical research as preclinical animal models for different diseases such as cancer, infectious and non-infectious diseases (Matulka and Wagner, 2005). To carry out these experiments different test compounds have to be administered to the animals through various routes which form a critical and integral part of all animal studies (Turner *et al.*, 2011). Administration of a substance can be done by oral, intravenous, subcutaneous and intraperitonial routes (Shimizu, 2004). The route of administration depends upon the purpose of study and it should closely resemble the probable route of administration to humans (Anderson andSwearengen , 2006). The voluntary intake by the animal via the oral route is an ideal way. Oral medication may be accepted by rat, mice and rabbit voluntarily if they are palatable or sweet taste. Routinely, oral feeding can be done either through mixing with food and water or by using orogastric and nasogastic gavage tubes in laboratory animals for liquid formulation (Harkness *et al.*, 2013; Van Loo *et al.*, 2002). Administration of tablets or capsules by the oral route is a challenging task (Harkness *et al.*, 2013) and its voluntary intake is not possible with animals. When retention of drug is the prerequisite for any research, then precise and accurate dosing is important. Liquid solution can be administered easily as compared to solid tablet (Varga, 2013). However, force feeding by syringe may cause trauma to the soft tissues inside the mouth or rupture of esophagus and chances of faulty lung dosing for the animals (LASA Good practice guideline, 1998). Hence, to address this specific problem dissociative anesthesia was used for intragastric administration of a radioactive Metformin tablet. In our study, accurate dosing is important for evaluation of gastric-retentive nature of the formulation by *in-vivo* imaging technique. This was achieved by the precise use of the ketamine anesthesia. The technique was standardized according to the animal response and body weight for safe administration of the tablet to the rabbit.

Materials and Methods

Radioactive Formulation: Metformin tablet (Tablet-5mm diameter) was weighed and a hole was drilled into it, filled with a radioactive solution of ^{99m}Tc–DTPA (approximately 400- 600µci) and sealed using molten gelucier. This radiolabelled Metformin tablet was used for oral administration.

Animal Scintigraphy Imaging: Four healthy, male New Zealand White Rabbits (Body Weight 3.0- 3.5kg) were used. Animal study protocol was approved by BARC, Animal Ethics Committee, Mumbai, (Approval No. BAEC/01/14). Animal restraining was done by using Ketamine and Xylazine by intramuscular route. One fourth of calculated dose of anesthesia was given prior to the oral dosing. Oral administration of radiolabelled Metformin tablet followed by normal saline was given. Subsequently a calculated total anesthesia dose was given for imaging studies. Scintigraphy sequential static imaging was done by using dual head gamma camera. The animal was placed in supine position and imaging was carried till 6 hrs.

Results

In our investigation, we have developed a simple method to facilitate the easy administration of radiolabelled tablet to rabbit through oral route and studied its transit and retention in the gastrointestinal tract. In first part of the experiment, the tablet was administered by conventional method, by directly placing the tablet into the oral cavity with the aid of blunt end forceps and further ingesting 1 ml normal saline. By this method, animal could not swallow the tablet easily and major amount of activity was observed in the oral cavity (69.2%), followed by esophagus (8.2%) and gastric region (22.5%) respectively (Fig. 1). To overcome this issue, the test animals were subjected under the influence of mild dissociative anesthesia and the animal head was held in the upright position during the administration. This has served in wide opening of the oral cavity of rabbit which facilitated the placement of tablet deep back into the oral cavity. Subsequently, administration of normal saline made it easier for animal to swallow the tablet. Gavaging by this method showed substantial activity in stomach (92.6%) followed by esophagus (3.6%) and oral cavity (3.1%) respectively (Fig.1) at 5 min post administration. Further evaluation by gamma scintigraphy images demonstrated that the gastro-retentive formulation in the form of uniformly swollen tablet was successfully retained in the stomach up to 6 hr (Fig.2).

Discussion

The current short clinical article addresses the issue associated with oral gavaging of tablet in laboratory animal. The conventional way of oral administration to laboratory animal is by mixing with foodstuff. Oral gavaging requires technical skills to avoid wrong administration into the lung (Turner, 2011). The current investigation requires proper oral gavaging of radiopharmaceuticals with high accuracy in administered dose in experimental animals. Therefore, traditional method of admixture with food would prove unsuitable. In the first part of experiment, tablet administered by conventional method showed difficulty in administering the tablet. The rabbit failed to swallow the tablet voluntarily which could be attributed to flavour or palatability issues (Harkness, 2010) or poor acquaintance with such kind of oral dosing. The resulting study showed maximum amount of activity in oral cavity (Fig.1). Studies on similar lines were reported earlier wherein formulations viz. microparticles suspension and microballoons were orally administered to rabbits by gavaging (Baskar *et al*, 2010; Yadav and Jain, 2011). As these formulations were in liquid state it was easy to administer them by the oral route (Varga, 2013). In another study (Ali *et al.,* 2007) radiolabelled Metformin solution was given in the form of capsule by oral route. Our aim was to administer an intact tablet in the stomach of rabbit via oral route. To perform this, a modified methodology was used wherein the animals were anesthetized with mild dissociative anesthesia. This facilitated easy opening of the oral cavity of animal without giving much stress. In addition, the animal head position and saline administration helped in easy transit of tablet in the stomach. This easy passage way for tablet from esophagus to stomach could be associated with gravitational force in upright position and presences of swallowing reflex under mild dissociative anesthesia (Nebendal, 2000; Varga, 2013). In the present study, intragastric location of radioactive tablet was confirmed under gamma camera. Scintigraphy imaging was conducted till 6hrs, as it was analogous to the half-life of 99mTc (Saha, 2010). The gamma scintigraphy image (Fig.2) revealed successful gastric retention of radioactive tablet in the stomach up to 6hrs.

Conclusion

Intragastric gavage of solid tablets in rabbits is really difficult task as compared to liquids. However, as reported in this communication, skillful utilization of dissociative anesthesia makes an easy and perfect oral intragastric administration of a tablet in laboratory animals.

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Fig 1. Distribution of Radioactive Tablet: Use of anesthesia in oral administration of radioactive tablet in rabbit

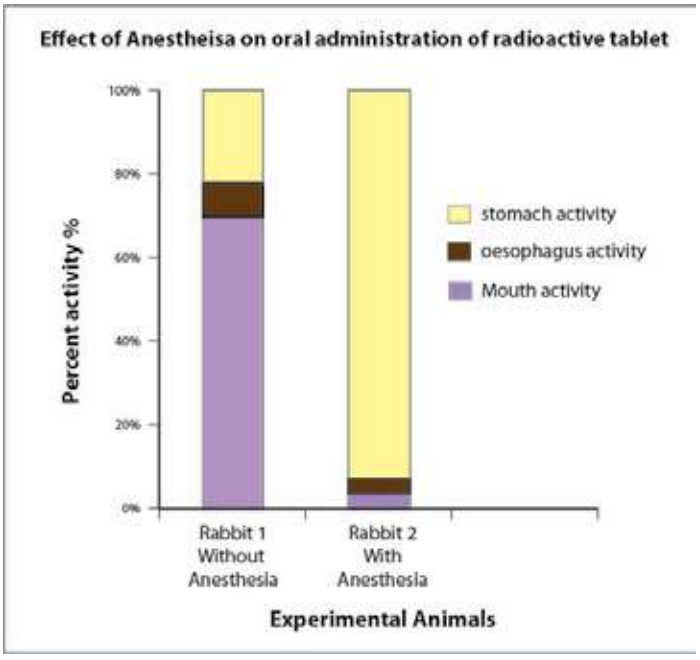

Fig 1. Scintigraphy Image: Intragastric administration of radioactive tablet in rabbit. Upper arrow mouth activity and lower arrow stomach activity