Magnetic marker monitoring allows to characterize effects of exogenous factors on esophageal transit of solid drug forms

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1. Introduction

The number of reports about esophageal damage due to ingested medication in solid drug forms has steadily increased since the first description by Pemberton in 1970 [1-4]. In both, patients with esophageal disorders and subjects without an apparent esophageal abnormality, the upper third of the esophagus is the common site where foreign body entrapment and medication induced esophagitis occur [3-7]. The predisposition of this site has been proposed to be due to compression of the esophagus by the left main stem bronchus, the aortic arch, the left atrium, or an increased left atrial size [7;8]. Whether such topographic relations actually cause the entrapment of foreign bodies is not proven and appears unlikely, since they do not impede the passage of a large bolus of food [9].

Several medications have been identified that can damage the esophageal mucosa, especially the ingestion of emepronium bromide, slow release potassium chloride, and doxycycline tablets [7;10;11]. Currently, the frequent use of non-steroidal anti-inflammatory analgesics is believed to play a major role in the increasing incidence of drug induced esophageal damage [12]. Esophagitis may develop causing retrosternal pain and dysphagia with the risk of esophageal ulceration or even stricture formation. Deaths resulting from drug induced esophageal perforation or hemorrhage have been reported [3]. Therefore, it is generally recommended to swallow tablets with a large volume of water in upright position, in order to avoid such complications.
However, these recommendations are not based on systematic experimental studies. They rather result from general experience, and the understanding of deglutition mechanisms of bolus swallowing in healthy volunteers and patients with esophageal dysphagia.

Dysphagia is a common symptom with a prevalence between 1.6% and 15% in the middle-aged and elderly general population [13;14]. In the absence of a structural obstruction, dysphagia is often caused by an esophageal motility disorder. Although several techniques are available to investigate nonobstructive dysphagia, esophageal manometry is the gold standard for the diagnosis of esophageal motility disorders since specific manometric criteria are established to diagnose these diseases [15]. However, manometry has some inconvenience due to the necessity of nasogastric intubation with the manometry catheter, and it requires expertise and experience for both study performance and interpretation of the manometric traces.

Many disorders of the esophagus that cause dysphagic symptoms are characterized by abnormal esophageal motor function, with disruption of propulsive transit of ingested food, respectively tablets or capsules. Esophageal scintigraphy is generally accepted to be the most easily applicable test of esophageal transit. Scintigraphy is non-invasive, comfortable for the patient, involves little radiation exposure, and provides a rapid quantitative evaluation of esophageal transit. Computerized analysis permits detailed assessment of solid and liquid bolus transit under physiological conditions.
Videoesophagography is a sensitive qualitative test for esophageal bolus transit and frequently used as the first investigation in patients with suspected esophageal motor disorders. Although often performed with the subject in upright position, barium esophageal studies are sometimes done with the subject in supine position. The transit of the bolus is believed to be the result of the esophageal peristalsis, without much influence of gravity [16].
The three diagnostic tools mentioned above have different important advantages and disadvantages. In general practice videoesophagography is a useful diagnostic procedure for initial evaluation of patients with dysphagia, mostly after exclusion of obstructive alterations by endoscopy. Besides exposure to radiation, this examination is accurate, cost effective, and well tolerated by the patients. Because of low radiation exposure and ease of quantitation, scintigraphy is performed if quantitative evaluation of esophageal transit is needed.

These methods reflect the current standard in the evaluation of patients with dysphagia, and also to determine the esophagogastral transit of orally administered drug dosage forms. Knowledge about the gastrointestinal transit and exact localization of the dissolution of solid drug forms are important aspects in the development of new drugs. In general, besides endoscopy and magnetic reso-

nance imaging, scintigraphy and videoesophagography have been used to gain such information. However, these procedures have not been standardized for this purpose. They are performed either in supine or upright position and with different quantities of a liquid bolus.

Thus, the aim of our study was to assess exogenous factors, like body position and volume of the liquid bolus, on esophageal transport of orally administered solid drug forms in healthy volunteers. We used a new method called magnetic marker monitoring (MMM), to investigate these questions, because of the high tempospatial resolution of this method, and restrictions by ethical reasons to expose healthy volunteers to radiation.
Biomagnetic measurements have already been used in other disciplines of medicine, especially in cardiology (magnetocardiography) [17], and neurology (magnetoencephalography) [18]. Wherever muscles and nerves generate ionic currents, biomagnetic measurements can be used. In Magnetic Marker Monitoring, biomagnetic measurements is combined with signal-processing techniques of magnetic marker [19]. The major advantage of this passive magnetometric method is the very high tempospatial resolution and the fact that no radiation is needed.

2. Methods and Materials

Esophageal transit studies were undertaken with the method of magnetic marker monitoring in five healthy volunteers. None of the subjects had any symptoms or history of upper gastrointestinal disease. The study was approved by the University Ethics Committee, and each subject provided written informed consent.

2.1 Magnetic Procedure

To reduce environmental magnetic fields, we performed the measurements in a room shielded against natural magnetism from outside. Measurements were done with a 63 channel flat SQUID device (DC to 64 Hz, sampling frequency at 250 Hz). The location of the marker during the transport was determined off-line by fitting the magnetic measurement data using a magnetic dipole model.

2.2 Swallowing Procedure

Five volunteers swallowed 5 magnetically marked capsules (MMC) (16.1 mm x 5.5 mm) with 5, 25 or 50 ml of water in upright (60°) and supine position (0°), respectively. After entering the stomach, the capsules desintegrated immediately, so that the magnetic moment vanished.

3. Results

At swallowing the MMC´s in *upright* position with 5 ml of water, 30 % of the capsules were retained in the esophagus. At a liquid bolus of 25 ml of water only 10 % of the capsules were not directly transported into the stomach, and at 50 ml of water none of the capsules were retained in the esophagus.
At swallowing a capsule in *supine* position with 5 ml of water, 70 % of the capsules were retained in the esophagus. At a liquid bolus of 25 ml of water 30 % did not reach the stomach. With 50 ml of water only 5% of the capsules were trapped in the esophagus.
In *upright* position, the esophageal transit time of the MMC was 5.3s at 5ml, 4.8s at 25ml and 1.2s at 50ml, respectively. The mean transit time at swallowing the capsules in *supine* position was 7.6 s at 5ml, 5.4 s at 25 ml and 4.6 s at 50 ml.

Supine / Upright	5 ml		25 ml		50 ml	
Velocity	7,7 cm /s	4,1 cm/s	4,4 cm/s	5,0 cm/s	4,6 cm/s	17,2 cm/s
Transit time	7,6 s	5,3 s	5,4 s	4,8 s	4,6 s	1,2 s
Retention rate	70 %	30 %	30 %	10 %	5 %	0 %

Tab. 1: Effects of body position and liquid bolus volume on esophageal transport of solid drug forms.

4. Discussion

Over the last 30 years clinical and experimental reports have shown that retention of ingested pills in the esophagus can occur, and that a variety of medications can produce esophageal injury [1-4;6;20;21]. Initially, drug induced esophageal damage was believed to be limited to patients with gastrointestinal motility disorders. Subsequently, it became evident that this phenomenon can also take place in subjects without deglutition dysfunction.

The present data show that retention of solid drug forms is dependent on the volume of the liquid bolus and the body position at swallowing. In a supine position, 70% of the capsules were retained at 5 ml of water. Whereas only 30% of the same capsules were trapped in the esophagus in upright position. At deglutition with 50 ml of water an enlodgement in the esophagus still occurred in 5%, but none of the capsules were retained in the esophagus in upright position at this quantity of liquid.
These results are closely associated with the esophageal transit time of the capsules swallowed. We observed a strong volume dependency in the transit time of capsules in upright position but not in supine position. Tablets taken with 50 ml of water had a five times shorter transit time in comparison to ingestion of equal tablets with only 5 ml of water. Whereas, swallowing of the capsules in horizontal body position generated no significantly faster

transport of the capsules into the stomach, which generally takes several seconds to begin after a deglutition.
This observation and the fact that it took only 1,2 s to transport the tablet into the stomach in upright body position at 50 ml of water, suggests that the transport velocity of the capsules in upright position was independent from the propulsive motor function of the esophagus.
The present study confirms previous results, that it is common for solid pharmaceutical formulations to remain in the esophagus for prolonged periods, and that entrapment of capsules in the esophagus also occurs in healthy volunteers [2;23]. In addition, they show that the volume of the liquid bolus induces a significantly faster transport of the capsules in upright body position, without having a significant influence on velocity of the capsules in supine body position. Furthermore, the volume of the liquid bolus has a considerable effect on the retention rate of the ingested capsules especially in supine as well as in upright body position.
Further examinations with simultaneous assessment of esophageal manometry and transport of solid drug forms by MMM will elucidate the role of esophageal motility on the transport of solid drugs.
The method of MMM allows for the first time to investigate the effect of exogenous factors on the esophageal transport of solid drug forms in healthy volunteers with high tempospatial resolution. Further, this innovative technique may open new ways to evaluate alteration of esophageal transit in gastrointestinal motility disorders, such as achalasia, nutcracker esophagus, diffuse esophageal spasm, and sclerodermia without exposure to radiation.

5. Literature References

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