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Note

Scintigraphic verification of adherence of a chitosan formulation to the human oesophagus

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Abstract

It is well known that adherence of a drug product, e.g. a gelatine capsule, to the oesophagus can cause oesophageal injury, which can be severe if the medicinal agent has corrosive properties. In a recent study we investigated by means of gamma scintigraphy whether chitosan granules dispensed in gelatine capsules had gastro-retentive properties. In one of ten volunteers the formulation lodged in the oesophagus. This case is reported here. The capsule adhered initially to the distal oesophagus. The capsule shell had started to disintegrate within 5 min, with some radioactivity detectable in the stomach. However, about two thirds of the radioactivity remained detectable in the oesophageal region for 1.75 h. This could be explained on the basis that there had been adherence not only of the gelatine shell but also of chitosan granules to the oesophageal mucosa. In evaluating potential for causing oesophageal injury it is not enough to consider only the mucoadhesive properties of the outermost layer of a drug product, because the filler may also have such properties. When new excipient materials are introduced, evaluation of their mucoadhesive tendencies is important.

Keywords: Adherence; Oesophagus; Chitosan; Gelatine; Gamma scintigraphy

1. Introduction

Oesophageal adhesion by dosage forms was recognised as early as 1970, when it was reported that tablets containing potassium chloride caused oesophageal injury [1]. Since then there have been many studies of tendencies of various kinds of pharmaceutical formulations to adhere to the oesophagus. Risk of adhesion has been found to be high, e.g. with gelatine capsules [2]. It was realised that some common pharmaceutical materials which adhere to mucosa as they hydrate should not be used in connection with the administration of drugs suspected of causing oesophageal injuries. In the late 1990 s adhesion of formulations to the oesophagus again became a topic of concern when it was found that administration of aminobisphosphonates, new drug substances for the treatment of osteoporosis, could result in severe oesophageal lesions [3]. More than 70 drugs in common use have now been reported to be associated with oesophageal injury [4].

In recent years, there has been increasing interest in the pharmaceutical field in discovering new excipient materials of natural origin. One such material is chitosan, a monograph on which was included in the fourth edition of the European Pharmacopoeia in 2002 (chitosan hydrochloride). Our group has studied microcrystalline chitosan (MCCh) base as a gel-forming excipient. In adhesion studies using the isolated porcine oesophagus we found that tablets containing conventional chitosan or various grades of MCCh had marked tendencies to adhere to oesophageal mucosa [5]. These in vitro findings suggest that chitosans might be among the excipients that should not be used in formulations containing drugs associated with oesophageal injury. In a recent gamma scintigraphic study in human volunteers we investigated whether MCCh granules dispensed in gelatine capsules had gastro-retentive

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properties [6]. In one of the ten volunteers the formulation adhered to the oesophagus. Consequently, results relating to this volunteer were excluded from analysis. This case is reported in detail in this note. This may be the first report of visualisation of the entire course of adherence and detachment of a formulation over a period of time in a human being.

2. Materials and methods

2.1. Formulation

The granules contained 95% of microcrystalline chitosan (MCCh, mean molecular weight 150 kDa, approximate extent of deacetylation 75%) (Novasso, Finland), 3.4% of lactose (Pharmatose DCL 21, DMV International, Netherlands) and 1.6% of natural-abundance samarium oxide (Sm_2O_3) (purity 99.9%) (Aldrich, USA). The granules (260 mg) were dispensed in size-0 gelatine capsules (Ph.Eur.). Preparation of the granules has been described in detail elsewhere [6].

Forty-eight hours before administration the ^{152}Sm in the granules was activated in a thermal neutron flux to the gamma-emitting nuclide ^{153}Sm, using a 250 kW TRIGA Mark II nuclear research reactor (General Atomics, USA) at the VTT Technical Research Centre of Finland. The neutron flux was 1.2×10^{12} $cm^{-2}s^{-1}$ and the irradiation time 5.5 min. The neutron activation process has been described in detail elsewhere [6].

2.2. Gamma scintigraphic study

The subject of the case reported here was a 22-year-old healthy male volunteer weighing 74 kg, of body-mass index 23 kg m^{-2}. A capsule containing the granules was administered with 180 ml of water, with the subject in a sitting position, at 8 a.m., after the volunteer had fasted overnight for at least 12 h. The volunteer was not allowed to eat or drink during the 3 h imaging period. One minute after administration gamma images, each of 1 min duration, were recorded continuously for 30 min, after which six images, each of 1 min duration, were recorded every 15 min. During imaging the subject was in a supine position beneath the gamma camera. At all other times the volunteer was able to move freely. Gamma-counts were detected by means of a dual-head gamma camera (ADAC Forte, ADAC Laboratories, USA) equipped with LEGP collimators. The study protocol and approval given to it by various authorities have been described in detail elsewhere [6].

3. Results and discussion

Fig. 1, the image obtained 5 min after administration, shows that the capsule containing the granules is situated

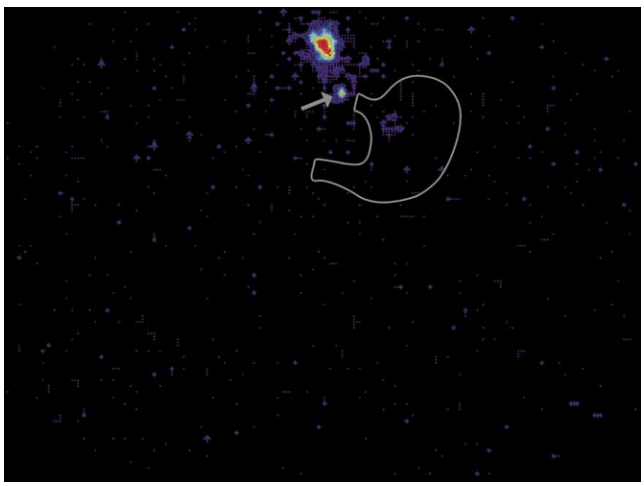

Fig. 1. Gamma image 5 min after capsule administration. The arrow indicates the ^{57}Co marker at the tip of the sternum.

above the sternum marker and therefore still in the oesophagus, above the gastro-oesophageal junction. Disintegration of the capsule shell had obviously commenced because a small amount of radioactivity from the $^{153}Sm_2O_3$ in the granules is evident in the stomach area. Fig. 2 shows that the number of gamma-counts detected in the stomach region was minimal up to 15 min but then increased. At the same time counts from the oesophageal area started to decrease, reaching a level of 300 to 350 min^{-1} at 45 min. After 1.75 h the number of counts from the oesophageal region dropped sharply, to 100 min^{-1}.

Normally, the oesophageal transit time for capsules, tablets or small particles is short, only some 10 to 20 s [2,7]. It is, however, well known that adhesion of dosage forms to the oesophagus can occur in up to 20% of cases [8]. It is therefore not surprising that a gelatine capsule lodged in an oesophagus in our study. The risk of adhesion is particularly high if a formulation is ingested with little or no water, and the subject is recumbent or semi-recumbent. In our study the capsule adhered even though it had been swallowed with plenty of water, with the subject in a sitting position. The gelatine shell had started to disintegrate within 5 min of administration, and radioactivity in the oesophageal area

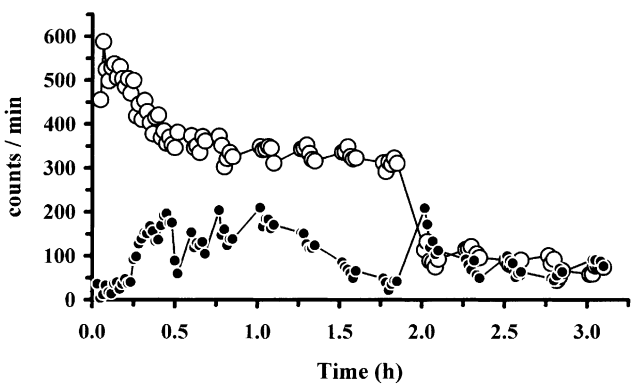

Fig. 2. Gamma-counts measured over time from two regions of interest: (○) distal oesophagus; (●) stomach.

had started to decline as capsule contents began to reach the stomach. Radioactivity declined slowly, by approximately one third, reaching a fairly constant level 45 min after administration. This phase could be explained on the basis that not only the gelatine shell but also chitosan granules were adhering to the oesophageal mucosa. Almost all of the capsule contents had become detached from the oesophagus and reached the stomach 1.75 h after administration.

Our explanation that chitosan might also have adhered to the oesophagus is in accordance with results obtained in a previous study by us, in which it was found that chitosan tablets had a marked tendency to adhere to isolated porcine oesophagus [5]. Results of previous in vitro studies have also shown that chitosan adheres to porcine gastric mucosa [9]. However, it has been thought that adhesion in the oesophagus is less efficient than adhesion in the stomach, because physiological conditions differ markedly in the two locations. Our in vivo finding suggests that retention in the oesophagus of a chitosan formulation of the kind studied is possible. Because the chitosan grade studied has exhibited a fairly marked tendency to adhere to porcine oesophagus in vitro [5] it is possible that granules containing chitosan adhered to the oesophageal mucosa after disintegration of the capsule shell in the oesophagus had commenced. Further studies, including a placebo controlled study in human volunteers need, however, to be carried out to confirm this surmise. If the results of such studies showed that there is a risk of oesophageal adherence with chitosan, its use would need to be avoided in formulations containing drug substances associated with oesophageal injury.

Chitosan, in addition to its use in pharmaceutical preparations, is used throughout the world in parapharmaceutical products, as a fat binder in cholesterol-lowering formulations and in slimming formulations. Failure of capsules and tablets to move rapidly through the oesophagus is a problem associated not only with pharmaceutical formulations but also with non-medical natural products. It has, for example, been reported that guar gum in a slimming product hydrated and formed a large viscous mass in the oesophagus, resulting in oesophageal obstruction [10]. Because amounts of chitosan in parapharmaceutical products are high, the daily intake usually amounting to several grams, caution might be needed in relation to such products. The substantial amounts of gel-forming agent and the large size of the product could make them likely to stagnate in the oesophagus.

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