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Simethicone Coated Cellulose as an Oral Contrast Agent for Ultrasound of the Upper Abdomen

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Ultrasound (US) examination of the upper abdominal retroperitoneum may be compromised by artifacts due to presence of gas in the stomach and adjacent bowel loops [1,2,3]. This can result in diagnostically suboptimal images. Attempts at filling the stomach with water and thereby reducing acoustic artifacts caused by intraluminal gas have been suggested [4]. However, while drinking water, more air may be ingested resulting in increased artifacts [2].

Methylcellulose has been proposed as an oral ultrasound contrast agent for scanning the upper abdomen [3,5]. Together with simethicone, which has also been previously reported as an ultrasound agent to decrease bowel gas [6], cellulose leads to a uniform low level intraluminal echogenecity and reduction of gas artifacts, by displacement and adsorption of any intraluminal gas. We therefore hypothesized that combining the cellulose with an antifoaming agent like simethicone would facilitate visualization of the pancreas and other retroperitoneal anatomical structures.

In this preliminary study, we evaluated efficacy of simethicone–coated cellulose as an oral US contrast agent for imaging the pancreas and other retroperitoneal structures during ultrasonography of the upper abdomen.

PATIENTS AND METHODS

Thirteen patients (six men, seven women; age range, 34–81 years; mean, 56 years) who were highly suspected of having upper abdominal retroperitoneal pathology and were therefore referred for an abdominal ultrasound study were enrolled in the study. The study protocol was approved by the Human Studies Research Subcommittee of the institution. Informed consent was obtained from all the patients.

Patients were randomized to receive either contrast agent ($n = 11$) or a control agent ($n = 2$) using a randomization chart which was conceived prior to undertaking the study. The physician conducting the ultrasound study and the patient were blinded to the agent.

The contrast agent (SonoRx^R, Bracco Diagnostics, Princeton, NJ, USA) used for this study consisted of 7.5 g/l of 22-micron cellulose with 0.25% simethicone coating along with 0.2 g/l of medical anti foaming agent A (simethicone, USP), 0.1 g/l of sodium lauryl sulfate, 2.4 g/l of citric acid, 0.54 g/l of orange oil, 0.06 g/l of FD & C Yellow #6, 20 g/l of fructose, 1 g/l of sodium benzoate and purified water to 1 litre. The control agent used in this study was made up of purified water, citric acid, orange oil, fructose and preservatives. The agent was delivered in ready to drink liquid form in a glass container measuring 473 ml. Prior to administering the agent the container was inverted and shaken vigorously in order to resuspend any material settled at the bottom. The patient was asked to ingest up to 400 ml of either contrast or control agent, within 15 min. If the patient was unable to ingest the entire dose, the actual amount ingested in the 15 min was measured and recorded. Vital signs were recorded before and following the ingestion of contrast.

The enrolled patients underwent ultrasound imaging of the abdomen before and within 15 min after ingesting either contrast or control agent, in supine and right decubitus positions. Additional scanning was also performed in the sitting position if the clinical condition of the patient permitted to do so. The pre- and post-contrast ultrasound imaging were performed by the same physician. Each patient fasted for at least 4 h prior to the ultrasound evaluation. Ultrasound imaging was performed with a high resolution unit (Acuson 128; Acuson, Mountain View, CA, USA) using a 3.5 MHz or 5 MHz sector transducer depending on the patient habitus. The total scanning time, including the pre- and post-contrast imaging, averaged about 40 min. All the enrolled patients tolerated and ingested the full dose of either the contrast or control agent

Besides the routine imaging procedure of the abdomen, targeted ultrasound imaging of the pancreatic head, body and tail, the pancreatic duct, splenic vein, abdominal aorta and the paraaortic region was performed immediately prior and immediately after administration of either control or contrast agent in transverse and longitudinal planes. During the scanning, these specific anatomical structures were scored as follows: 0 = non-diagnostic image, cannot identify area of interest; cannot exclude nor detect pathology; 1 = poor, marginally diagnostic image, limited delineation, low-confidence level in excluding or detecting pathology; 2 = fair; diagnostic image, fair delineation, fair level of confidence in excluding or detecting pathology; 3 = good, diagnostic image, good delineation, good level of confidence in excluding or detecting pathology; 4 = excellent; diagnostic image, excellent delineation, high confidence in excluding or detecting pathology. Postcontrast images were also evaluated for potential gallbladder contraction. All patients underwent additional confirmatory imaging studies and/or surgery within 15 days of the study, which included computed tomography (CT) and surgery in two patients, CT and endoscopic retrograde cholangio-pancreatography (ERCP) in four patients, ERCP alone in three patients, magnetic resonance imaging and endoscopic ultrasound in one patient and CT alone with clinical follow-up in three patients.

Statistical analysis using the one sided Wilcoxon Signed Rank Test was used to determine the statistical significance

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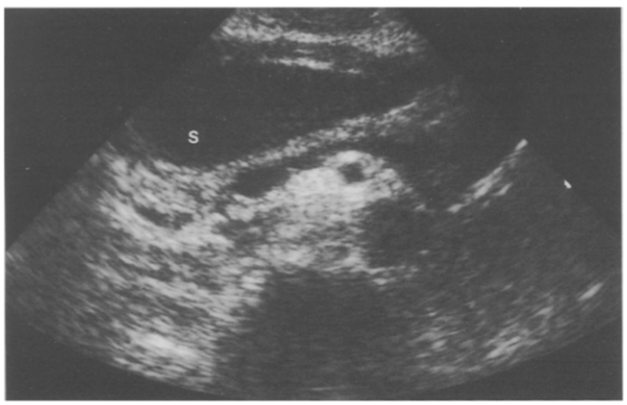

Fig. 1 – Ultrasound image (transverse plane) of the pancreas after oral administration of simethicone-coated cellulose contrast, in the same patient, showing the large acoustic window provided by the contrast agent filled stomach (S). The pancreatic head, body, the splenic vein, and the superior mesenteric artery are depicted well.

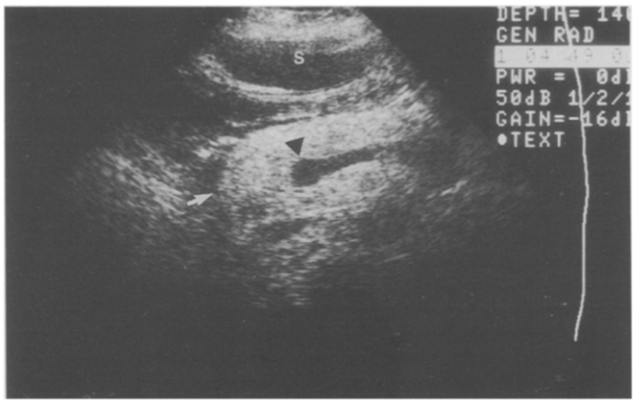

Fig. 2 – Ultrasound image (transverse plane) of the normal pancreas, following administration of simethicone-coated cellulose contrast agent. The pancreatic head (arrow) and the portal venous confluence (arrowhead) are well delineated. Note the contrast agent filled stomach (S).

between the pre- and post-contrast scores. A P-value of <0.05 was considered statistically significant and indicated that the difference between the pre- and post-contrast imaging was greater than due to chance alone.

RESULTS

The post-dose scanning with the contrast agent revealed statistically significant improved visualization of all selected areas, with the exception of the pancreatic duct. Marked reduction in the bowel gas artifacts, from the stomach, duodenum and bowel, was noted with improved sound transmission and ability to visualize the retroperitoneal areas of interest (Figs 1 & 2). A summary of the median values for the evaluated pre- and post-contrast scores, along with the P-values is shown in Table 1. Among the 11 patients who were given the contrast agent, in two patients postdose images revealed presence of pancreatic lesions which could not be seen on the predose scans. In these two patients, confirmatory studies which included CT followed by surgery revealed presence of focal pancreatitis in the head of the pancreas and adenocarcinoma of pancreatic head, respectively. In four patients significantly better delineation of pathology (seen on pre-contrast images) was noted (Fig. 3). Confirmatory imaging studies with MRI and endoscopic sonography revealed an uncinate process mass in one patient, with CT and ERCP showed pancreatic head enlargement with 2.5 cm mass, pancreatic and biliary duct obstruction due to distal common bile duct stone, and pancreatic head mass with peripancreatic haziness along distal common duct obstruction in the remaining three patients, respectively.

In the two patients administered the control agent, postdose scanning demonstrated distention of the stomach and better delineation of the gastric wall. However, no statistically significant difference was noted in visualization of the selected areas when compared to the pre-dose scanning. Confirmatory CT scans in these patients demonstrated presence of focal pancreatitis in one patient and normal scan in the other.

None of the patients demonstrated significant side-effects or gallbladder contraction following the administration of contrast.

DISCUSSION

Upper gastrointestinal ultrasound imaging, especially of the pancreas and retroperitoneum, maybe marred by presence of gas in the stomach and the bowel. Development of an oral ultrasound contrast agent for overcoming these problems has been slow. This is mainly because ultrasonography has been considered to be a readily available non-invasive modality and the inclination towards other imaging modalities (CT, MRI) for difficult cases [7]. Prior attempts with water and/or glucagon to reduce gas artifacts have met with inconsistent results in routine clinical practice [2,3,8].

Cellulose is a recognized safe, non-nutritive, well tolerated food additive with negligible toxicity. Because of favourable bulk and surface tension properties cellulose has been evaluated in the past for ultrasound imaging of the upper gastrointestinal tract especially of the pancreas with encouraging results. However, a recent study with cellulose as an ultrasound contrast agent was performed in healthy volunteers [5] who were administered 800 ml of the

Table 1 – Assessment of upper abdominal structures by ultrasound: summary of median values along with P-values for pre- and post-contrast reader scores

	Pancreas				*Splenic vein*	*Abdominal aorta*	*Paraaortic lymph nodes*
	Head	*Body*	*Tail*	*Duct*			
Pre-contrast	2	3	2	2	3	2	2
Post-contrast	3	3*	2	2	3	3	3
	$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.07$	$P < 0.05$	$P < 0.05$	$P < 0.05$

Scores: 0, non-diagnostic; 1, poor; 2, fair; 3, good; 4, excellent. * While the median values are restricted to the five categories and can be equal, the statistical test and P-values consider the entire distribution. Thus a P-value can be significant even if the median values are equal.

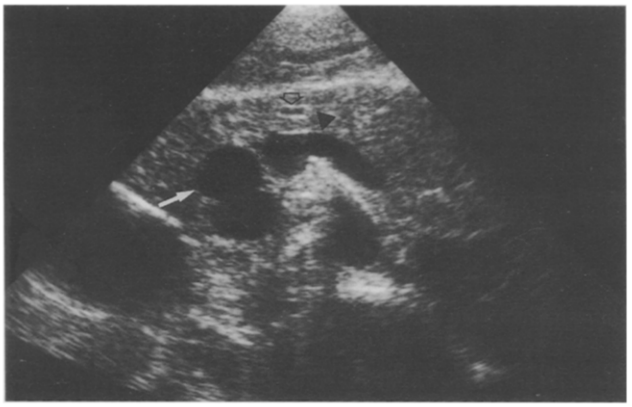

Fig. 3 – Post-contrast ultrasound image (transverse plane) of the pancreatic head and body showing significant dilatation of the distal common bile duct (arrow) with no evidence of stones. Also depicted well are the splenic vein (arrowhead) and the pancreatic duct (open arrow).

agent. Our study involved administration of a more compliant dose of 400 ml in patients with highly suspected upper gastrointestinal disease. Together with simethicone, cellulose leads to a uniform low echogenicity and reduction of gas artifacts in the bowel and the stomach, by displacing and adsorbing the gas. Combining the cellulose with an antifoaming agent like simethicone probably allowed a lesser, more compliant dose to be administered in order to facilitate an optimal ultrasound study and enable better visualization of the pancreas and other retroperitoneal anatomical structures without hindrance from gas artifacts.

In our study we found significant improvement in the visualization of the pancreas, abdominal aorta, paraaortic region and splenic vein. The two patients, in whom postdose scans revealed pancreatic lesions not seen on the predose, the postdose findings significantly affected the clinical management. The lack of statistically significant difference in visualizing the pancreatic duct predose from postdose, was probably due the absence of significant dilatation of the duct in majority of the patients. Although the two patients in our study who received the control agent, demonstrated good distention of the stomach and visualization of the stomach wall, there was no statistically significant difference in visualization of the selected retroiperitoneal areas, due to artifacts caused by ingested air along with the control agent.

We believe that simethicone coated cellulose can be an effective oral contrast agent which can be used even in situations where patients with abdominal disease present to the emergency in the non-fasting state. Use of simethicone coated cellulose contrast agent in these patients may allow, a cost effective modality such as ultrasound to be used effectively to screen them for retroperitoneal disease and guide them into further imaging studies only as required.

Our study was limited by the small number of patients who were administered the contrast agent ($n = 11$) and the placebo ($n = 2$) However, this being a preliminary study for use of simethicone coated cellulose in patients highly suspected of having upper gastrointestinal disease, our main aim was to assess the potential of the agent as an effective oral gastrointestinal contrast agent. The use of control agent was mainly to randomize the administration of contrast and keep the assessing radiologist blinded. The lack of significant difference in visualizing the retroperitoneal areas of interest with the control agent must therefore be interpreted with caution.

Simethicone-coated cellulose as an oral ultrasound contrast agent enhances ultrasound imaging of the pancreas and other retroperitoneal anatomical areas with fewer gas artifacts and greatly improves reader confidence in assessing these areas. Further studies, in future, with larger patient population would be needed to assess the full potential of this contrast agent and also compare its efficacy in comparison with water.

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