Review Article

Revisiting Oral Barium Sulfate Contrast Agents[1]

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Oral contrast agents used during CT colonography (CTC) are valuable and may reduce false positive and false negative detections due to stool and residual fluid. Electronic cleansing algorithms are feasible, and oral contrast agents can eliminate the CTC requirement for a clean colon. Recent work shows oral contrast frequently adheres to polyps, with a preference for those with villous histology, a characteristic of advanced polyps. This finding encourages the development of contrast agents that highlight polyps at greatest risk for progression to malignancy. Our review summarizes numerous aspects of oral barium sulfate contrast agents as well as tests to assess adherence and coating ability of the agents, offering arenas to explore and tools for evaluation.

Key Words. CT colonography; colonic polyps; villous adenoma.

With the coming era of oral contrast-enhanced CT colonography (CTC, or virtual colonoscopy), this is an opportune time to revisit oral barium sulfate contrast agents. As stool and isoattenuating residual fluid are common causes of false negative and false positive detections during CTC, marking colon contents with oral contrast agents may improve the accuracy of CTC (1–6). Indeed, studies using oral contrast agents have shown them to be valuable and suggest that they be routinely administered (7–12). Electronic cleansing algorithms that remove opacified fluid are feasible and allow for three-dimensional endoluminal imaging of oral contrast−enhanced studies (8, 9, 13–17). Oral contrast agents may also eliminate the requirement for a clean colon, as opacified stool and residual fluid can be distinguished either electronically or visually from polyps and normal colonic mucosa (13, 14, 18–21).

The use of oral contrast agents to purposefully coat abnormal colonic mucosa during CTC has not previously been a subject of interest. However, recent research shows that oral contrast agents often coat polyps with a preference for those at risk for villous histology, a property of advanced polyps (22). This finding may allow characterization of colonic mucosa at a level of detail smaller than generally thought possible with CTC.

In order to study oral contrast agents and their role as general opacification or targeted coating materials, it is necessary to review the complex formulation of their contents and address why they coat colonic mucosa. These questions have not been addressed for some time but have become relevant again with the use of contrast-enhanced CTC. Due to proprietary information restrictions, little is known about the exact ingredients and makeup of current oral contrast agents, leaving many questions to be answered by future research. Our review summarizes various aspects of oral barium sulfate preparations and provides possible arenas to explore when developing contrast agents that will preferentially adhere to polyps or normal mucosa.

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ORAL BARIUM SULFATE SOLUTION BASICS

Available Formulations

Oral barium sulfate contrast agents are available in powder or liquid forms; powders need to be reconstituted with water and liquids may need to be diluted. Barium sulfate agents are superior to water-soluble contrast media in their ability to define the mucosal surface and their resistance to dilution (23, 24). As the pH of the gastrointestinal tract may range from 0.8 to 8.0, different formulas have been created to optimize coating for specific studies (25). Double contrast barium enemas (DCBEs, the study that approximates coating seen during CTC) usually use concentrations of barium sulfate in the range of 50−61% w/w or 80−100% w/v (26, 27).

There are many brands of barium sulfate available for clinical use. The major U.S. manufacturers are E-Z-Em (Lake Success, NY; http://www.ezem.com/) and Tyco Healthcare (Mansfield, MA; Mallinckrodt subsidiary and Lafayette products, Hazelwood, MO; http://imaging.mallinckrodt.com/).

Labeling

In the past, labels on barium sulfate suspensions were not to be believed. In his 1953 paper, Hodges stated, "The labels appear to have been composed by sales managers rather than chemists or pharmacists and seem calculated to mislead rather than to inform" (28). Labeling laws of the United States Pure Food and Drug Act did not require precise or complete labeling of "inactive ingredients," and inquiries to manufacturers were "sometimes ignored, evaded, or, worse, returned with the fallacious statement that no additives are used" (29). Miller detailed the usually less-than-helpful formulas and correspondence received from manufacturers in the course of his 1965 study (29). Some manufacturers labeled their products as "colloidal barium sulfate," indicating the preparation had particles ranging from 0.1 to 0.001 μm with a state of hydration that made them stable in water without suspending agents, but experiments showed this labeling was used inaccurately (28). While a substantial number of additives had been mentioned in patient and radiologic literature or disclosed on labels, Miller comments in his 1983 book chapter that manufacturers maintain secrecy as to the detailed contents of their preparations (30). While labeling laws have become stricter since these papers were published, manufacturers may still use vague terms such as "suspending agents" instead of specifically identifying the additives used.

Purpose

Oral barium sulfate contrast agents for DCBEs create a thin, radiodense coat on the colonic wall that allows the identification of mucosal abnormalities. The goal is to attain a coating of 0.01 g of barium sulfate/cm^2 of surface area, independent of particle size or the concentration of the preparation (31). The topography of the surface to be coated is important, as adsorption into grooves is consistently higher than total adsorption (32). One study goes so far to say that the description of coating colon strips must be broken down into "barium retained in the crevices" and "barium remaining adherent to the elevated areas or ridges" and shows that at low concentrations almost all of the barium falls into the former category (33). A summary of the properties of barium sulfate preparations and their clinical relevance is presented in Table 1.

BARIUM SULFATE PARTICLES

Particle Size

Particle size and size distribution can vary with the method of preparation, with particles from four preparations in one study ranging from 0.07 to 0.70 μm (34). Another study mentions "excellent suspensions" with average particle size of 4 μm and a maximum of 12 μm (29). Miller notes that preparations all have various ranges of micron-sized particles, some measuring from 0.1 to 44.0 μm or more (30). Dry blending of pulverized barium ores produces larger particles with a gritty texture, wet formulations are less gritty, and chemical precipitation from solution produces rather uniform fine-particle bariums (25, 27). Small particle suspensions have longer shelf-lives, as they resist sedimentation, but this may not be important when preparations are reconstituted immediately before examinations (35). As particle size decreases, surface area increases dramatically. This increases adsorption of water and thus the viscosity of the suspensions (36).

For gastric examination, "high density" suspensions with large particles have been considered superior to "low density" suspensions with small particles for coating the mucosa, as mucosal grooves are defined by the large particles that collect in them (35). However, some authors do not consider particle size an important predictor of mucosal coating (31).