ASGE Technology Status Evaluation Report: radiographic contrast media used in ERCP

To promote the appropriate use of new or emerging endoscopic technologies and those technologies that impact on endoscopic practice, the American Society for Gastrointestinal Endoscopy Technology Assessment Committee has developed a series of status evaluation papers. This process presents relevant information about these technologies to practicing physicians for the education and the care of their patients. In many cases, data from randomized controlled trials are lacking and only preliminary clinical studies are available. Practitioners should continue to monitor the medical literature for subsequent data about the efficacy, the safety, and the socioeconomic aspects of these technologies.

BACKGROUND

Water-soluble iodine-based contrast media (CM) is injected into the biliary and the pancreatic ducts during the performance of endoscopic retrograde cholangiopancreatography (ERCP).[1] Most of our knowledge regarding the efficacy, the safety, and the side effects of various CM, however, derive from their intravenous use in radiology and only, to a lesser degree, from their use in ERCP. This report reviews the use of CM in ERCP, including its relation to image quality, the likelihood for systemic absorption, and the risk for, and means of, reducing adverse reactions. There are no evidence-based standards of practice for prophylaxis against contrast reactions during the performance of ERCP. Current clinical practices are commonly based on radiologic recommendations for intravenous administration of CM.

TECHNICAL CONSIDERATIONS

All CMs currently available can be classified into one of 4 groups: ionic monomer, ionic dimer, nonionic monomer, and nonionic dimer. All are benzoic acid derivatives with molecular weights less than 2000. They possess one or two benzene rings and, therefore, are monomers or dimers. They are hydrophilic, with low lipid solubility and a low binding affinity for proteins. They move freely in the extracellular space. The number of particles into which they dissociate in solution determines the osmolality of these media. The number of iodine atoms in the parent molecule determines the density of the CM and, therefore, the degree of attenuation of x-ray photons.

Ionic monomers dissociate in solution into cations (e.g., sodium or methylglucamine) and anions (the iodine-containing benzene-ring component, such as iothalamate or diatrizoate). These compounds are highly osmolar (~1500 mOsm/kg for 300 mg iodine/mL) and are termed high osmolality contrast media (HOCM). Nonionic CM does not dissociate and has the lowest osmolality (~600 mOsm/kg for 300 mg iodine/mL) and is termed low osmolality contrast media (LOCM). Ionic dimers dissociate into two particles but carry 6 iodine atoms, so that the osmolality remains low for the degree of x-ray attenuation achieved.

EFFICACY AND EASE OF USE

The effect of CM on image quality during ERCP is the resultant interaction of density, viscosity, and osmolality. Although no optimal iodine concentration has been defined for ERCP, the most commonly used CMs provide between 150 and 300 mg iodine/mL. Such concentrations are derived from vascular and urographic experience where, in general, equivalent iodine concentrations produce equivalent images for the same radiographic conditions. Dilution of HOCM directly affects radiographic quality. The image quality appears to be similar when comparing HOCM and LOCM.[2] However, HOCM has become the standard agent used for ERCP, primarily on the basis of its low cost, approximately 20 to 40 times less than that of LOCM.[1]

The quality of fluoroscopy and the technique of injection also influence the quality of images obtained. Ease of injection, especially through small-diameter catheters,

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is greatly affected by CM viscosity. Clinical experience suggests that small gallstones within large ducts may be better imaged with dilute contrast, whereas strictures and pancreatic-duct anatomy are better imaged with full-strength contrast. The need for increased volumes and the introduction of air during syringe changes are potential disadvantages of diluting contrast.

SAFETY AND CLINICAL DATA

The osmolality and the ionic nature of the CM are believed to be the major factors responsible for many of the adverse events that occur after intravascular administration. It has been postulated that low osmolar agents may be safer than high osmolar agents for the performance of ERCP, because reduced osmotic fluid shifts across ductal mucosa and pancreatic acini may yield less prominent increases in intraductal pressures. However, this has not been confirmed in clinical studies of postprocedure pancreatitis or other local complications.

SYSTEMIC ABSORPTION

The risk for serious adverse reactions largely relates to the amount of contrast that is systemically absorbed, which, in turn, depends on the volume and the pressure of injection, the duct studied (greater during pancreatography), and the iodine concentration of the contrast agent. The rise in serum iodine concentration associated with instillation of CM during ERCP is about 1/100 that seen with intravenous administration.[3] Diagnostic ERCP yields 0.6% of the systemic iodine load that results from coronary angiograms.[4] Thyroid function has been used as an indirect marker of systemically delivered iodine, and no clinical thyroid abnormalities have been identified in these studies.[4,5]

SYSTEMIC REACTIONS

Systemic adverse reactions to CM used in ERCP have been documented, but their true incidence is unknown. Adverse reactions can be characterized as idiosyncratic or nonidiosyncratic, based on their proposed mechanisms. In general, nonidiosyncratic reactions are most likely dose and osmolality related, whereas idiosyncratic (anaphylactoid) reactions usually occur immediately. Acute CM reactions can be subdivided into minor, intermediate/moderate, and severe (Table 1).[6] Minor reactions are self-limiting, are usually of short duration, and, in general, do not require specific therapy; intermediate or moderate reactions, in most cases, respond well to supportive treatment; and severe reactions, while very rare, may require immediate resuscitative efforts. For this reason, it is important that appropriate emergency medications and resuscitative equipment are readily available. Delayed reactions are defined as occurring between 1 hour and 7 days after the contrast injection and usually are mild. While it may be difficult to verify the association of delayed adverse events to CM use, they are assumed to occur in 2% to 8% of patients who receive intravenous CM.[6] The prevalence of intravenous CM reactions is lower with LOCM than with HOCM.[7] Fatal reactions are exceedingly rare with both types of CM (1:170,000), and there is no difference in associated mortality between the two types.[6,8]

The data specific to ERCP-related CM reactions are very limited, prompting us to review the literature for intravenous CM. It is important to acknowledge that neither skin testing nor test challenge doses have been predictive for significant reactions related to intravenous exposure. Patients at increased risk for adverse reactions include those with a history of allergic diathesis, e.g., asthma, and those with a prior reaction to CM. Use of intravenous LOCM in such patients would decrease the risk of reactions compared with HOCM.

PROPHYLAXIS AGAINST SYSTEMIC REACTIONS

There is no evidence-based standard of practice for prophylaxis against contrast reactions during the performance of ERCP. Current clinical practices are commonly based on radiologic recommendations for intravenous administration of CM. A single, small survey of 42 physicians noted that 8% had personal experience with a suspected CM reaction at ERCP, and 83% used prophylaxis in patients with a prior reaction to CM or food allergies, e.g., shellfish.[9]

Prophylaxis with corticosteroids helps decrease the risk of reactions to intravascular administration of CM but does not eliminate it completely. Clinical experience has demonstrated that corticosteroids should be administered a significant time before the procedure; a single dose within 2 hours of the procedure is inadequate to provide a protective benefit.[10] All grades of systemic reactions occur less frequently with LOCM than with HOCM; the combination of steroid pretreatment plus intravenous LOCM yielded a lower rate of adverse reactions than placebo plus LOCM.[11] Most authorities combine corticosteroid pretreatment and LOCM in patients with a history of a moderate or severe anaphylactoid reaction to intravenous CM.[10,12]

Several premedication regimens have been proposed by the American College of Radiology to reduce the frequency and/or the severity of reactions to intravenous CM. Neither of these approaches has been tested in the setting of ERCP, thus, their use cannot be recommended as being evidence based. Two frequently used regimens[13] are the following:

1. Prednisone, 50 mg by mouth at 13 hours, 7 hours, and 1 hour before CM, plus 50 mg diphenhydramine

TABLE 1. Categories of acute reactions*

Mild		
Nausea, vomiting	Altered taste	Sweats
Cough	Itching	Rash, hives
Warmth	Pallor	Nasal stuffiness
Headache	Flushing	Swelling: eyes, face
Dizziness	Chills	Anxiety
Shaking		
Treatment: Requires observation to confirm resolution and/or lack of progression but usually no treatment; patient reassurance usually is helpful.		
Moderate		
Moderate degree of clinically evident focal or systemic signs or symptoms including:		
Tachycardia/bradycardia	Hypotension	Bronchospasm, wheezing
Hypertension	Dyspnea	Laryngeal edema
Pronounced cutaneous reaction		
Treatment: Clinical findings should be considered as indications for immediate treatment; these situations require close, careful observation for possible progression to a life-threatening event.		
Severe		
Life-threatening with more severe signs or symptoms, including:		
Laryngeal edema	Profound hypotension	Unresponsiveness
Convulsions	Clinically manifest arrhythmias	Cardiopulmonary arrest
Treatment: Requires prompt recognition and treatment; almost always requires hospitalization.		

*Data from the American College of Radiology Committee on Drugs and Contrast Media.[13]

(Benadryl; Pfizer, New York, NY) intravenously, intramuscularly, or by mouth 1 hour before the CM injection.

2. Methylprednisolone, 32 mg by mouth 12 hours and 2 hours before contrast medium injection. An antihistamine, as in regime 1, also can be added to this regimen.

Alternatives to contrast-based ductography during performance of therapeutic ERCP in patients at very high risk of serious CM reactions include the use of radiographic imaging with ''air contrastography''[14] and the use of cholangioscopy or pancreatoscopy without fluoroscopy.[15]

RISK ASSOCIATED WITH POST-ERCP PANCREATITIS

A variety of risk factors for post-ERCP pancreatitis have been identified.[16,17] In theory, the intraductal presence of CM could provoke pancreatitis[18]; yet, no clinical risk has been identified specifically based upon media type. A recent meta-analysis revealed no statistical difference in the risk of clinical post-ERCP pancreatitis with the use of HOCM vs. LOCM[19]; however, high osmolar contrast was associated with an increased incidence of asymptomatic elevations of pancreatic enzymes. The analysis included a single crossover study and 5 randomized controlled trials in favor of LOCM, and 11 others that showed no benefit of one CM over another.[19]

ANTIBIOTICS IN CONTRAST MEDIA

The addition of nonabsorbed aminoglycoside antibiotics to CM has been advocated by some centers to decrease septic complications of ERCP.[20] There are few studies that examine this question, and none have demonstrated a significant clinical advantage, although most have been small and thus subject to a type II error.[21-23]

TABLE 2. Characteristics of radiographic contrast media*

Classification and contrast media	Ionic monomer (HOCM) Diatrizoate [Renografin] [RenoCal] [Hypaque] [Urografin] Iothalamate [Conray] Metrizoate Ioxithalamate Iodamide Ioglicate	Ionic dimer (LOCM) Ioxaglate [Hexabrix]	Nonionic monomer (LOCM) Iopamidol [Isovue] Iohexol [Omnipaque] Ioversol [Optiray] Iopromide [Ultravist] Ioxilan [Oxilan] Iopentol	Nonionic dimer (LOCM) Iotrolan [Iotrol] Iodixanol [Visipaque]
Osmolality mOsm/kg H_2O	1400-2300	600	400-800	290
Cost per 50 mL	$3-$7	$37	$35-$50	$45-$55

HOCM, High osmolality contrast media; *LOCM,* low osmolality contrast media.
*Data from Kimmey et al[1] and the American College of Radiology Committee on Drugs and Contrast Media.[13]

FINANCIAL CONSIDERATIONS

The costs of CM used during performance of ERCP vary widely. Typically, 50-mL bottles of HOCM cost $3 to $7, compared with $35 to $55 for LOCM, (Table 2). These costs may be separately billable to private insurers predicated on individual contract arrangements. Medicare includes the cost of contrast in the global facility (ambulatory payment classification) reimbursement schedule for hospital or endoscopy center outpatient procedures and in the Diagnosis Related Group payments for inpatient procedures.

RECOMMENDATIONS

The safety data derived from studies of the intravascular use of LOCM cannot be translated to ERCP in view of their low incidence of serious adverse events with nonvascular use. The evidence is lacking to support LOCM as a method for decreasing ERCP complications.

There is no justification for the routine use of LOCM during ERCP. In patients considered at high risk for CM-related reactions (i.e., those with a prior serious anaphylactoid reaction to intravascular CM), premedication and/or substitution of LOCM may be considered as an option based on the above-mentioned theoretical considerations.

The low frequency of sepsis after adequate biliary and pancreatic drainage at ERCP and the lack of data argue against the practice of routinely adding antibiotics to CM. Additional data are needed regarding the use of antibiotics in contrast media for those disease states in which optimal drainage cannot be accomplished.

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