

CLINICAL REVIEWS

Iodinated Contrast Sensitivity in ERCP

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ABSTRACT

Iodine contrast media are detectable in the bloodstream after ERCP, and sensitivity reactions have been described. The risk is very small, and the phenomenon is therefore difficult to study. This review discusses the possible need for preventative strategies, and recommends that endoscopists consider the issue and define their own policies. (*Am J Gastroenterol* 2000;95:1398–1401. © 2000 by Am. Coll. of Gastroenterology)

INTRODUCTION

Systemic adverse reactions to iodine-containing contrast media (CM) used during ERCP have been reported (1–4). They are very rare, but the exact incidence is unknown. Bilbao *et al.* reported only three minor adverse reactions (rash) after 8681 ERCPs. This figure was based on a voluntary postal survey and cannot be considered exact or complete (2). In a similar retrospective review, one incidence of shock was documented after “more than 2000 ERCPs” (3). Catalano *et al.* studied, in a prospective fashion, the incidence of “acute allergic reactions” during ERCP in 25 patients with documented prior reaction to *i.v.* CM. One incidence of postprocedure pruritus was observed (4). Opinions on appropriate prevention strategies vary, and no formal guidelines have been published. The rarity of reactions makes study and consensus difficult. The review covers relevant available data, and discusses the possible preventative strategies.

CONTRAST MEDIA ARE ABSORBED AFTER ERCP

Systemic absorption of CM after ERCP is well documented (1, 2, 5–11). Urographic visualization of contrast has been observed on plain films after ERCP in 5–37% of cases (5, 9–11). CT scanning detected renal excretion of CM in 69% of patients (8). Serum concentration of CM increased significantly in 76% of patients after ERCP (7). Mann *et al.* measured serum iodine concentration before and after ERCP (6). A highly significant increase was seen in all patients, but this was substantially lower (100 times) than is found with intravenous (*i.v.*) administration of the same amount of contrast (6).

LESSONS FROM RADIOLOGY: ADVERSE REACTIONS AFTER INTRAVASCULAR ADMINISTRATION OF CM

The issue of adverse reactions after intravascular administration of CM has been studied extensively (12–27). Adverse reactions to CM can be classified as mild (nausea, vomiting, pruritus, diaphoresis, flushing, and mild urticaria), moderate (faintness, severe vomiting, profound urticaria, mild bronchospasm, mild hypotension, mild tachycardia, or bradycardia) and severe (hypotensive shock, angioedema, respiratory arrest, cardiac arrest, convulsions, and death) (4, 13). According to the underlying mechanism, reactions can be divided into nonidiosyncratic and idiosyncratic (anaphylactoid). Nonidiosyncratic reactions are related to the dose and osmolality of the contrast medium and include hypertension, arrhythmia, cardiac depression, ECG changes, flushing, nausea, vomiting, renal failure, and hypo- and hyperthyroidism (6, 12, 13, 27). The idiosyncratic reactions are not dose-dependent, occur immediately or within 20 min after contrast exposure and consist of urticaria, bronchospasm, angioedema, laryngospasm, shock, cardiac arrest, and death (13, 27). Because of the relatively small absorption of contrast, nonidiosyncratic reactions are not observed during ERCP (6). On the other hand, idiosyncratic reactions have been described (1–4). For that reason the following discussion will concentrate on the idiosyncratic adverse reactions.

Based on large studies from the radiological and cardiological literature we have a better understanding of adverse reactions occurring after intravascular administration of CM, including the following points. First, the incidence of adverse reactions in the general population is 1–12% (12, 13, 21, 22, 27). Second, risk factors for reaction to CM include: a) Prior reaction to CM increases the likelihood of a repeated adverse reaction (prevalence of 17–35%), although in a given individual, a repeat reaction may not occur (12, 13, 23, 24); and b) Patients with a history of allergic diathesis (asthma in particular), but no prior reaction to CM, are at increased risk (prevalence of 14.5%) (12, 13, 27). The predictive value of a specific food allergy, such as to shellfish or dairy products, previously thought to be helpful, is now recognized to be similar to that of other food allergies. Third, adverse reactions cannot be predicted by the use of skin testing or challenge with a test dose of CM (13, 24).

Fourth, prophylactic premedication in patients with a prior reaction to CM decreases the risk of subsequent reac-

tion but does not eliminate it (12, 13, 14, 27). Multiple regimens have been tested. Corticosteroids are the essential component and should be included in any premedication protocol. Greenberger *et al.* directly compared three regimens in a prospective, nonrandomized fashion (14). The first regimen (415 cases) consisted of a combination of: 1) prednisone 50 mg orally (*p.o.*) 13 h, 7 h, and 1 hour before the procedure; and 2) diphenhydramine hydrochloride (Benadryl) 50 mg *p.o.* orally or intramuscularly (*i.m.*) 1 h before the procedure. In the second regimen (180 cases), ephedrine sulfate 25 mg *p.o.* 1 h before the procedure was added to the prednisone-diphenhydramine combination. In the third regimen (100 cases), cimetidine 300 mg *p.o.* 1 h before the procedure was added to the prednisone-diphenhydramine-ephedrine combination. The lowest incidence of adverse reactions to CM occurred with the second prophylactic regimen (5%). The incidence of reactions with regimens 1 and 3 was 11% and 14%, respectively.

The American College of Radiology recommends three alternative prophylactic regimens in high-risk patients before intravascular administration of CM (27): 1) Oral corticosteroid/antihistamine: prednisone 50 mg *p.o.* at 13, 7, and 1 h before the procedure, plus diphenhydramine 50 mg *i.m.* or *p.o.* 1 h before contrast administration; 2) Oral corticosteroid alone: methylprednisolone 32 mg *p.o.* 12 and 2 h before procedure; or 3) Intravenous corticosteroid/antihistamine: hydrocortisone 200 mg *i.v.* at 13, 7, and 1 h before the procedure, plus diphenhydramine 50 mg *i.m.* 1 h before contrast administration. Because oral administration of steroids is preferable to intravascular, this regimen is reserved for patients who cannot take medications by mouth.

Fifth, pretreatment with *i.v.* corticosteroids immediately before the procedure is not effective (25–27). An interval of ≥ 6 h between the corticosteroid administration and the injection of CM is recommended, regardless of the route of steroid administration (27).

Sixth, the use of nonionic/low-osmolality CM decreases the risk of an adverse reaction when used intravascularly (12, 15–20, 27). A decrease in the prevalence of urticaria, bronchospasm, angioedema, and cardiac arrest is reported (12, 27). In patients with a prior reaction to CM, the use of nonionic media resulted in a significant decrease in the total number of reactions (11.24% vs 44.4%) and in the number of severe reactions (0.18% vs 0.73%) (12). Nonionic/low-osmolality CM have lower reaction rates than the combination of premedication plus conventional ionic/high-osmolality agents (27). A further reduction in adverse reactions is seen when nonionic/low-osmolality CM are combined with prophylaxis in patients with a prior reaction to CM (27).

ALTERNATIVE CONTRAST MEDIA FOR ERCP

Nonionic CM has been directly compared with conventional CM in studies attempting to decrease the incidence of pancreatitis after ERCP (28–32). Two prospective double-blind trials reported by Bedford *et al.* failed to show an overall

decrease in the incidence and severity of post-ERCP pancreatitis with the use of nonionic CM (29, 30). Furthermore, no difference was seen in different groups of patients and procedures (diagnostic ERCP vs diagnostic ERCP with sphincter of Oddi manometry vs therapeutic ERCP) (30). At present, the literature supports the contention that the incidence and severity of pancreatitis after ERCP is not altered by the use of ionic or nonionic CM. Unfortunately, since the goal of these trials was to evaluate the incidence of post-ERCP pancreatitis, the incidence of adverse reactions to CM was not reported. Meglumine gadoterate is a rare-earth paramagnetic contrast agent used in magnetic resonance imaging that also has some radiocontrast properties unrelated to iodine. Although safe, it cannot be recommended for routine ERCP because of poor visualization of the biliary tree and pancreas (33). Air could be used as a contrast medium for endoscopic cholangiography, but its value has not been studied.

CURRENT CLINICAL PRACTICE

We surveyed, by questionnaire, (Table 1) a total of 42 endoscopists (25 from academic centers and 17 from community practice) attending an endoscopy conference. As we suspected, current clinical practice varies widely.

Most of the responders in our survey have extensive experience with ERCP. Only 8% had personal experience of CM reactions at ERCP (two cases of urticaria and one seizure).

The majority of the practitioners (83%) do use prophylactic measures in patients with a prior reaction to CM or food allergy (shellfish). The most commonly used regimen (48%) is prednisone given *p.o.* in three doses (usually 12, 6, and 1 h before the procedure). The dose of prednisone varies from 10 to 50 mg. One-third of responders give *i.v.* steroids within 1 h before the procedure. A combination of oral prednisone the day before and intravenous steroids within 1 h before ERCP is used by 14%. Antihistamine is added to the steroid premedication by 51%, and cimetidine by 12%.

When the prior allergy to CM is discovered immediately before the ERCP, the majority of the endoscopists will perform the procedure after premedication with *i.v.* steroids (74%); the remainder postpone it and give an overnight oral regimen of steroids.

Most practitioners (63%) will use nonionic/low-osmolality CM in case of prior reaction, and 8% use nonionic CM in all patients regardless of prior history of adverse reaction.

Most endoscopists (72%) did not have a formal agreement (*i.e.*, written endoscopy unit policy) with their partners on how to approach the problem of contrast sensitivity in ERCP.

WHAT DO WE DO?

Because of the rarity of reactions, it is unlikely that different prophylactic regimens will ever be tested in numbers suffi-

Table 1. Questionnaire Responses From 42 Endoscopists

Questions/Answers	Response (%)
Which scenarios best fit your practice?	
Ignore all statements about prior reaction to contrast or allergic diathesis	7 (17%)
Use prophylaxis in selected patients	35 (83%)
If you use prophylaxis, do you use it if the patient reports:	
Allergic diathesis (e.g., asthma, urticaria etc.) but no history of contrast reaction	0 (0%)
Prior reaction to contrast or food (shellfish)	22 (52%)
Prior reaction to contrast only (ignore food)	13 (31%)
Your regimen if/when prophylaxis is used is:	
Oral prednisone in three doses starting the day before the ERCP X	17 (48%)
Oral prednisone the day before the ERCP plus intravenous steroids immediately prior to the procedure	5 (14%)
Intravenous steroids immediately prior to the procedure	11 (32%)
Use low osmolality contrast media for the ERCP with no added premedication	2 (6%)
If you use steroid prophylaxis do you add:	
Diphenhydramine hydrochloride	17 (51%)
Cimetidine	4 (12%)
Ephedrine sulfate	0 (0%)
If the prior reaction is recognized immediately prior to ERCP do you use:	
Intravenous steroids immediately prior to the procedure	26 (73%)
Postpone the ERCP and give >12 hours oral steroids prophylaxis	7 (20%)
Use low osmolality contrast media for the ERCP with no added premedication	2 (6%)
Do you use low osmolality contrast media in "allergic" patients?	26 (63%)
Are your opinions agreed by your group (i.e. in a written unit policy)?	12 (28%)
Have you ever seen a "contrast reaction" at ERCP (please specify)?	3 (8%)

cient to provide definitive guidance. We recommend that each endoscopy unit/provider and team review the issue (preferably with radiological colleagues) and formulate a policy. Some may conclude that the risk is so small that it can be ignored. Documentation of the agreed policy should provide some legal protection in the rare case of an adverse reaction.

Our policy is to consider patients to be at increased risk if they report any prior reaction to CM or an allergic diathesis. For those patients at increased risk, our unit policy is to do the following: 1) Establish the absolute necessity of the ERCP; 2) Discuss the increased risk of adverse reaction to CM with the patient; 3) Premedicate with steroids *p.o.* starting the day before ERCP (we use 20 mg of prednisone *p.o.* 13, 7, and 1 h before the procedure); 4) Use nonionic/low-osmolality CM; 5) Postpone the ERCP and give a full premedication regimen *p.o.* if an allergy to CM is discovered immediately before the procedure; and 6) Ensure that emergency therapy is available immediately.

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Received Aug. 17, 1999; accepted Feb. 1, 2000.

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