

Exposure to Iopamidol After Endoscopic Retrograde Cholangiopancreatography

Assessing pancreatic toxicity

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Iopamidol is an iodinated nonionic monomer and low-osmolar contrast medium (LOCM) used almost during each endoscopic retrograde cholangiopancreatography (ERCP) for visualization of either or both primary pancreatic or biliary ducts. During ERCP, the pancreas is exposed to chemical, hydrostatic or physical injury caused by injection of iopamidol solutions through the cannulated Vater ampulla. The aim of this paper is to assess recent literature findings of potential pancreatic toxicity of iopamidol and confront them with experimental findings, as post-ERCP pancreatitis is a severe, life threatening condition. Even if LOCM are considered safe in what post-ERCP pancreatitis is concerned, literature findings are discrepant. Nevertheless, iopamidol-containing water solutions were reported to cause pancreatic cell damage on both clinical and in vivo animal studies. Main toxic effect is considered that of osmolality. To conclude, larger, multicentric studies and better designed toxicity definitions are needed for a more thorough assessment of potential iopamidol-related post-ERCP pancreatitis.

Keywords: iopamidol, toxicity, pancreatitis, endoscopic retrograde cholangiopancreatography

ERCP is a frequently performed gastrointestinal endoscopic procedure in which a special endoscope called duodenoscope is inserted in the upper digestive tract up to the duodenum in order for the Vater ampulla to be cannulated [1]. Afterwards, water-soluble iodine-based contrast media (CM) is injected through a transampullary catheter into the biliary and pancreatic ducts [2]. One of the most widely used CM in Romania is iopamidol. Unfortunately, as most of the literature findings and guidelines recall, knowledge regarding CM efficacy, safety and side effects derives in the vast majority of cases from their intravenous use [3]. As up to date guidelines state, CMs available today can be classified depending on the number of benzene rings possessed into one of the following four groups: ionic monomer, ionic dimer, nonionic monomer, and nonionic dimer CMs – all being benzoic acid derivatives with molecular weights less than 2000 [3]. While ionic CM have osmolalities over 1400 mOsm/kg and are considered high osmolar contrast media (HOCM), nonionic CM are characterized by osmolalities between 300 and 800 mOsm/kg and therefore are considered low osmolar contrast media (LOCM) [2, 4]. Examples of nonionic monomer LOCM are Iopamidol, Iohexol, Ioversol, Iopromide, Ioxilan, Iopentol. These are high-priced CMs with osmolalities ranging from 400 to 800 mOsm/kg.

On the other hand, iopamidol is used not only in ERCP or other endoscopic contrast-enhanced procedures. Firstly, the substance was designed to be used as a CM for angiography, excretory urography or myelography. Afterwards, iopamidol has started being used to enhance computed tomography whole-body imaging especially in what vascular abnormalities and malformations or solid tumors are concerned. To date, iopamidol is most widely used as intravascular CM for computed tomography. Subsequently, many studies assessed potential side effects of iopamidol, especially regarding allergic reactions and kidney toxicity, as iopamidol is administered mainly intravenously and excretion is almost entirely urinary. Peak

plasma concentrations occur rapidly allowing almost instant post-injection visualization of organs, but afterwards urinary excretion is a very slow process. This is why most of the studies focused on potential nephrotoxic effects of iopamidol, and furthermore, warnings and counter indications were stated for intravascular use of iopamidol in patients with renal impairment. Specific recommendations regarding dose adjustment of iopamidol in renal impairment are not stated, but iopamidol is contraindicated in patients with chronic kidney disease or acute renal failure or impairment, especially in absence of post-exposure hemodialysis. Systemic concentrations of iopamidol after intrabiliary and intrapancreatic administration during ERCP were not thoroughly studied.

Iopamidol and its chemical properties

Iopamidol is an iodinated nonionic monomer and low-osmolar CM, extensively used during angiography, excretory urography, myelography and computed tomography imaging. Iopamidol was approved by the FDA on December 31st, 1985. Iopamidol is an organic compound used as water soluble radiographic contrast medium, and acts by blocking x-rays as they pass through the body, thereby allowing body structures not containing iodine to be visualized [5]. Chemical structure of iopamidol is shown in figure 1. Chemical and physical properties of iopamidol are summarized in table 1.

It was established by several studies on the toxicity of CMs that chemotoxicity depends on the use of carboxyl groups in molecules, while hydroxyl groups are considered less toxic – even if iopamidol has no carboxyl groups, it has five hydroxyl groups per tri-iodo-benzoic acid molecule, and osmotoxicity depends on ionicity which subsequently depends on the presence of both carboxyl and hydroxyl groups [6, 7]. This is the main reason why non-ionic dimeric contrast agents with as low osmolality levels as possible have been created. On the other hand the degree of opacity produced by iopamidol is directly proportional to the total

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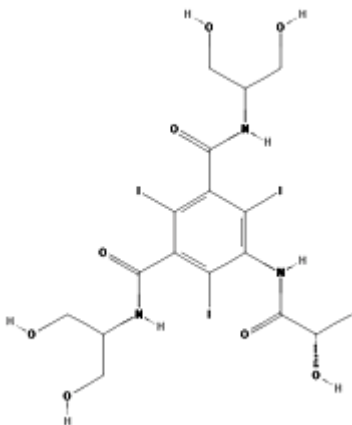


Fig. 1. 2D Iopamidol structure

amount of the iodinated contrast agent in the path of the x-rays, therefore, when compared to other LOCMS, radiopaque efficacy of iopamidol depends rather on the amount administered than the specific agent used [8]. The visualization of body structures is dependent upon the distribution and elimination of. Trade names of iopamidol include Iopamiro®, Isovue®, Iopamiron®, Solustrast®, or Niopam®.

Table 1
CHEMICAL AND PHYSICAL PROPERTIES OF IOPAMIDOL

Molecular Weight	777.08529 g/mol
Molecular Formula	C ₁₇ H ₂₂ I ₃ N ₃ O ₃
XLogP3	-2.4
Hydrogen Bond Donor Count	8
Hydrogen Bond Acceptor Count	8
Rotatable Bond Count	10
Exact Mass	776.854109 g/mol
Monoisotopic Mass	776.854109 g/mol
Topological Polar Surface Area	188 Å ²
Heavy Atom Count	31
Formal Charge	0
Complexity	583
Isotope Atom Count	0
Defined Atom Stereocenter Count	1
Undefined Atom Stereocenter Count	0
Defined Bond Stereocenter Count	0
Undefined Bond Stereocenter Count	0
Covalently-Bonded Unit Count	1

Post-ERCP pancreatitis

One of the most frequent and severe complications of ERCP is post-ERCP pancreatitis. The incidence of such complication varies from 1.6 to even 15.7% [9,10], although transient increase in serum pancreatic enzymes may occur in as many as 75% of patients [11]. Plenty of factors are considered contributors to induction of pancreatic tissue damage alongside ERCP and endoscopic sphincterotomy. Not to be eluded are also personal individual characteristics especially those related to anatomy of the pancreas and bile ducts and immunological parameters. The experience of the endoscopist and technical parameters of duodenoscopes and sphincterotomes are also not to be neglected. Even if in theory the intraductal presence of CM could cause local toxicity and pancreatitis [12], guideline studies suggest that no clinical risk has been identified to be specifically linked to such CM [3]. However, there is high suspicion in the literature about the influence that CM osmolality has on the risk of post-ERCP pancreatitis. Nevertheless, there are also some procedure-related risk factors for CM related post-ERCP pancreatitis – the volume of CM injected leading to parenchymal acinarization and high pressure CM injection [13]. Especially high pressure pancreatic duct CM injection with subsequent prolonged

acinar filling due to ductal occlusion and/or repeated ductal cannulations are associated with a higher risk of post-ERCP pancreatitis [6]. A relatively recent clinical report enforced that CM related post-ERCP pancreatitis is a complication resulting from a combination of pressure and subsequent contrast exposure of the pancreas [14], this hypothesis being afterwards confirmed by recent experimental studies.

Experimental part

Findings on four patients with post-ERCP pancreatitis were assessed in order to evaluate potential toxicity of iopamidol. All cases were patients previously diagnosed with multiple choledocholithiasis and gallbladder stones, without clinically or biologically manifest pancreatitis. ERCP with endoscopic sphincterotomy and stone removal was primary elective indication in all patients and procedures were performed by two experienced endoscopists in the Institute of Gastroenterology and Hepatology of Iasi, Romania, between January and March, 2016. Deep sedation and bowel movements control were achieved. In all cases, intra-procedural cholangiography followed by endoscopic sphincterotomy and stone extraction was performed. Selection of cases for the toxicity study was made according to the fact that all four patients needed a second ERCP for repeated extraction of bile duct stones (after 48 to 72h). Moreover, in all four cases, first ERCP was a difficult procedure due to multitude of bile duct stones, repeated cannulation of primary bile duct and time span of procedure. Most importantly, in all four cases, during the first ERCP large amounts of iopamidol were infused (60, 40, 40, 50mL iopamidol 100%). In contrast, second ERCP was characterized by usage of diluted iopamidol 50% with amounts not exceeding 40mL of iopamidol solution 50% infused.

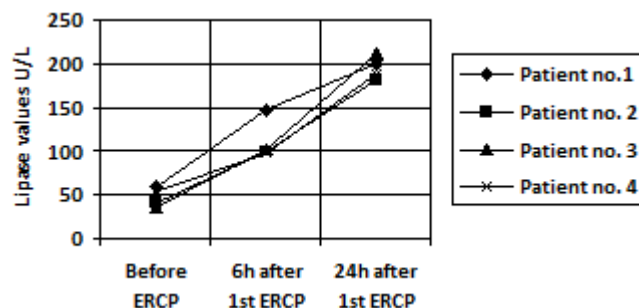


Fig. 2. Lipase dynamics, 6h and 24h between first and second ERCP, post-ERCP pancreatitis was diagnosed by more than 3 fold elevation of lipase levels after ERCP

Dynamics of lipase and C-reactive protein (CRP) between the two procedures (6h and 24h) were studied and pancreatic ERCP-guided brush cytology was obtained during the second procedure. All patients showed ascendant dynamics of both lipase levels and CRP up to more than 180 U/L lipase and 22 mg/dL CRP, as shown in figures 2 and 3 respectively. In all patients, both lipase and CRP levels were characterized by prolonged and continuous elevation towards 24h. Pain started mildly after the procedure and needed analgesics control 12 h after the procedure. Cytology of the main pancreatic duct was obtained with techniques similar to those used with brush cytology of the bile duct using wire-guided brush is used to collect cytologic material from the pancreatic duct. Cytology characteristics of ductal epithelium were studied: cytoplasm, nuclei and architectural features. This is the less invasive method for obtaining pancreatic cells in a clinical experimental study. Subsequently, accuracy of

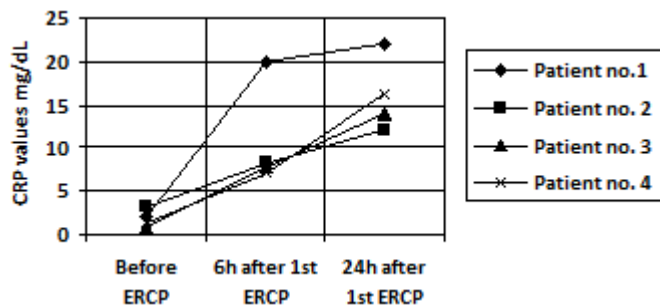


Fig. 3. CRP dynamics, 6h and 24h between first and second ERCP

pancreatic brush cytology is satisfactory and complication rates for pancreatic cytology are not significantly higher than routine ERCP complications incidence. All patients showed necrotic background cells, cellular debris, and saponification necrosis with various degrees of reactive changes in the ductal epithelia. Typical changes in pancreatic duct brush cytology are showed in figure 4. No patient developed severe macroscopic necrotic pancreatitis after ERCP and both lipase elevation and CRP levels reached back normal levels 4 to 7 days after the procedure. Even if pancreatic duct brush cytology is itself characterized by a high risk of post-procedure pancreatitis, interestingly, no patient developed sustained pancreatitis after second ERCP. Furthermore, two possible explanations could coexist: firstly the possible additional cause of pancreatitis may have been persistent bile duct stones after first ERCP and endoscopic sphincterotomy altogether with large amounts of CM infusion; secondly, pancreatic duct brush instrumentation may have helped the clearance of Wirsung duct, in this way helping pancreatic and toxic phenomena heal.

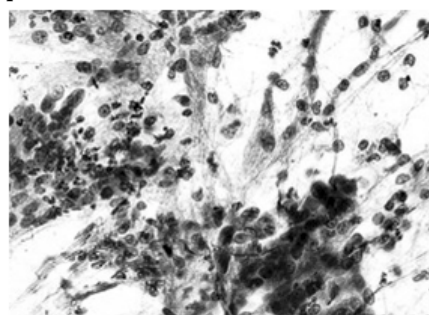


Fig. 4. Pancreatic duct brush cytology showing acute pancreatitis defined by inflammation, with foamy macrophages infiltration of the duct cells and saponification necrosis, H&E stain

Valuable recent experimental findings by Jin et al., 2015, on pancreatic exposure to radiocontrast agents suggests that even brief exposure to low concentrations of CM induces aberrant cytosolic Ca^{2+} signals selectively in mouse and human pancreatic acinar cells by activation of Ca^{2+} dependent phosphatase calcineurin linked in vivo to pancreatic nuclear factor k-light-chain-enhancer of B cells (NF- κ B) activation and pancreatitis [15]. Past studies have shown that acidic contrast is linked to mediation of severity of pancreatitis in rats [16]. Experimental in vitro and ex vivo studies results are consistent with the clinical findings on pancreatic duct brush cytology and are attested by enzymatic and inflammatory response dynamics of the patients included. On the other hand, no study assessed the role of CMs viscosity in pancreatic toxicity, as temperature may strongly affect this parameter, to that extent that CMs may be warmed before procedures. Nevertheless, in what post-ERCP pancreatic toxicity is concerned, such practices should be considered as just speculations, as no study to date assessed such positive effect.

Pancreatitis is considered to debut inside acinar cells, one of the earliest critical factors in most experimental

models being induction of large amplitude and sustained Ca^{2+} signaling [17, 18]. Principal regulator of inflammation in pancreatitis was found to be the transcription factor NF- κ B, which can subsequently induce inflammatory genes IL6, Spi2a, transforming growth factor- β and IL1 β [19-22]. It was subsequently confirmed that presence of CMs induces Ca^{2+} signaling and calcineurin activation in the primary acinar cells causing also increase in NF- κ B luciferase directly proportional with CMs concentration and time of exposure [15]. Recent research may also suggest that CMs might contain a triglyceride lipid emulsion with potential liberation into toxic nonesterified fatty acids when exposed to pancreatic lipases during ERCP [23, 24]. Unfortunately, clinical studies aimed to assess potential toxicity of iopamidol that would require extensive pancreatic tissue sampling would be hardly feasible as either ERCP pancreatic duct brushing or endoscopic ultrasonography guided fine needle aspiration are extremely invasive procedures and would in very few cases be indicated as secondly repeated procedure after therapeutic ERCP.

Metanalysis findings

There is one single metanalysis in the literature assessing the possible role of CMs as a contributing factor for post-ERCP pancreatitis. This role seems dependent on the osmolality of the CM, HOCM supposedly being associated with a higher incidence of post-ERCP pancreatitis or at least elevation of pancreatic enzymes. In this respect, as the findings of this metanalysis show, one randomized crossover study and 5 randomized control trials have suggested a benefit from using LOCM, while 11 other studies have shown no difference between HOCM and LOCM as to what post-ERCP pancreatitis is concerned [25]. However, such discrepancies could be explained by the lack of unitary definition standards for post-ERCP pancreatitis. Same study indicates that on animal in vivo studies morphologic changes in the pancreatic duct epithelium were demonstrated shortly after CM injection and less damage was noted after LOCM injection [25]. Therefore, for the moment we should refrain from stressing differences between HOCM and LOCM even if LOCM would be desirable choice.

Results and discussions

Post-ERCP pancreatitis was proven to result from a combination of pancreatic ductal pressure and CMs exposure, as each additively worsens disease outcome [15]. These findings are confirmed by clinical data showing that insertion of pancreatic duct stents that would lower intraductal pressure on the first hand, and injecting only the minimal necessary amount of CM during ERCP on the other hand - both may work as prophylaxis measures for post-ERCP pancreatitis [26-27]. At a cellular level, the toxicity process was explained by Ca^{2+} signalling emerging 1-2 minutes CM exposure, with mimicked high amplitude peak-plateau preceding acinar cell injury and pancreatitis [15, 17, 28]. The debate on whether HOCM or LOCM should be electively used for minimizing post-ERCP pancreatitis incidence is still going. Studies suggesting the superiority of LOCM (iopamidol being included as we stated in this category) were based mainly on the incidence of asymptomatic elevation of pancreatic enzymes - biochemical pancreatitis. Nevertheless, such pancreatitis are not to be considered mild or 'not severe' cases, as they enrole same complications and same potential worse outcome. There is no justification of mandatory use of iopamidol or other LOCM during ERCP. However, in patients

considered at high risk for CM-related reactions, prophylactic premedication and prior substitution of LOCM may be an option at least based on theoretical considerations [3]. Main downsides on potentially statistically significant studies involving CMs reside in the small number of patients included in studies leading to lack of direct delimitations between various causes on pancreatic damage occurring post-ERCP in the study groups. Therefore, the studies may reasonably be considered biased. However, when objective findings even on such series of cases are sustained by statistically significant animal and in vitro studies, a higher degree level of confidence of the results is achieved.

Conclusions

Iopamidol is a relatively old and well known LOCM. Despite high costs comparative to HOVM, Iopamidol is largely available in Romania and is frequently and routinely used as CM in ERCP. Post-ERCP pancreatitis development status is an important quality indicator of ERCP. Moreover, when it is dependent on the specific type of CM used, once more careful selection of radio-contrast substances should be performed. As it was seen in CMs studies, data from large randomized controlled trials or meta-analyses are frequently lacking and only singular trials are available. To date, no local clinical trial to evaluate iopamidol safety and efficacy was performed. Literature analysis shows that iopamidol should be a safe and efficient CM for ERCP especially when used strictly in minimal necessary amounts and concentrations. Independently on the iodinated CM used, the amount of iodine injected was shown to be direct proportional to the amplitude of potential CM-related side effects. All in all, local clinical trials are needed and practitioners should always monitor medical literature for the newest data regarding safety, efficacy and benefits of substances and technologies used.

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