Adverse reactions to iodinated contrast media

Abstract  Adverse reactions to iodinated contrast media (ICM) are more likely to develop in patients with asthma, a history of allergy or contrast reaction and in those who are debilitated or medically unstable. These reactions can be divided into renal and general, and the latter are subdivided into acute and delayed. Acute general reactions can be minor, intermediate or severe. Fatal reactions are rare. The introduction of low-osmolality agents has caused an overall reduction in the number of non-fatal contrast reactions. Prompt recognition and treatment of acute adverse side effects to ICM is invaluable and may prevent a reaction from becoming severe. Familiarity with cardiopulmonary resuscitation is essential for successful management of life-threatening reactions. Contrast-media-induced renal impairment can be reduced with the use of low-osmolality contrast media and extracellular volume expansion. The use of ICM in diabetic patients receiving metformin should be carried out with care to avoid metformin-induced lactic acidosis. However, this problem is mainly observed in patients with diabetic nephropathy.

Keywords  Contrast media · Side effects · Prevention · Treatment

Introduction  The first iodinated contrast medium to be used in clinical practice was sodium iodide, which was introduced in the 1920s. However, high toxicity and poor radiographic contrast limited the clinical use of this preparation. The breakthrough in the use of iodinated contrast media (ICM) came in the 1950s with the introduction of sodium and meglumine salts of tri-iodinated benzoic acid, which are of much lower toxicity in comparison to earlier preparations but very hyperosmolar, with an osmolality five to eight times that of the blood [1]. The second major breakthrough came in the 1970s with the introduction of low-osmolality ICM, which was achieved by converting tri-iodinated benzoic acid into a non-ionic molecule by replacing the carboxylic acid (COOH) radical with an amide (CONH₂). This molecule does not dissociate in solution, providing three atoms of iodine with only one active particle (a ratio of 3:1) compared with a ratio of 1.5 (3 iodine atoms:2 particles) for high-osmolality ICM (Fig. 1). Another development was the introduction of the mono-acid dimer, in which two tri-iodinated benzoic rings are linked together with a bridge and the COOH of one ring is converted into an amide. This gives the same iodine:particle ratio of 3:1 in solution, since there are 6 iodine atoms and 2 active particles in one molecule (Fig.1). The osmolality of the ionic dimeric contrast media is almost the same as that of the non-ionic monomeric agents and is about twice that of the blood at an iodine concentration of 300 mg I/ml. In the 1980s non-ionic dimeric ICM were introduced; two non-ionic tri-iodinated benzoic rings were attached, giving an iodine:particle ratio of 6:1 since there are 6 iodine atoms and only 1 active particle in each molecule (Fig. 1). The osmolality of this class of ICM is similar to that of the blood [1, 2].

Thus, there are currently four classes of ICM available for clinical use: high-osmolality ionic monomers,
low-osmolality non-ionic monomers, low-osmolality ionic dimers and iso-osmolar non-ionic dimers. They are provided at various iodine concentrations and have different physicochemical properties (osmolality, viscosity, hydrophilicity, ion content and pH).

This review will present the pharmacokinetics and side effects of intravascular administration of ICM as well as the prevention and treatment of the latter. The side effects in this review are classified into renal and general and the latter are subdivided into acute and delayed [2]. The pathophysiology of these adverse reactions will also be discussed. The review does not cover the haematological and organ-specific reactions to ICM (with the exception of the kidney). Side effects associated with intrathecal or other routes of administration of ICM and treatment of adverse reactions in children are not addressed in this review.

**Pharmacokinetics**

After intravenous administration of ICM, 70% of the injected dose diffuses from plasma to extracellular space within 2–5 min. Reverse diffusion from extracellular space to the plasma also takes place. Complete equilibrium between plasma and interstitial space occurs about 2 h after injection [3]. Continuous elimination of ICM from plasma into the urine occurs following the intravascular administration. The ICM molecules are filtered through the glomeruli without tubular re-absorption and are not metabolised before elimination. The kidneys are the main route of elimination, less than 1% of injected ICM being excreted extrarenally [4]. The elimination half-life following intravascular administration in patients with normal renal function is about 2 h, and 75% of the administered dose is excreted in urine within 4 h [3, 4]. In patients with renal impairment and reduced glomerular filtration rate the excretion of ICM by the kidneys is prolonged and can last for several weeks. The extrarenal elimination through bile and intestine is also increased [3, 4].

**General adverse reactions to ICM**

**Predisposing factors**

There are several predisposing factors to contrast reactions (Table 1). The incidence of severe adverse reactions increases in the presence of these risk factors. A history of allergy was found to increase the incidence of severe reactions to ICM by a factor of 3 and a history of previous adverse reaction to ICM by a factor of 5 with either high- or low-osmolality ICM. A history of asthma increases the risk of severe reactions by a factor of 10 with high-osmolality ICM and factor of 6 with low-osmolality ICM [2, 5, 6, 7, 8].

**Acute**

Acute reactions to ICM can be divided into minor, intermediate and severe. The minor reactions include flushing, nausea, arm pain, pruritus, vomiting, headache