Contrast Agent

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8.1 Basics

The clinical situation determines the investigation strategy. Unenhanced studies using CT are used, on the one hand, to investigate high-contrast structures (skeletal and lung parenchyma), and on the other hand, for haematoma detection. Examinations of parenchymal organs and soft tissues benefit from parenteral contrast media application. In the majority of abdominal conditions, intestinal contrast radiography is worthwhile.

Contrast agents increase the contrast by enhancing density variations in the organ to be depicted and the surrounding tissue. Contrast agents can cause side effects, and therefore there is a duty to provide clarification to the patient.

8.2 X-Ray Contrast Agent

8.2.1 Properties of X-Ray Contrast Agent

X-ray contrast media absorb X-rays to a greater (positive X-ray contrast agent) or lesser (negative X-ray contrast agent) extent than the surrounding tissue. Positive X-ray contrast agents are compounds with a high atomic number, e.g. barium sulphate- and iodine-containing compounds. Barium sulphate-containing suspensions are used mainly in gastrointestinal diagnosis, resulting in a sustained contrast agent coating of the mucosa, and can be combined with negative X-ray contrast agent, e.g. air (double contrast technique). Because barium sulphate is insoluble, administration in cases of suspected perforation or aspiration is contraindicated. In these cases, water-soluble iodinated contrast agents, e.g. Peritrast, should be used.

Iodinated contrast agents are fat- or water-soluble. Fat-soluble compounds have been used for lymphography. The water-soluble compounds are the most commonly used of all X-ray contrast media, e.g. for angiography, cholecysto- and cholangiography, urography and myelography. With regard to iodine-containing compounds, a distinction is made between ionic and non-ionic contrast agent. Ionic compounds have a higher osmolality than blood (hyperosmolar). During intravasal application, water can be extracted from the extravasal space and thus the endothelium can be damaged and pain caused. Non-ionic compounds are less hyperosmolar than ionic compounds and are thus better tolerated. Modern iodinated contrast agents have a low viscosity and are non-ionic. They are eliminated mainly via the kidneys, and to a lesser extent via the intestines, the hepatobiliary system and the salivary glands.

Non-ionic contrast agents are well tolerated in general, with serious allergic side effects rarely to be expected. The data provided in the literature varies between 1:10,000 and 1:100,000. Patients must be informed of the risk of thyroid and renal dysfunction, as well as of an allergic reaction leading to shock. Patients should also be informed of a general feeling of warmth throughout the entire body, which is to be expected shortly after the injection, as well as a metallic taste in the mouth. Because side effects can occur, the indication for the administration of contrast agents must be critically considered in each individual case, an accurate medical history and possible risk factors ascertained and the amount of contrast agent must be reduced to the diagnostically required measure.

8.2.2 Influence of Thyroid Function

To a minor extent, the iodine bonded to the benzene ring exists in the form of free atomic iodine and is absorbed by the thyroid gland. Therefore, functional diagnosis or radioiodine treatment of the thyroid is not possible for weeks to months following administration of an iodine-containing contrast agent. In patients with latent hyperthyroidism or autonomous adenoma, it can lead to thyreotoxicosis. In this regard, various thyroid values (fT3, fT4 and TSH basal value) should be known prior to the administration of an iodinated contrast agent. If an iodine exposition is indicated, sodium perchlorate can be administered 30 min prior to contrast agent administration, and then given for a further 5 days, before hyperthyroidism can be excluded.

8.2.3 Influence on Renal Function

Contrast agents for use on the kidneys have a tubulotoxic effect, in particular on pre-damaged kidneys. In older patients, diabetics and patients with elevated creatinine, the contrast agent dosage should be reduced and, in addition, a sufficient fluid supply should be ensured before contrast agent application. In various studies, it has been shown that sufficient fluid intake with 1,000–2,000 ml NaCl 0.9% solution, administered intravenously, results in increased renal perfusion and thus leads to dilution of the nephrotoxic contrast agent in the tubules. Contrast agent-induced nephropathy can be reduced by means of adequate hydration and potentially through the use of the iso-osmolar, non-ionic contrast medium iodixanol.

8.2.4 Contrast Agent Reactions

The majority of contrast agent reactions occur within the first 20–30 min after application, 75% even within the first 3–5 min. Contrast agent reactions are divided into four severity levels:

- Severity level 1: skin reactions and minor general symptoms
- Severity level 2: haemodynamic and gastrointestinal symptoms
- Severity level 3: anaphylactic shock
- Severity level 4: anaphylactic shock with cardiac and respiratory arrest

The **therapeutic approach** depends on the severity level.

Severity Level 1. Application of an H1 receptor antagonist, H2 receptor antagonist.

Severity Level 2. In addition, corticosteroids are to be administered intravenously. The reference dose is 3 mg of prednisolone/kg body weight. Corticosteroids with a lower mineral corticoid content act rapidly.

Severity Level 3 and Level 4 Contrast Agent Reactions. Anaphylactic shock is life threatening. An emergency physician should be consulted. Adrenalin should be slowly injected under pulse control using the indwelling needle. Adrenalin administration can, if necessary, be repeated. Subsequent clinical monitoring at a monitoring/intensive care ward is necessary.

8.2.5 Hypersensitivity Reactions

Nausea, vomiting, erythema, urticaria, bronchospasm, laryngospasm, seizures and anaphylactic shock may occur. The history regarding previous contrast agent administration or allergic predisposition is particularly important. The frequency of lethal complications following intravenous contrast agent administration is 1:100 applications for ionic contrast agents and 1:1,000,000 applications for non-ionic contrast agents.

8.3 MR Contrast Agents

8.3.1 Characteristics of MR Contrast Agents

Magnetic resonance (MR) contrast agents enhance tissue contrast by affecting the relaxation times of the affected tissue. Most often, the paramagnetic substance gadolinium is used. The highly toxic Gd 3^+ ion is bound to a chelating agent, e.g. DTPA. Other elements that can be used, at least experimentally, are manganese and ferritin.

Gadolinium-based contrast agents have a low level of protein formation, are not metabolised and are distributed in the extracellular space. The blood–brain barrier is usually not crossed. The half-life time in the blood circulation is approximately 90 min. It can be administered in a dosage of 0.1–0.3 mmol / kg body weight. In the case of pathological processes in the central nervous system in which the blood–brain barrier is impaired, disrupted sensitivity can be detected. Gadolinium accumulates there, shortens the T1 relaxation time and thus leads to a signal increase on the T1-weighted image.

Organ-specific contrast agents have managed to considerably increase sensitivity and specificity, in particular in the case of liver diagnosis. These are mainly superparamagnetic iron particles that are first phagocytosed by the liver and therefore only accumulate in the healthy liver tissue that is equipped with hepatocytes. By shortening the T2 relaxation time, the healthy liver becomes dark on the T2-weighted image, while the lesions remain bright. The contrast agent manganese-DPDP is absorbed by hepatocytes and leads to a long-lasting signal increase in the liver parenchyma. The substance does not enter tumour cells.

8.3.2 Contrast Agent Reactions

Allergic reactions to MR contrast agents are rare, but can also be life-threatening (Table 8.1). The mechanism is unknown. Most likely, the immune system is activated and histamine is released.

Table 8.1 Reactions to MR contrast agents

Reaction	Frequency
Nausea, vomiting	0.42%
Local sensation of warmth	0.41%
Headaches	0.26%
Paraesthesia	0.13%
Vertigo	0.10%
Seizures	0.03%
Urticaria	0.03%
Allergic skin reactions	0.07%
Flash burn	0.06%
Cardiovascular reactions	0.04%

To date, no late reactions have been published as having been detected as a result of iodine-containing contrast agents. Typical reactions to gadolinium-based contrast agents do not vary significantly from those to iodine-based contrast media.

With regard to incompatibility reactions to contrast media, a distinction is made between **early reactions** (up to 60 min after injection) and **late reactions** (60 min to 3 days after injection)

- Early reactions: nausea, vomiting, urticaria, erythema, angio-oedema, bronchospasm, vasovagal reaction, glottal oedema, anaphylactic shock, dyspnoea, circulatory reaction
- Late reactions: redness, hives, swelling, nausea, diarrhoea, headache, dizziness, rigour, tremors, flu-like symptoms

Preparation of a Patient with a Contrast Agent Allergy

If a contrast agent allergy is known, the patient should be prepared for the examination accordingly (Table 8.2).

Only non-ionic contrast agents are approved for endovasal application, with low-molar non-ionic contrast agents used as a preference. There are essentially two ways of preparing the patient:

- Prophylactic short infusion with H1 and H2 blockers
- Prophylactic corticosteroid administration

Premedication is required only in patients with a known history of contrast agent reaction. In elective examinations, corticosteroids should be administered 12 h before the examination. The chemotoxic effect will probably not be sufficiently attenuated by the corticoids, and thus a combination with H1 blockers is recommended (Table 8.2).

Preparation at Increased Risk of Iodine-Induced Hyperthyroidism

Because iodine-containing contrast agents contain free iodine in a concentration of up to 20 µg/µl, during a normal CT examination around 2–3 mg of free iodine are administered, a quantity equal to 10 to 40 times the normal daily dose. The incidence of the development of thyrotoxicosis is about 0.03–0.2%, both in

Table 8.2 Preparation of a patient with a contrast agent allergy

Medication	Time of application
40–50 mg prednisolone	12–24 h before the examination
300 mg of cimetidine, 20–50 ml of NaCl Alternative: 50 mg ranitidine i.v.	30 min to 2 h before the examination
50 mg diphenhydramine i.v. Alternative: 2 mg clemastine	Immediately prior to the examination

euthyroid and hyperthyroid patients. Prophylaxis is the subject of controversial debate, particularly in patients from iodine-deficient regions. Indications for premedication exist in cases of known hyperthyroidism, Graves' disease, autonomous adenoma, nodular goiter, and in cases of papillary or follicular thyroid carcinoma.

The following factors or underlying medical conditions increase the risk of iodine-induced hyperthyroidism:

- Known hyperthyroidism
- Graves' disease
- Latent hyperthyroidism in cases of autonomous adenoma
- Papillary thyroid carcinoma
- Follicular thyroid carcinoma

These patients also require special preparation prior to examination with iodinated contrast agents; in the case of elective examination, this is performed in accordance with the information in Table 8.3, whereas in the case of emergency examinations, Table 8.4 applies.

Table 8.3 Preparation of the patient in the case of increased risk of iodine-induced hyperthyroidism – elective examination

Medication	Time of application
Sodium perchlorate: 300 mg	3 x daily From 1 day prior to the examination until 8–14 days after
Thimazol: 30 mg	Once daily From 1 day before until 28 days after

Table 8.4 Preparation of the patient in the case of increased risk of iodine-induced hyperthyroidism – emergency examination

Medication	Time of application
Sodium perchlorate: 1 × 800 mg	Before the examination and 3 × 300 mg for 8–14 days afterwards
Thimazol: 1 × 30 mg	Before examination and for 28 days

Patients with Renal Insufficiency

In renal failure patients a strict diagnostic evaluation should be performed and the patients should be sufficiently hydrated should contrast agent application be required. Particular attention must be paid to the glomerular filtration rate, which can be calculated using specific formulae, based on the serum creatinine level and the age and sex of the patient:

$$\text{Creatinineclearance} - \text{rate} = \frac{(140 - \text{Age}) \times \text{Body weight (kg)}}{\text{Serum creatinine (micromol/l)} \times 0.81}$$

For women, a correction factor of 0.85 can be applied rather than 0.80 l.

Nephrogenic Systemic Fibrosis After Application of Some Gadolinium Contrast Medium

The rare disease "nephrogenic systemic fibrosis" (NSF) has recently been associated with the use of gadolinium-containing MR contrast agents. NSF is a rare systemic disease similar to scleroderma, which is associated with extensive fibrous tissue. In January 2007, the German Federal Ministry for Pharmaceuticals and Medical Devices (Bundesamt für Arzeimittel and Medizinprodukte, BfArM) reported on a new adverse drug effect that had been observed in 2006. The disease has thus far occurred exclusively in patients with renal impairment. It has occurred most frequently in patients with chronic renal failure, whereby 90% of patients required dialysis. The precise incidence of NSF is not known. Since NSF can lead to serious disabilities and can potentially be lethal, strict criteria must be applied to the indication in renal failure patients. In cases of NSF, erythematous papules, brownish plaques, and marked thickening and hardening of the skin develop, which can lead to contractures and increasing immobility.

The US Food and Drug Administration (FDA) emphasises that in at-risk patients any gadolinium-containing contrast agent can lead to NSF. At-risk patients should be advised about the risk of NSF. Alternative methods of examination or an unenhanced MRI should be considered. Only small quantities of gadolinium-based MR contrast agents should be used. The value of dialysis is unclear. The FDA recommends prompt dialysis for patients with a GFR < 60 ml/min/1.73 m². Each case of an NSF should be reported to the competent authorities.

8.4 Ultrasound Contrast Agent

Microbubbles of a defined size can be used as an ultrasound contrast agent. The gas bubbles increase the backflow of the ultrasonic waves and thus enhance the signal. Ultrasound contrast agents remain intravascular and do not pass into the interstitium. They are used for the improved demarcation of lesions in parenchymal organs, especially the liver, but also in cardiac echocardiogram and cranial ultrasound examinations.