Post-Marketing Surveillance of the Safety Profile of Iodixanol in the Outpatient CT Setting: A Prospective, Multicenter, Observational Study of Patient Risk Factors, Adverse Reactions and Preventive Measures in 9953 Patients

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Post-Marketing Surveillance of the Safety Profile of Iodixanol in the Outpatient CT Setting: A Prospective, Multicenter, Observational Study of Patient Risk Factors, Adverse Reactions and Preventive Measures in 9953 Patients

CT-Untersuchungen mit Iodixanol in der klinischen ambulanten Routine. Eine prospektive, Multizenterstudie zur Risikoabschätzung von Nebenwirkungen und Präventivmaßnahmen bei 9953 Patienten

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Zusammenfassung

Ziel: Nicht-interventionelle Studie bei ambulanten, kontrastmittelunterstützten CT–Untersuchungen zur
1. Häufigkeitsabschätzung präventiver Maßnahmen zur Risikoreduktion von Nebenwirkungen
2. prospektive Erfassung von Nebenwirkungen (Häufigkeit und Schweregrad) nach Gabe des isoosmolaren Röntgenkontrastmittels Iodixanol
3. Abschätzung des Einflusses präventiver Maßnahmen auf Häufigkeit und Schwere der beobachteten Nebenwirkungen

Material und Methoden: Ausgewertet wurden die Angaben zu 9953 Patienten aus 66 radiologischen Zentren/Praxen in Deutschland. Patientencharakteristika und Applikationsparameter von Iodixanol sowie Reaktionen mit möglichem ursächlichen Zusammenhang mit Iodixanol wurden durch standardisierte Patientenbögen erfasst und bis zu sieben Tage nach Kontrastmittelapplikation ausgewertet.

Ergebnisse: Insgesamt zeigten 55,5 % der Patienten einen oder mehrere Risikofaktoren (z. B. 4,4 % eingeschränkte Nierenfunktion, 8,5 % Diabetes mellitus, 20,6 % erhöhten Blutdruck). Ein Drittel der Praxen setzte keinerlei präventive Maßnahmen ein. Patienten mit bekanntem Risiko für allergoide Reaktionen wurden häufiger medikamentös prämediziert (0,5 – 50,5 %). Häufigste präventive Maßnahme bei Patienten mit renalen Risikofaktoren war die orale (< 8 %), gefolgt von der intravenösen Hydrierung (1 %). Nebenwirkungen, überwiegend Hypersensitivitätsreaktionen, wurden für 77 Patienten berichtet (0,74 %), davon bei 3 Patienten (0,03 %) als schwerwiegend eingestuft.

Schlussfolgerung: Der Einsatz präventiver Maßnahmen bei ambulanten CT-Untersuchungen war insgesamt gering, bei Risikopatienten je nach Anamnese etwas häufiger. In der klinischen Routine bei ambulanten CT-Untersuchungen zeigte sich das isoosmolare Iodixanol bei annähernd 10 000 Patienten als sehr verträglich. Es konnte keine Kor-

Abstract

Purpose: Non-interventional study in outpatient, contrast-enhanced CT
1. to determine the extent of preventive measures for risk reduction of adverse drug reactions after contrast-enhanced CT examinations.
2. to prospectively determine the incidence and severity of adverse drug reactions occurring after administration of the iso-osmolar contrast medium iodixanol
3. to determine a possible influence of preventive measures on the incidence/severity of adverse drug reactions.

Materials and Methods: Evaluable documentation was provided for 9953 patients from 66 radiology centers across Germany. Patient characteristics, aspects of iodixanol administration, and adverse events with an at least "possible" relationship were documented on a standardized case report form (CRF) and were evaluated up to seven days after contrast medium administration.

Results: About 55.5 % of patients showed one or more risk factors (e. g. impaired renal function 4.4 %, diabetes mellitus 8.5 %, hypertension 20.6 %). One third of the sites did not implement any preventive measures. Patients with a known risk for an allergy-like reaction were more likely to receive pharmacologic preventive treatment (0.5 – 50.5 %). Oral hydration was the main preventive measure in patients with renal risk factors (< 8 %) followed by intravenous hydration (1 %). Adverse drug reactions, mainly hypersensitivity reactions, occurred in 77 patients (0.74 %), but were classified as serious in only 3 patients (0.03 %). No statistically significant correlation between risk factors, preventive measures, and adverse reactions could be found.

Conclusion: The use of preventive measures for CT examinations in this outpatient setting was generally low with risk patients being pre-medicated

relation zwischen Risikofaktoren, Präventivmaßnahmen sowie der Häufigkeit von Nebenwirkungen gefunden werden.

Kernaussagen:

- Präventivmaßnahmen selten bei ambulanten CT-Untersuchungen
- Geringe Rate an akuten und verzögerten Nebenwirkungen nach Iodixanol
- Kein erkennbarer Zusammenhang zwischen Risikofaktoren, Präventivmassnahmen und Nebenwirkungen

more often, depending on their history. In the routine outpatient setting, iso-osmolar iodixanol was very well tolerated in almost 10 000 patients undergoing diagnostic CT. The rate of acute and delayed adverse reactions was low. No correlation could be found between risk factors, preventive measures and the incidence of adverse drug reactions.

Key Points:

- Rare use of preventive measures for outpatient CT examinations.
- Low rate of acute and late adverse drug reactions to iodixanol.
- No correlation between risk factors, preventive measures and adverse drug reactions.

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Background

Adverse drug reactions associated with the administration of iodinated contrast media (CM) are generally rare and mild in nature, but severe and even life-threatening reactions may occur. Much controversy surrounds the issue of preventive measures to reduce either allergy-like reactions or renal reactions in the outpatient setting. For the prevention of allergy-like reactions, pre-treatment with steroids (and antihistamines) seems to be the preferred method, as described in a survey done by the European Society of Urogenital Radiology (ESUR) in 2001. However, the issue is still under debate, as even the ESUR, which recommends pre-medication in patients at high risk for allergy-like reactions, has stated that clinical evidence for the usefulness of preventive measures is limited [1]. Different studies have established that (intravenous) hydration prior to and after CM administration has beneficial effects on the incidence of contrast-induced acute kidney injury (CI-AKI), previously known as contrast-induced nephropathy (CIN) [2–4]. Most of these studies were set in a clinical environment and were controlled clinical trials where the use of preventive measures was predefined and not left to the discretion of the treating physician. However, there is general consensus that hydration is the most important measure to prevent CI-AKI [1]. There are only a few randomized controlled studies comparing the CI-AKI risk after oral and intravenous hydration with inconsistent results [5, 6]. A current meta-analysis found no significant difference between pre-procedural intravenous and oral volume expansion for the prevention of CI-AKI [7].

As computed tomography (CT) becomes more readily available and technology continues to broaden the potential applications for CT, the number of CT scans performed worldwide each year will continue to increase [8, 9]. It therefore becomes increasingly important to seek additional information about current preventive measures and the extent to which they are used, especially in the outpatient setting.

This Non-Interventional Study (NIS) was specifically designed to investigate this issue. It is intended to provide information about the use of preventive measures, especially in the context of patient risk profiles and their potential impact on the incidence of adverse drug reactions. It is intended to give further insight regarding the extent to which preventive measures are used, for what type of patients (all patients, or only certain risk groups), and which types of preventive measures are most commonly used.

Material and Methods

The NIS was performed as a prospective, non-randomized, multicenter, open-label study in 66 German radiology centers. Data from outpatients receiving a diagnostic CM-enhanced CT with administration of iso-osmolar iodixanol in accordance with the Summary of Product Characteristics were documented on standardized case report forms (CRF). The sites were asked to document subsequently all patients scheduled for a CT examination with iodixanol. Patients were to be included only once, even if they had several CT scans during the recruitment period of the NIS. Patient recruitment lasted from June 2009 to January 2010. The German Federal Institute for Drugs and Medical Devices (BfArM), the National Associations of Panel Doctors (KVB) and the representative body of the Statutory Sickness Funds were notified of the performance of this study.

To harmonize the documentation of risk factors, the standardized CRF included a predefined list of potential risk factors (risk of adverse events, renal risk factors) based on the ESUR definitions in 2009. CRF parameters included: patient demographics (age, gender), medical data (risk profile [based on physician's assessment]: previous allergy-like reaction to a CM, allergies requiring treatment, asthma, heart failure, diabetes requiring treatment, renal impairment, kidney surgery, proteinuria, hypertension, gout, intake of nephrotoxic drugs, and clinical signs of dehydration), region of investigation (head/neck, chest/lung, abdomen/pelvis, upper extremities, lower extremities, **Table 1**), contrast medium used (iodixanol 270mgI/ml, iodixanol 320mgI/ml [VISIPAQUE™, GE Healthcare]), mode of injection (manual versus power injection), flow rate, total CM volume, occurrence of adverse reactions (acute or late), and preventive measures taken. Any preventive measures taken were recorded. The measures were categorized as follows: oral hydration, i. v. hydration withdrawal of concomitant medication, initiation of pharmacological measures to prevent CI-AKI, premedication. Due to the non-interventional character of the NIS, only patient data being part of

Table 1 Region of investigation.

Tab. 1 Untersuchte Körperregionen.

region of CT (by frequency)	number of patients[1] n (%)
abdomen/pelvis	4909 (49.3 %)
thorax/lung	3314 (33.3 %)
head/neck	2539 (25.5 %)
lower extremities	41 (0.4 %)
upper extremities	25 (0.3 %)

[1] More than one answer possible, ratios and percentages based on available and evaluable data.
Mehr als eine Option möglich, Zahlen und Prozentangaben basieren auf verfügbaren und berechenbaren Daten.

their physician's daily practice routine were documented. No additional investigations were performed.

On an additional site questionnaire, every center documented once the type of CT scanner (number of rows), the CM temperature at injection, the type of injection (manual versus power injector), and the type of fluid used for i. v. hydration (saline, half saline, or sodium bicarbonate).

Recorded adverse events were classified into acute reactions occurring within one hour of CM administration (while the patients were still on site), and late reactions, occurring from 1 hour up to one week after CM administration. The investigators had been instructed to request their patients to report any adverse events occurring up to seven days after CM administration. These late adverse events were documented on a separate AE report form.

The sample size calculation was based on the results of a previous NIS [10]. The sample size calculation resulted in a total of 12 000 patients needed to obtain a sufficient number of patients in each subgroup (risk patients for allergy-like or renal reactions), taking into account an estimated dropout rate of 5 %.

Data entry was carried out according to guidelines including double data entry and checks for plausibility and consistency. Implausible data in the database were either corrected, if appropriate, or queried with the radiologist for correction or confirmation. If there was no confirmation or correction from the radiologists, this information was recorded as "missing" and was not included in the analyses. Adverse drug reactions (ADRs) were coded according to MedDRA version 11.0. Data were analyzed using descriptive statistics, with SAS software version 9.1. The Chi-square test was used to test for differences in acute and late reactions in relation to preventive measures and risk factors. As a certain amount of missing data is inevitable in NIS studies, all ratios/percentages are based on available and evaluable data.

Results

Surveillance population

66 radiologists in private clinic-based (non-hospital) practice contributed to this study. The NIS started on June 1, 2009 and was terminated on January 13, 2010 with the closure of the NIS database. In this period 9953 patients had been documented. 401 CRFs arrived after closure of the study database and were not included in the treatment analysis population. Nevertheless, these "late arrivals" were included in the safety population, which thus included a total of 10 354 patients.

Table 2 Risk factors.[1]

Tab. 2 Risikofaktoren.[2]

risk factor (by frequency)	number of patients (%)
age > 70 years	3119 (31.3 %)
hypertension (risk factor for elevated SCr)	2044 (20.6 %)
diabetes mellitus requiring treatment	845 (8.5 %)
cardiac insufficiency	553 (5.6 %)
renal insufficiency	435 (4.4 %)
asthma	379 (3.8 %)
allergy requiring treatment	272 (2.7 %)
prior renal surgery	253 (2.5 %)
nephrotoxic medication (regular intake)	251 (2.5 %)
gout	207 (2.1 %)
prior allergy-like reaction to CM	97 (1.0 %)
dehydration	87 (0.9 %)
proteinuria (risk factor for elevated SCr)	12 (0.1 %)

[1] As assessed by the radiologist.
[2] Eingeschätzt durch den Radiologen.

More than half of the patients had at least one known risk factor (55.5 %) that suggested they might be at higher risk for allergy-like or renal adverse reactions. Patient demographics and procedural information are given in **Table 2**.

The individual assessment of patient risk factors was done by the physician performing the examination (as mandatory for NIS, without any additional testing). The group of renal risk patients included 435 patients (4.4 %), for whom a more recent SCr was available to the physician in 89.7 % (390/435) of patients. Whereas the CRF asked for SCr values only, physicians supplied additional eGFR values for another 133 patients. 12 patients had an eGFR < 45 ml/min/1.73 m², 76 patients < 60 ml/min/1.73 m², with the mean eGFR being 60.6 ml/min/1.73 m². As this was a non-interventional study, no post-CM administration SCr values were measured/recorded since this is not part of the routine in the outpatient setting.

Contrast medium administration

60 % of the patient population received the iso-osmolar CM iodixanol 270 mgI/ml, 40 % received the iso-osmolar CM iodixanol 320 mgI/ml (subsequently referred to as iodixanol 270 and iodixanol 320). 40 sites used iodixanol 270 exclusively, 19 sites used iodixanol 320 exclusively. Only 7 sites used both concentrations. The total administered CM volume was reported for 9933 patients, with a median of 100 ml. The mean volume did not differ significantly between iodixanol 270 and iodixanol 320, **Table 3**.

Safety

77 patients (0.74 % of all patients) from 29 sites experienced adverse reactions (ADR). Reactions of 53 patients (0.51 %) were classified as hypersensitivity reactions. 19 patients (0.18 %) experienced nausea immediately after CM administration. Only one of the patients with a prior allergy-like reaction to CM experienced an allergy-like reaction in this study (non-serious hypersensitivity reaction, no preventive measures). **Table 4** shows the details of all ADRs.

Three adverse reactions were classified as serious (0.03 % of all patients). All three occurred while the patients were still on-site.

Table 3 Demographics and procedural information.[1]

Tab. 3 Demografische Information und Details zur Applikation.[2]

gender (# of patients)	male	5056
	female	4893
age (years) (n = 9949)	mean/SD	61.3/14.88
iodine concentration	(mgI/ml)	(# of patients)
	270	5956
	320	3977
total volume (ml) (n = 9933)	mean/SD	92.5/23.08
	median	100

[1] Ratios and percentages based on available and evaluable data.
[2] Zahlen und Prozentangaben basieren auf verfügbaren und berechenbaren Daten.

Table 4 Characteristics and incidence of adverse drug reactions (ADRs) reported by > 1 patient.

Tab. 4 Art und Häufigkeit akuter und verzögerter Nebenwirkungen (ADR), falls mehr als bei 1 Patienten beschrieben.

	no. of patients (%)/no. of events
SOC/preferred term	**(N = 10 354)**
any system organ class[1]	**77 (0.74) 208**
skin and subcutaneous tissue disorders	54 (0.52) 89
pruritus	22 (0.21) 22
erythema	17 (0.16) 17
rash	13 (0.13) 13
urticaria	12 (0.12) 12
swelling face	4 (0.04) 4
generalized erythema	3 (0.03) 3
rash macular	3 (0.03) 3
rash generalized	2 (0.02) 2
skin burning sensation	2 (0.02) 2
urticaria	2 (0.02) 2
immune system disorder	57 (0.55) 57
hypersensitivity	53 (0.51) 53
anaphylactoid reaction	3 (0.03) 3
anaphylactoid shock	1 (0.01) 1
gastrointestinal disorder	22 (0.21) 26
nausea	19 (0.18) 19
vomiting	5 (0.05) 5
general disorders and administration site condition	12 (0.12) 13
feeling hot	4 (0.04) 4
swelling	3 (0.03) 3
sensation of foreign body	2 (0.02) 2
infections and infestations	6 (0.06) 6
rash pustular	6 (0.06) 6
respiratory thoracic and mediastinal disorder	5 (0.05) 5
throat irritations	3 (0.03) 3
sneezing	2 (0.02) 2
eye disorders	3 (0.03) 3
eyelid edema	2 (0.02) 2
nervous system disorder	3 (0.03) 3
cardiac disorder	2 (0.02) 2
investigations	2 (0.02) 2
blood pressure decreased	2 (0.02) 2

[1] ADRs experienced by only one patient are not detailed (exception: anaphylactoid shock is listed, as this was a serious reaction).
Nebenwirkungen, die nur einmalig auftraten wurden nicht aufgeführt (Ausnahme: Anaphylaktischer Schock als schwere unerwünschte Nebenwirkung).

Table 5 Serious adverse drug reactions.

Tab. 5 Schwerwiegende Nebenwirkungen.

gender	**female**	**female**	**female**
age[1] [years]	41	62	60
latency	acute	acute	acute
prior reaction to CM	no data available	no data available	no
sADR as summarized (PT)	anaphylactoid shock (shock, loss of consciousness, anaphylactoid shock)	anaphylactoid reaction (not further specified by the physician)	hyper-sensitivity (hypersensitivity, throat irritation, paraesthesia oral)
outcome	recovered	recovered	recovered

[1] At time of event.
Zum Zeitpunkt der Untersuchung.

One patient was hospitalized for observation due to an anaphylactic reaction, which lasted for 75 minutes. The second patient experienced a hypersensitivity reaction and was therefore hospitalized overnight for observation. The third patient was classified as serious due to the severity of the reaction. All three patients recovered fully. **Table 5** shows the overview of the serious ADRs.

Acute and late reactions

Acute reactions occurred in 35 patients (0.34 %), with a median latency of 44 minutes. Acute reactions were mainly hypersensitivity reactions, including skin and/or subcutaneous reactions (n = 29), and gastrointestinal disorders (n = 20), mostly nausea directly after CM application (n = 18).
40 patients (0.39 %) experienced late reactions. All 40 patients had skin/subcutaneous reactions with the majority of them coded as hypersensitivity reactions (39 patients). 48.5 % of the late adverse reactions required treatment, mostly in the form of antihistamines/antiallergics being provided by general practitioners (56.25 %), medical specialists (37.5 %), or the hospital (6.25 %). No late renal reactions were reported.
In two patients, latency was unknown due to missing data.

Preventive measures

The following preventive measures were recorded: oral/i. v. hydration, before/after CM administration, withdrawal of drugs (e. g. biguanides, NSAIDs), initiation of pharmacological measures to prevent CI-AKI (e. g. NAC) or specific premedication to prevent allergy-like reactions (e. g. steroids, antihistamines).

Preventive measures by participating sites

Of the 66 sites, about 1/3 did not apply any preventive measures, regardless of their patients' risk profile. 29 (44 %) of the 66 sites hydrated part of their patients either orally (8.2 %; 814) or i. v. (1 %; 97 patients). Two sites hydrated all patients (one site only orally, one site only i. v.) regardless of their risk profile for CI-AKI. Only 3 centers documented using either sodium bicarbonate or half-normal saline (0.45 % NaCl) for i. v. hydration, while all others used normal saline (0.9 % NaCl).

Table 6 Preventive measures.

Tab. 6 Präventive Maßnahmen.

risk factor	patients receiving preventive measures % of patients with that risk factor/ % patients without that risk factor			
	oral hydration	i. v. hydration	NSAID treatment stopped	treatment with NAC
impaired renal function (n = 435)	21.5 7.8	6.0 0.6	0.0 0.1	1.4 0.0
previous kidney surgery (n = 253)	11.9 8.1	3.6 0.8	0.0 0.1	0.0 0.1
diabetes mellitus (n = 845)	10.9 7.9	2.2 0.8	0.4 0.0	0.2 0.1
proteinuria (n = 12)	75.0 5.5	16.7 0.8	0.0 0.1	0.0 0.0
regular intake of nephrotoxic medication (n = 251)	14.3 8.5	5.2 0.8	2.4 0.0	0.4 0.1
dehydration (n = 87)	34.5 7.9	17.2 0.8	1.1 0.1	0.0 0.1

Relationship between risk factors and preventive measures

Risk for allergy-like reactions

Patients with a higher risk for allergy-like reactions had been defined as patients with allergies requiring treatment, asthma, or a previous allergy-like reaction to CM. Of the 272 patients with documented allergies, 0.7 % received steroids and 4.8 % received antihistamines prior to CM administration. Of the patients with asthma (n = 379), 0.5 % received steroids and 0.8 % antihistamines. Patients without those risk factors received steroids and antihistamines in comparable ratios. Only patients with a history of allergy-like reaction to CM were pretreated significantly more often. In this group of 97 patients, 21.6 % received steroids and 50.5 % antihistamines. Among patients without this risk factor, hardly any received steroids or antihistamines (0.0 % and 0.2 %, respectively).

Risk for CI-AKI

Patients with a higher risk for CI-AKI were defined as patients with impaired renal function, previous kidney surgery, regular intake of nephrotoxic medication, proteinuria, diabetes mellitus, and signs of dehydration.

The NIS identified that appropriate preventive measures (hydration, withdrawal of nephrotoxic medication, treatment with NAC) were used more frequently in these risk patients, mainly in the form of either oral or i. v. hydration. **Table 6** shows the different pre-treatments in relation to the presence of renal risk factors.

Relationship between adverse drug reactions, preventive measures and risk factors

The overall incidence of allergy-like adverse drug reactions in patients with one or more risk factors for such reactions was 0.69 % compared to 0.63 % in patients without any risk factors. Risk patients (history of allergy-like reaction to CM) receiving preventive medication did not show a significantly lower rate of adverse events, compared to risk patients with no preventive medication (statistical testing [FISHERs exact test]: difference not significant). No renal adverse reactions were reported.

A logistic regression analysis failed to reveal any correlation between risk factors, preventive measures, and the incidence of adverse drug reactions. **Table 7** shows the adverse reactions in relation to preventive measures for patients with risk factors for acute/late reactions.

Table 7 Patients with adverse reactions by risk factors for acute/late reactions and preventive measures.

Tab. 7 Patienten mit Nebenwirkungen und Risikofaktoren für Akut- und Spätreaktionen im Vergleich zu Präventivmaßnahmen.

patients with adverse reactions: n (% patients)				
	acute reaction		late reaction	
appropriate preventive measure[1]?	yes	no	yes	no
risk factor				
previous allergy-like reaction	0 0.0 %	2 0.3 %	0 0.0 %	4 0.6 %

[1] Appropriate measure: antihistamines or steroids (allergy-like reactions) and hydration.
Angemessene Behandlung: Antihistamine oder Steroide (Allergieähnliche Reaktionen) und Hydration.

Discussion

Adverse drug reactions (ADRs) associated with the administration of iodinated contrast media (CM) are generally rare and mild in nature, but severe and even life-threatening reactions may occur. Adverse reactions are grouped into acute reactions, occurring up to one hour after CM administration, and late reactions, occurring from 1 hour up to one week after exposure to CM [11]. Acute reactions often present as allergy-like or anaphylactoid reactions and range in severity from mild symptoms like urticaria and itching to severe reactions such as cardiopulmonary arrest and death (< 1/100 000 patients) [12, 13]. The majority of late reactions are mild to moderate skin reactions which are considered as late hypersensitivity reactions [14]. Risk factors for both acute and late reactions include previous adverse reactions (previous late reactions predispose for late reactions and previous immediate reactions for immediate reactions) to CM, a history of allergy, or asthma [14, 15]. Risk factors for CI-AKI include age, congestive heart failure, use of nephrotoxic drugs, and chronic kidney disease, especially diabetic nephropathy [1, 16, 17].

The present NIS aimed at evaluating the incidence of adverse drug reactions in relation to individual patient risk factors and preventive measures taken to prevent such ADRs. In this regard, radiologists from 66 outpatient radiology sites across Germany documented data of roughly 10 000 patients undergoing CM-enhanced diagnostic CT with the non-ionic iso-osmolar contrast medium iodixanol.

Although the number of total adverse drug reactions is apparently low (77 patients, 0.74 %), the findings are in agreement with published studies on ADRs after CT scans [18 – 20]. In these studies adverse events after i. v. CM administration ranged between 0.2 % and 3.1 %. Similar ADR rates were also observed in larger trials [21, 22]. The number of allergy-like adverse drug reactions is comparable to other published NIS with non-ionic contrast media [10, 23].

The incidence of serious adverse drug reactions was very low (0.03 %) and all SAE occurred in the radiology office allowing for immediate medical intervention. Importantly, no serious late reaction was reported which is in accordance with the literature describing severe late reactions to be very rare [14].

The incidences of both acute and late adverse reactions were low but consistent with a previous study (0.34 % and 0.39 %, as compared to 0.32 % and 0.42 %) [10]. To record late adverse reactions, patients had been instructed by the physicians to report any adverse events occurring between one hour and seven days after CM administration. However, it is a limitation of this non-interventional trial that AE reporting relied on patient collaboration and thus some late events may not have been reported to the investigator. Hypersensitivity reactions were the most common reactions among both acute and late reactions, occurring in 53 of 77 patients.

As in a previous NIS [10], more than half of the patients had one or more of the documented risk factors. Even though 7.5 % of all patients were considered to be at risk for an allergy- like reaction, only a rather small part of them received preventive treatment despite guideline recommendations [10, 15]. Measures to prevent allergy-like reactions were applied very heterogeneously depending on the kind of risk factor: antihistamines were given in 50 % versus 0.2 % of the patients with/without previous allergy-like reaction in 4.8 % vs. 0.5 % of patients with/without allergies, and in 0.8 % vs. 0.7 % of patients with/without asthma. Steroid premedication was used in 22 % of the patients with a former allergy-like reaction (21 of 97). As only one of the 97 patients with a former allergy-like reaction to a CM experienced a reaction during this study, no treatment effect was seen in terms of adverse event reduction. The data obtained within this NIS therefore do not suggest that patients with previous reactions to CM are at increased risk for experiencing another ADR after re-exposure to a CM. However, the overall low number of reactions limits the value of this statement which differs from the risk described in the literature and subsequent guideline recommendations.

Measures to prevent CI-AKI are recommended by the ESUR. Our study also aimed at determining whether preventive measures are commonly used in the outpatient setting. The data suggest that measures to prevent CI-AKI were used very heterogeneously. One third of the sites did not use any preventive measures for patients at increased risk for CI-AKI, whereas others pre-treated all of their patients, regardless of their risk profile. Overall, the most common preventive measure was oral hydration, which was provided to 16.5 % of patients with renal insufficiency/previous kidney surgery/proteinuria. In patients with clinical signs of dehydration, preventive measures were taken more often (34.5 %) although it is not clear whether hydration was used to protect the kidneys or to remedy the dehydration itself. In total, i. v. hydration was only given in 5.2 % of the patients with the previously mentioned risk factors. Regarding the type of fluid used for i. v. hydration, results are in accordance with other studies indicating that normal saline is the preferred hydration agent rather than half-normal saline (92.5 % versus 5 % of the sites using normal versus half normal saline) [3].

Discontinuation of nephrotoxic medication, although recommended by guidelines and SmPC for patients with renal insufficiency, was not done for patients with renal risk factors in this NIS [24, 25]. The reason for this discrepancy could be the general structure of the outpatient setting system. With patients being transcribed by the general practitioner for diagnostic imaging, radiologists may not be aware of specific diseases or medications in order to be able to withdraw the respective drug before administering CM.

The incidence of CI-AKI could not be assessed in this NIS due to the unavailability of post-CM SCr values in the routine outpatient setting. In the absence of post- SCr values, the only possible conclusion in terms of possible renal function deterioration from this NIS is that obviously no acute kidney failure occurred, as this would probably have been reported as an adverse event to the investigator.

In summary, there was no statistically significant evidence to suggest a relationship between any of the risk factors, preventive measures and adverse drug reactions. The finding that preventive measures are rarely used in the outpatient setting except in certain high risk patients with e. g. former allergy-like reaction to a CM may be explained by two factors: physicians might not be aware of current recommendations in this regard or might not consider preventive measures useful except in highest risk patients.

Conclusion

Preventive measures to reduce the risk of contrast medium-induced adverse drug reactions are not widely used in the outpatient setting, neither for the prevention of allergy-like reactions nor for the prevention of CI-AKI. The underlying reasons for this behavior have not been analyzed so far.

To assess the motivation for or against the use of preventive measures, additional studies should be performed, especially in the outpatient setting where few data are available regarding the daily routine due to the fact that most clinical trials are being performed in hospital settings. In summary, ADR incidence after the use of the iso-osmolar contrast agent iodixanol was very low (the incidence of acute and late adverse reactions was 0.34 % and 0.39 %, respectively) with a very rare incidence of serious adverse reactions (0.03 %). Patient-related risk factors and preventive measures did not seem to influence the incidence of adverse reactions. However, final conclusions in this regard cannot be drawn, as the total number of events was too low to allow for proper statistical testing of the significance of the results and due to the limitations of this non-interventional study regarding the observational period. Although this study was not designed to compare the frequency of adverse events between various contrast media, the rare frequency of adverse events observed in a large outpatient population in this real-world CT setting indicates that iodixanol is a safe contrast medium in the outpatient setting even when recommended preventive measures are not applied.

Clinical relevance of study:

- Rare use of preventive measures for outpatient CT examinations.
- Low rate of acute and late adverse drug reactions to iodixanol.
- No correlation between risk factors, preventive measures and adverse drug reactions.
- Iodinated radiographic contrast media (CM) are considered safe diagnostic agents with a low incidence of adverse drug reactions.

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