

ORIGINAL ARTICLE

The role of iodine in hypersensitivity reactions to radio contrast media

K. Scherer, T. Harr, S. Bach and A. J. Bircher

Allergy Unit, Department of Dermatology, University Hospital Basel, Basel, Switzerland

Clinical & Experimental Allergy

Summary

Introduction Hypersensitivity reactions to iodinated radio contrast media (RCM) are either immediate-type (IT) or delayed reactions (DT). In IT, the pathomechanism is unclear. In DT, delayed positive patch (PT) and intradermal tests (IDT) and RCM-specific T cells suggest a T cell-mediated mechanism. In both, the role of iodine has not been clarified; however, patients are often labelled as 'iodine allergic'. Occasionally, positive skin tests to iodine-containing drugs are observed.

Objective We investigated the presence of hypersensitivity to iodine in patients with a history of hypersensitivity reactions to RCM.

Methods Nineteen patients with a history of IT ($n = 9$) or DT ($n = 10$) to RCM were investigated. Skin prick tests, IDT and PT with several RCM and iodine formulations were carried out. All underwent oral provocation with Lugol's solution (LS). Two patients each with iodine mumps, contact dermatitis to iodized antiseptics and chronic idiopathic urticaria served as control or proof of concept.

Results In the IT group, skin tests were positive in three out of nine patients to one RCM. One patient with negative skin tests reacted twice to oral iodine with urticaria. In the DT group, sensitization to one or several RCM was identified in 10 out of 10 patients. In seven out of 10 patients, additional sensitizations to the iodine formulations were found. Two patients developed a mild exanthema after oral provocation with LS.

Conclusion We have previously demonstrated in patients with iodine mumps that an oral challenge with LS is a valid means to elicit hypersensitivity reactions to iodine. In 19 patients, we showed that iodine is rarely the eliciting agent in hypersensitivity reactions to RCM. Only one patient with a late urticaria to an RCM with a late urticaria to LS and two patients with DT and broad sensitization to all RCM tested reacted to LS with an exanthema. In most cases, more likely the RCM molecules and not iodine are the eliciting compounds.

Keywords allergy, exanthema, hypersensitivity, iodine, Lugol's solution, provocation test, radio contrast media

Submitted 16 August 2008; revised 14 August 2009; accepted 17 August 2009

Correspondence:

Prof. Dr A. J. Bircher, Allergy Unit,
Department of Dermatology, University
Hospital Basel, Petersgraben 4, 4031
Basel, Switzerland.
E-mail: bircher@uhbs.ch

Introduction

Diagnostic and interventional procedures using iodinated radio contrast media (RCM) are being performed with increasing frequency over the last years [1, 2]. Although the rate of side-effects from iodinated-RCM is rather low, the increasing frequency of usage accounts for a steadily increasing number of patients who experience hypersensitivity reactions after administration of a RCM.

RCM are tri-iodinated benzene derivatives with different side chains at positions 1, 3 and 5 that can be classified into four main groups according to their chemical structure and osmolality: ionic monomers with high osmolality, non-ionic monomers with low osmolality, ionic

dimers with low osmolality and non-ionic dimers with intermediate osmolality (Fig. 1) [3–5]. Hypersensitivity reactions to RCM are either immediate reactions occurring within 1 h after RCM exposure or so-called non-immediate delayed reactions (DT), which – in this context – become typically apparent more than 6–12 h after administration [6–8], with the immediate-type (IT) hypersensitivity comprising about two-thirds of all reactions.

Until recently, IT hypersensitivity reactions to RCM were mostly thought to present a non-IgE-mediated anaphylaxis, based on the osmolality of RCM leading to direct complement activation, because patients frequently react on first contact with the drug and may tolerate the same drug upon a later exposure. Data from the Comité

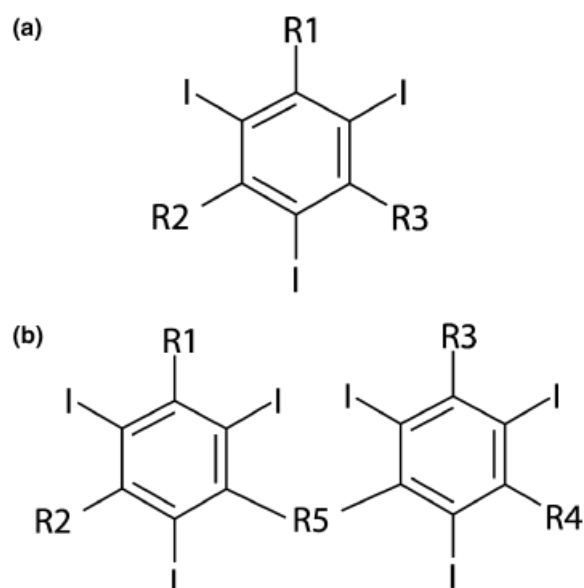


Fig. 1. Basic chemical formula of monomeric (a) and dimeric (b) iodinated radio contrast media [4].

Interdisciplinaire de Recherche et le Travail sur les Agents de Contraste en Imagerie, however, showed positive intradermal tests (IDT) in up to 70% of patients with a history of a severe anaphylaxis to RCM, suggestive of an IgE-mediated pathophysiology [9]. Previous data obtained by Laroche et al. [10] demonstrated the release of histamine and tryptase from basophils and mast cells in patients with anaphylaxis after RCM. The prevalence of severe anaphylaxis is much higher after administration of ionic contrast media (0.1–0.4%) than after non-ionic contrast media (0.02–0.04%), as assessed in Japanese and American patient groups, respectively [4, 7, 11, 12]. However, the mode of sensitization, in case of an IgE-mediated mechanism remains unclear. It has been proposed previously that sensitization occurs in halogenated-benzene derivatives that are used as food additives, pesticides and herbicides [3, 13], but currently there is little evidence for this hypothesis.

DT reactions, sometimes called non-immediate hypersensitivity reactions, usually present themselves as macular or macular-papular exanthema, although various types of severe hypersensitivity reactions such as toxic epidermal necrolysis, allergic vasculitis or flexural exanthema [4] have been reported. Most seem to be T cell mediated [14, 15]. Also, urticarial eruptions accompanied by angioedema and/or flush are classified as non-immediate reactions in the literature [8] due to the rather unfortunate, non-morphological classification at an arbitrary cut-off time-point of 1 h after administration of the drug. Also, IT drug hypersensitivity reactions may occur after a time span longer than 1 h after administration, especially if co-factors or metabolites are involved.

In DT reactions, the non-ionic dimers seem to be more often causative than the non-ionic monomers [16], although not all reports support this [17]. RCM-specific T lymphocytes have been shown to be involved [7], which is supported by positive patch tests (PT) [18], positive IDT at late reading points [8, 19], lymphocyte transformation tests (LTT) [15, 20] and histology [20, 21]. In addition, these reactions can not be prevented by premedication, as it has been repeatedly reported in patients with DT hypersensitivity to RCM [22].

In contrast to IT reactions, cross-reactivity among the RCM, even across the four groups, is common in DT reactions [15, 23]. Based on this observation and the fact that positive PTs to iodized antiseptics have been demonstrated in RCM-allergic patients, a central role of iodide has been suggested [23, 24]. This, however, has so far not been supported by much evidence and is rejected by some [15].

Patients with hypersensitivity reactions after administration of RCM are often wrongly labelled to be allergic to iodine because all RCM possess one or more benzene rings that are substituted with iodine in three positions (Fig. 1). This label has considerable consequences, especially for future treatments including contrast media applications. Even among physicians, knowledge of unwanted risks and side-effects and further consequences for these patients is limited [25]. Little is known to date on the role of iodine or iodide in these RCM solutions as an elicitor of an immune response or the epitopes for binding of the T cell receptor or IgE molecules [15, 23, 24].

We evaluated the presence of hypersensitivity to iodine in patients with a history of either an IT or a DT reaction to an RCM by skin tests and oral provocation tests.

Methods

Nineteen patients (seven male, 12 female, mean age: 62 years) with a history of an IT ($n=9$) or a DT ($n=10$) hypersensitivity reaction to RCM were investigated. Two patients with iodine mumps [25], two with contact dermatitis to iodized antiseptics and two with chronic idiopathic urticaria served as proof of concept. Some of these patients had been included in the study by Brockow [19].

Depending on the clinical reaction, skin prick tests (SPT), IDT with immediate and late readings and PT with several RCM and different iodine formulations were performed according to the study protocol and test procedure published by Brockow et al. [19]. SPTs, IDT and PT were performed with at least the first four of the following plus the culprit drug: Iodixanol, Ioxaglate-Meglumine, Iopamidol, Amidotrizoate, Ioxithalamate-Meglumine, Iohexol, Iopentol, Iomeprol, Ioversol, Iopromide, Iobitridol and Iotrolan (for chemical structures, see [3]). The majority of patients were tested with all of these. PT with different iodine formulations were performed with the following substances: povidone-iodine, iodine in petrolatum and in

Table 1. (a) Immediate type hypersensitivity reactions and (b) delayed type hypersensitivity reactions

								Patch test		
Patient No.	Putative culprit	Prick test RCM		IDT 20' RCM		IDT 24–48 h RCM		RCM		Iodine
		Series	Putative culprit	Series	Putative culprit	Series	Putative culprit	Series	Putative culprit	Series
<i>(a) immediate type reactions</i>										
1	Iopromide or Iomeprol	0	0	0	0	0	0	ND	ND	ND
2	Ioxithalamate	0	0	0	0	0	0	ND	ND	ND
3	Unknown	0	0	0	0	1	Unknown	0	0	1
4	Iobitridol	0	0	1	1	ND	ND	ND	ND	ND
5	Unknown	0	0	0	0	0	0	ND	ND	ND
6	Iobitridol	0	0	0	0	0	0	0	0	0
7	Iodixanol	0	0	1	1	0	0	ND	ND	ND
8	Iopromide	0	0	0	0	0	0	ND	ND	ND
9	Unknown	0	0	0	0	0	0	ND	ND	ND
<i>(b) delayed type reactions</i>										
10	Iobitridol	0	0	0	0	1	1	1	1	1
11	Iopromide, Iomeprol	0	0	0	0	1	1	1	1	1
12	Iomeprol	0	0	0	0	1	1	1	1	1
13	Unknown	ND	ND	0	0	1	Unknown	1	Unknown	0
14	Ioversol	0	0	0	0	1	1	1	1	0
15	Iomeprol	0	0	0	0	0	0	1	1	1
16	Iodixanol	0	0	0	0	1	1	0	0	1
17	Unknown	0	0	0	0	1	Unknown	1	Unknown	0
18	Iodixanol	0	0	0	0	1	1	0	0	1
19	Iodixanol	0	0	0	0	0	0	1	1	1

Patient three surprisingly developed a late reaction in the IDT to Ioxaglate and Ioversol and was also positive in the PT to iodine in petrolatum (0.5% and 1%) and iodine in alcohol (0.5%).

Series, whole series of RCM tested (see text); 0, negative test result, 1, positive test result, ND, not done; RCM, radio contrast media; IDT, intradermal tests.

alcohol, Iodoform and potassium iodide in petrolatum. For summarized test results, see Table 1a (IT) and b (DT).

Some patients were exposed to a RCM during the course of a necessary radiologic examination or in the form of a challenge test with a skin test-negative substance (Table 2).

After exclusion of contraindications, control of thyroid function and obtaining informed consent, all underwent oral provocation with an iodine potassium iodide solution [5% Lugol's solution (LS), 75–300 mg iodine] by an incremental dose increase (Table 3). The amount of LS or the iodine dose, respectively, was in the same range (Table 3) as is usually applied for other indications for LS such as thyreotoxicosis (250–300 mg) and radiation emergencies (approximately 100–150 mg single dose). It was deliberately chosen to be higher than the average amount of iodine received during an RCM investigation to ensure reactivity despite the oral administration in contrast to the i.v. application of RCM. The patients with iodine mumps, who were included for proof of concept, were exposed to much lower doses and still reacted (Table 4). Patient No. 12 received lower doses due to renal insufficiency after kidney transplantation and non-Hodgkin lymphoma and

patient 13 due to polyglandular autoimmune syndrome with autoimmune thyroiditis. Apart from a slight pharyngeal or gastric irritation, no side-effects were observed in all 25 patients.

Results

Immediate-type hypersensitivity reactions

Nine patients with IT reactions after administration of RCM were investigated (Table 1a). Only in six cases the culprit RCM was known. Only in patients 4 and 7, a positive IDT to the culprit drug, suggestive of the presence of specific IgE, could be demonstrated. Patient 4 had reacted with sudden respiratory distress, followed by a pulmonary capillary leak syndrome during a CT-scan with Iobitridol; patient 7 had developed urticaria and dyspnoea 10 min after administration of Iodixanol, both consistent with an allergic type-I reaction. In patient 3, none of the skin tests was positive after 20 min, but a delayed positive reaction was identified in the IDT after 24 h to Ioxaglate and Ioversol, as well as to three iodine formulations in the PT. Two clinical reactions of that

Table 2. Exposure to RCM/provocation tests

Patient No.	Putative culprit	Exposition RCM
1	Iopromide Iomeprol	ND
2	Ioxithalamate	ND
3	Unknown	Tolerated unknown RCM
4	Iobitridol	ND
5	Unknown	ND
6	Iobitridol	ND
7	Iodixanol	ND
8	Iopromide	Tolerated unknown RCM
9	Unknown	ND
10	Iobitridol	ND
11	Iomeprol	Tolerated Ioxithalamate and Ioxaglate challenge test; DT reaction to Iopromide (skin test positive)
12	Iomeprol	DT reaction to Ioxaglate
13	Unknown	ND
14	Ioversol	DT reaction to Iopromide
15	Iomeprol	ND
16	Iodixanol	ND
17	Unknown	DT reaction to Iobitridol
18	Iodixanol	ND
19	Iodixanol	ND

Patient 8: intentional exposure to skin test-positive drug because of unavailability of skin test-negative drug in emergency situation. DT, delayed-type reaction; IDT, intradermal tests; ND, not done; RCM, radio contrast media.

patient in 1978, however, had clearly been severe anaphylactic reactions necessitating resuscitation, although the culprit could not be identified 29 years later. More recently, an unknown RCM was tolerated.

In the group of patients with clinical IT reactions, only patient 6 reacted to an oral challenge with LS. This particular patient suffered from pulmonary and cutaneous sarcoidosis treated with Infliximab. She had also suffered from mild recurrent urticaria for years. When challenged with LS (cumulative doses 150 mg iodine), she developed a generalized urticaria after 12 h only. To rule out an episode of her urticaria, she was challenged a second time with LS and reacted again after 11 h with a generalized urticarial reaction after a total of 150 mg iodine was given. To exclude that chronic urticaria can be aggravated by iodine, two other patients (23, 24) with severe idiopathic chronic urticaria were challenged with LS (total of 187.5 mg). Both tolerated oral iodine without any reaction.

Delayed-type reactions

Of the 10 patients with a DT reaction, all but two showed positive reactions in the IDT with delayed reading. Patients 15 and 19, who were negative in the IDT, reacted in the PT to the culprit drug; i.e. all patients had at least one positive

Table 3. Oral challenge test with Lugol's solution 5%

No.	Putative culprit	Challenge with lugol	[mg iodine]
1	Iopromide or Iomeprol	0	187.5
2	Ioxithalamate	0	225
3	Unknown	0	150
4	Iobitridol	0	212.5
5	Unknown	0	187.5
6	Iobitridol	Generalized urticaria twice	150
7	Iodixanol	0	187.5
8	Iopromide	0	187.5
9	Unknown	0	187.5
10	Iobitridol	0	187.5
11	Iomeprol	0	250
12	Iomeprol	Maculo-papular exanthema	300
13	Unknown	0	200
14	Ioversol	0	75
15	Iomeprol	0	100
16	Iodixanol	0	200
17	Unknown	Maculo-papular exanthema	187.5
18	Iodixanol	0	187.5
19	Iodixanol	0	187.5

[mg iodine], total amount of iodine administered in a fractionated fashion; 0, no reaction to oral challenge.

delayed skin test. Also, seven out of 10 had a positive reaction in the PT to at least one iodine formulation.

Patient 11 developed a flexural exanthema (SDRIFE) [4] after Iomeprol and again after Iopromide, which he had been given in an emergency situation despite positive skin tests to Iopromide. Premedication delayed the clinical reaction for 2 days. Upon challenge, he tolerated the skin-test-negative Ioxaglate–Meglumine and Ioxithalamate–Meglumine.

Patient 14 was exposed to Iopromide after this substance was negative in the PT and in the IDT with a delayed reading, but reacted with a maculopapular exanthema despite premedication. He also developed recall phenomena on his previously positive skin test sites. Patient 17 was challenged with the only skin test-negative RCM (of nine RCM tested) (Iobitridol), after having previously developed a generalized exanthema after exposure to an unknown RCM. He developed an exanthema after 8 h and also showed the recall phenomenon on all skin test sites. Patient 12 had a history of three exanthemas after application of Iomeprol. He developed a generalized maculopapular exanthema involving the face after exposure to Ioxaglate–Meglumine, which had been negative in the PT and also in the LTT [15]. The diagnosis of drug-induced exanthema was histologically supported. Complete cross-reactivity among all RCM was assumed and all iodinated RCM were banned; however, gadolinium-based MRIs were recommended as an alternative.

Patient 12 and patient 17 (Fig. 2) were the only ones to develop a generalized exanthema after an oral challenge with LS (patient 12: 300 mg iodine; patient 17: 187.5 mg iodine). These two were different from the other patients –

Table 4. Diagnosis, results of skin tests and provocation tests in the control group

No.	Diagnosis	Prick test RCM Series	IDT 20' RCM Series	IDT 24–48 h RCM Series	Patch test RCM Series	Patch test Iodine Series	Exposition RCM	RCM Substance	Challenge with lugol [mg iodine]
20	Iodine sialadenopathy	0	0	0	ND	ND	1	Ioxithalamate	1 [40 and 87.5]
21	Iodine sialadenopathy	0	0	0	ND	ND	1	Unknown	1 [62.5]
22	Contact dermatitis	0	ND	ND	0	1	0	Iopamidol	0 [250]
23	Contact dermatitis	0	0	0	0	1	ND		0 [200]
24	Chronic urticaria	ND	ND	ND	ND	ND	ND		0 [187.5]
25	Chronic urticaria	ND	ND	ND	ND	ND	ND		0 [187.5]

0, no reaction in skin test or oral challenge; 1, positive reaction; ND, test not done; RCM, radio contrast media; IDT, intradermal tests.

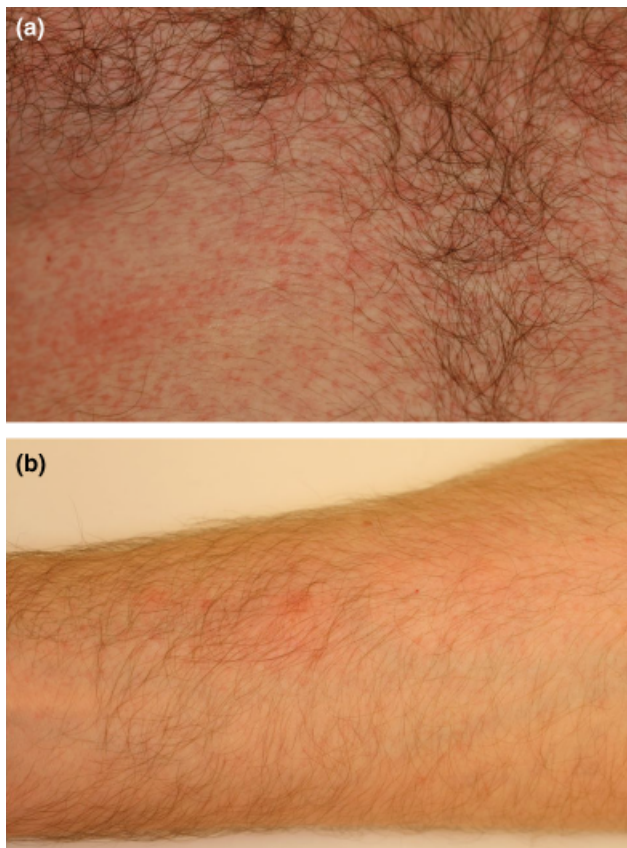


Fig. 2. (a) Patient 17: maculopapular exanthema on the trunk 24 h after administration of 187.5 mg Lugol's solution. (b) Recall phenomenon on the forearm on the skin test sites of different RCM 24 h after LS administration. The arrows in the figure indicate the barely visible recall phenomenon.

in that they had developed strongly positive skin test reactions to almost all RCM tested and had reacted to skin test-negative RCM in the challenge tests. In all other patients, skin test reactivity was limited to the putative culprit and one or two cross-reacting substances at the most. Based on the generalized cutaneous reaction to LS, both patients were presumed to be hypersensitive to iodine and were advised to avoid iodinated RCM.

Six patients were regarded as controls and proof of principle (Table 4): Two patients had been diagnosed

with iodine mumps [26, 27] (iodine sialadenopathy), an idiosyncratic condition to iodine of unknown pathophysiology; an immunologic mechanism has not been demonstrated [26] so far. Nevertheless, oral intake of iodine, as well as RCM exposure, resulted in reproducible swelling of the submandibular gland in both patients.

Two other control patients showed evidence of contact dermatitis to an iodine-containing antiseptic used in surgical interventions. Skin tests revealed a type-IV sensitization to an aqueous povidone-iodine solution in patient 21 and to iodine in petrolatum and Iodoform in patient 22, only. All skin tests with other iodine formulations as well as RCM were negative in both. Patient 21 had previously tolerated Iopamidol, and both tolerated oral challenge with LS (patient 21: 250 mg iodine; patient 22: 187.5 mg iodine).

Lastly, two patients with a longstanding history of severe chronic urticaria were challenged with LS to investigate whether iodine exposure can lead to exacerbation of an existing urticaria. Both tolerated the LS without an aggravation of their disease in contrast to patient 3, who had twice experienced an attack of urticaria after an oral challenge with LS. In this case it was concluded that free iodine in RCM was indeed the cause of her urticarial reaction.

Discussion

All patients were skin tested with the suspected culprit drug and one or more representatives of the four chemical subgroups of RCM: non-ionic monomeric RCM, non-ionic dimeric RCM, ionic monomeric RCM and the ionic dimeric RCM.

In DT sensitization typically presenting with maculopapular exanthema, we were able to demonstrate type-IV sensitization to the culprit plus one or more cross-reacting RCM in all cases. In one patient (16), we could identify a type-IV sensitization to the culprit (Iodixanol) only. For DT hypersensitivity, skin tests, especially IDT with delayed reading and PT, are valuable and, especially if combined, reliable diagnostic tools [19]. Among this group of patients, seven out of the 10 patients patch tested with

different iodine formulations also reacted to iodine-containing disinfectants or other iodine preparations (patients 10, 11, 12, 15, 16, 18, 19), even without a suggestive history of allergic contact dermatitis.

LS, a 5% iodine–potassium iodide solution, consists of 5% iodine and 10% potassium iodide in 85% water with a total iodine content of 130 mg/mL in the form of polyiodide ions. RCM preparations may contain 25–50 µg/mL free iodide [24]. Oral iodine is usually well tolerated as has been observed after the Chernobyl accident in 1989, where a large population of exposed individuals was preemptively treated [28]. LS is routinely given to patients with thyrotoxicosis and a saturated solution of potassium iodide is well known as systemic treatment for neutrophilic dermatoses or panniculitis such as erythema nodosum [29]. We now consider the optimal doses for oral provocation with the aim of excluding systemic hypersensitivity to be between 150 and 250 mg iodine and mostly used 187.5 mg iodine; however, contraindications such as renal insufficiency or thyroid disease have to be considered and the iodine dose has to be adapted. The two patients with iodine mumps are of special interest in this context. They had developed swelling of their submandibular gland several times after an intravenous administration of RCM and later showed an identical reaction after an oral challenge with LS [26, 27]. Iodine mumps or iodine sialadenitis is considered to be a rare idiosyncratic reaction that occurs usually about 24 h after exposure to iodine or iodide, such as in RCM, probably based on individual predisposition that has not been further characterized yet. Both were challenged with much lower doses than the other patients and controls and still reacted (Table 4).

Their example illustrates that oral challenge is in principle a valid diagnostic means to detect idiosyncratic reactions caused by the free iodide content of RCM. Obviously, iodine is not only absorbed in sufficient amounts via the oral route but is also presented in the right form to elicit a reaction. Two patients, who had been labelled 'allergic to iodine' after developing allergic contact dermatitis to an iodized antiseptic, were also orally challenged with LS. Although allergic contact dermatitis is a T cell-mediated disease, oral provocation with LS did not elicit an allergic reaction. A possible explanation could be an insufficient antigen presentation of iodine by oral exposure.

To investigate whether sensitization to free iodine or to the RCM molecule itself is causative for exanthemas after RCM administration, which has been suggested in the literature [23, 24], all 19 patients were orally challenged with LS. Of the 10 patients with DT hypersensitivity, two developed a generalized exanthema after oral provocation with LS, which substantiates the suspicion that iodine may be the elicitor in a particular subgroup. The two differed from the other eight in several ways: they had very strong positive reactions to most RCM tested and also in lym-

phocyte proliferation assays (performed at the Department of Allergology and Clinical Immunology in Bern, Switzerland [15], and W. Pichler personal communication).

Patient 12, who was also investigated by LTTs and expression of the activation marker CD69 on PBMC [15], reacted in the IDT to nine out of 12 RCM tested, and in the PT to eight out of 12 RCM. The negative substances in the IDT were amidotrizoate (ionic monomer), Iobitridol (non-ionic monomer) and Iotrolan (non-ionic dimer), and in the PT Amidotrizoate, Ioxithalamate (ionic monomer), Ioxaglate (ionic dimer) and Iotrolan, which demonstrates that his skin reactivity seems to be independent of the basic chemical structure of the RCM. His T cell clones showed a high degree of cross-reactivity to different RCM. Potassium iodide, however, did not induce relevant CD69 up-regulation in CD4⁺ and CD8⁺ cells and proliferation assays remained negative [15]. Apparently, the pathophysiology, resulting in a strong skin reactivity after oral exposure to LS, cannot be reliably reproduced at an *in vitro* cellular level.

Patient 17, who had reacted to an unknown RCM, also had positive skin test reactions to many RCM. In the IDT with a late reading, he reacted to nine out of 10 RCM and in the PT in five out of 10. Again, no pattern relating to a certain chemical group was distinguishable. He was challenged with Iobitridol, the only substance completely negative in all skin tests, and developed exanthema after 24 h. Also, after LS provocation, he developed exanthema and flare-up of former skin test sites (Figs 2a and b). LTT showed a very strong stimulation with most RCM tested, which correlates to observations by Torres et al. [30], who showed that LTT results correlate well with skin test results regarding cross-reactivity.

The clinical characteristics of the LS-negative patients with DT hypersensitivity to RCM were somewhat different: in most patients, positive skin tests were limited to the culprit and a few other RCM. Only patient 11 was also broadly sensitized, but as in the other seven patients we were able to identify at least one RCM that was tolerated upon exposure.

In contrast to Lerch et al. [15] we do not interpret the positive reactions in the PT to PVI and other iodine formulations as being solely irritative in nature, because all substances were tested at two different concentrations and in most cases there was a clear crescendo type of reaction. All reactions in the PT were positive to both test concentrations, although at the lower concentration, the test reactions were usually weaker.

In the IT hypersensitivity reaction, the pathomechanism is less clear. Because of the unreliability of skin tests, which, if negative, do not rule out allergic sensitization, patients were included in our study based on a convincing, well-documented history of an IT reaction with suggestive symptoms within 1 h after administration of an RCM. Two out of nine patients (22.2%) had a positive

IDT to the culprit, which is about the same rate (25%) that has been demonstrated in 122 IT reactors [19]. A non-IgE-mediated mechanism has been debated for a long time [31, 32], but in recent years, some evidence supporting an IgE-mediated mechanism has evolved. The high risk of recurrence is in favour of an IgE-mediated mechanism, although the low sensitivity of the skin tests so far does not clearly support an immunologic mechanism [19]. Using skin tests and basophil activation tests, Trcka et al. [5] recently demonstrated data suggesting an IgE-mediated mechanism as one possible pathway.

In our group, two patients (Nos. 4, 7) had a positive IDT to the culprit (Iobitridol and Iodixanol, respectively), but not to other RCM. We assume the positive predictive value in this case to be high. Another patient (No. 3) with a history of two episodes of severe anaphylaxis, necessitating resuscitation, reacted in the IDT with a late reading (after 24 h) to Ioxaglat and Ioversol, suggesting a delayed T cell-mediated mechanism. Brockow et al. [19] report two such patients with a late reactivity in the IDT after 10–24 h.

Only one patient (No. 6) who had completely negative skin tests in immediate and late readings reacted to LS. She had a history of a mild chronic recurrent urticaria. Twelve hours after the first oral administration of LS, she developed an episode of urticaria. When she was challenged again several weeks later, she reacted again after 11 h with urticaria only. Iodine as an elicitor was excluded in two controls with chronic urticaria. We therefore assume that this patient may present a rare IT hypersensitivity to iodine, although the allergenic determinant and mechanisms remain unknown. We have demonstrated that free iodine is the elicitor only in a few patients with a hypersensitivity reaction to RCM. Particularly in patients with broad skin test positivity to many different RCM, hypersensitivity to iodine seems to be a possible explanation and should be investigated. In such rare cases, the diagnosis of iodine allergy may be justified.

Acknowledgements

Conflict of interest: The authors do not declare any competing interests.

References

- 1 Toms AP, Cash CJ, Linton SJ, Dixon AK. Requests for body computed tomography: increasing workload, increasing indications and increasing age. *Eur Radiol* 2001; 11:2633–7.
- 2 Katzberg RW. Acute reactions to urographic contrast medium: incidence, clinical characteristics and relationship to history of hypersensitivity states – a commentary. *Am J Roentgenol* 2008; 190:1431–2.
- 3 Christiansen C. Hypersensitivity reactions to iodinated contrast media: an update. In: Pichler WJ, ed. *Drug hypersensitivity*. Basel: Karger, 2007; 233–41.
- 4 Arnold AW, Hausermann P, Bach S, Bircher AJ. Recurrent flexural exanthema (SDRIFE or baboon syndrome) after administration of two different iodinated radio contrast media. *Dermatology* 2007; 214:89–93.
- 5 Trcka J, Schmidt C, Seitz SC, Bröcker E-B, Gross GE, Trautmann A. Anaphylaxis to iodinated contrast material: nonallergic hypersensitivity or IgE-mediated allergy? *Am J Roentgenol* 2008; 190:666–70.
- 6 Brockow K. Contrast media hypersensitivity – scope of the problem. *Toxicology* 2005; 209:189–92.
- 7 Brockow K, Christiansen C, Kanny G et al. Management of hypersensitivity reactions to iodinated contrast media. *Allergy* 2005; 60:150–8.
- 8 Brockow K, Ring J. Radiographic contrast media hypersensitivity. New understanding of pathophysiology with implications for patient management. *Hautarzt* 2005; 56:32–7.
- 9 Laroche D, Dewachter P., Mouton-Faivre C., Clément O, the CIRTACI group. Immediate reactions following ICM injection: results of a 3-year prospective multicenter survey. *Contrast Med Mol Imaging* 2006; 1:81.
- 10 Laroche D, Aimone-Gastin I, Dubois F et al. Mechanisms of severe, immediate reactions to iodinated contrast material. *Radiology* 1998; 209:183–90.
- 11 Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seep P, Matsuura K. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese committee on the safety of contrast media. *Radiology* 1990; 175:621–8.
- 12 Wolf GK, Arenson RL, Cross AP. A prospective trial of ionic vs nonionic contrast agents in routine clinical practice: comparison of adverse effects. *Am J Roentgenol* 1989; 152:939–44.
- 13 Brasch RC. Allergic reactions to contrast media: accumulated evidence. *Am J Roentgenol* 1980; 134:797–801.
- 14 Christiansen C. Late-onset allergy-like reactions to X-ray contrast media. *Curr Opin Allergy Clin Immunol* 2002; 2:333–9.
- 15 Lerch M, Keller M, Britschgi M et al. Cross-reactivity patterns of T cells specific for iodinated contrast media. *J Allergy Clin Immunol* 2007; 119:1529–36.
- 16 Morcos SK, Thomsen HS. Adverse reactions to iodinated contrast media. *Eur Radiol* 2001; 11:1267–75.
- 17 Rydberg J, Charles J, Aspelin P. Frequency of late allergy-like adverse reactions following injection of intravascular non-ionic contrast media. A retrospective study comparing a non-ionic monomeric contrast medium with a non-ionic dimeric contrast medium. *Acta Radiol* 1998; 39:219–22.
- 18 Brockow K, Becker EW, Worret WI, Ring J. Late skin test reactions to radiocontrast medium. *J Allergy Clin Immunol* 1999; 104:1107–8.
- 19 Brockow K, Romano A, Aberer W et al. Skin testing in patients with hypersensitivity reactions to iodinated contrast media – a European multicenter study. *Allergy* 2009; 64:234–41.
- 20 Christiansen C, Dreborg S, Pichler WJ, Ekeli H. Macular exanthema appearing 5 days after X-ray contrast medium administration. *Eur Radiol* 2002; 12 (Suppl. 3):S94–7.
- 21 Gall H, Pillekamp H, Peter RU. Late-type allergy to the X-ray contrast medium solutrast (iopamidol). *Contact Dermatitis* 1999; 40:248–50.
- 22 Courvoisier S, Bircher AJ. Delayed-type hypersensitivity to a non-ionic radiopaque contrast medium. *Allergy* 1998; 53:1221–4.

- 23 Vernassiere C, Trechot P, Commun N, Schmutz JL, Barbaoud A. Low negative predictive value of skin tests in investigation delayed reactions to radio-contrast media. *Contact Dermatitis* 2004; **50**:359–66.
- 24 Bircher AJ. Ueberempfindlichkeit auf Jod: Rien ne va plus? *Akt Dermatol* 2006; **32**:44–9.
- 25 Confino-Cohen R, Goldberg A. Safe administration of contrast media: what do physicians know? *Ann Allergy Asthma Immunol* 2004; **93**:166–70.
- 26 Gilgen-Anner Y, Heim M, Ledermann HP, Bircher AJ. Iodide mumps after contrast media imaging: a rare adverse effect to iodine. *Ann Allergy Asthma Immunol* 2007; **99**:93–8.
- 27 Bach S, Anner A, Arnold A, Hohenstein E, Häusermann P, Bircher AJ. Delayed hypersensitivity reactions to iodinated contrast media in 2 patients: unusual manifestation as iodine mumps and flexural exanthem (SDRIFE). *Swiss Med Wkly* 2005; **135**:S14.
- 28 Kinalska I, Zarzycki W, Zonenberg A *et al*. Results of studies on the effect of radiologic contamination after the Czernobyl catastrophe and prophylactic iodine on thyroid morphology and function on inhabitants of North-East Poland. *Endokrynol Pol* 1991; **42**:215–35.
- 29 Sterling JB, Heymann WR. Potassium iodide in dermatology: a 19th century drug for the 21st century – uses, pharmacology, adverse effects and contraindications. *J Am Acad Dermatol* 2000; **43**:691–7.
- 30 Torres MJ, Mayorga C, Cornejo-Garcia JA *et al*. Monitoring non-immediate allergic reactions to iodine contrast media. *Clin Exp Immunol* 2008; **152**:233–8.
- 31 Maddox TG. Adverse reactions to contrast material: recognition, prevention, and treatment. *Am Fam Physician* 2002; **66**:1229–34.
- 32 Freed KS, Leder RA, Alexander C, DeLong DM, Kliever MA. Breakthrough adverse reactions to low-osmolar contrast media after steroid premedication. *Am J Roentgenol* 2001; **176**:1389–92.