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REVIEW

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Drug provocation tests (DPTs) of contrast media: Useful or not useful? – A narrative review

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ABSTRACT

Drug provocation tests (DPTs) are also used in some patients with a history of a contrast medium (CM)-hypersensitivity reaction. Since the use of contrast agents requires special knowledge that is present in radiology but not necessarily in allergology, this overview should close the knowledge gaps. The literature, and the package inserts of the industry dealing with DPTs in contrast hypersensitivity reactions was analyzed and the results presented. Historical analyses revealed that provocation tests were already done in the past, and called pre-testing. Due to disadvantages, this diagnostic tool was abandoned. A few years later, DPT was introduced as an innovative diagnostic procedure. The DPT has the 3 main disadvantages: a missing standardization, patients at risk (such as compromised renal function) are rarely taken into account, and a negative DPT does not exclude a subsequent CM reaction. DPTs (formerly called pre-testing) are a well-known method for diagnosing CM-related hypersensitivity reactions. Since the disadvantages of this diagnosis outweigh the advantages, we propose replacing DPT with routine contrast-enhanced imaging examination in radiology.

Keywords: Allergy, Contrast medium, Drug provocation test (challenge test), Intradermal test

INTRODUCTION

Drug provocation tests (DPTs) are established diagnostic tools for various drug allergies (eg, penicillin allergy) and are also used in some patients with hypersensitivity reactions to contrast media (CM).[1] CM hypersensitivity can significantly affect the patients, with reactions ranging from minor discomfort to severe, potentially fatal outcomes. With increasing importance of imaging diagnostics,[2] and the increasing number of radiological examinations, hypersensitivities are also increasing.[3] This is a process, which is still going on. This trend was interrupted briefly by the COVID-19 pandemic.[4] This means that the diagnosis of CM hypersensitivity reactions is becoming more and more important. Although there are currently several publications on the subject of DPTs for CM-hypersensitivity,[5–10] one should be critical.

Therefore, this overview shows the pros and cons and problems and risks involved in provoking contrast media; why test results may not be as relevant as sometimes expected, and how to perform a safe form of DPT.

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METHODS

Review of the literature

A literature search was conducted using the online databases PubMed, Google Scholar, and ScienceDirect. Some articles, though, come from other sources (eg, reference list of included papers). All papers published until March 2024 were included in the search. Title and abstract were screened to identify eligible papers. We used the following search terms: "drug provocation test", "pre-test(ing)", "contrast media", "contrast medium", "contrast medium allergy", and "hypersensitivity reaction" in different combinations.

Inclusion and exclusion criteria

Inclusion criteria: We included studies (original articles, reviews, case reports) describing pros and cons of DPTs of iodinated contrast media (ICM) and gadolinium-based contrast agents (GBCAs).

Exclusion criteria: Research articles and reviews published in languages other than English and German were excluded. Studies that focused on DPTs of other drugs than contrast media were also excluded. Furthermore, articles that did solely target skin tests (eg, patch test, prick test, and intradermal test) were not included. News articles, editorials, and letters were also kept out.

RESULTS

Paper selection

Initially, we found 164 papers, and excluded 101 of them. Finally, we used 63 papers[1-63] for the following review (Fig. 1).

Historical background

The DPT is regarded as a new tool for the diagnostic of CM hypersensitivity reactions since the 1990s. Is this true? A close search of the literature revealed that the idea and technique of the DPT already existed several decades ago in the form of so-called pre-testing. The origin of the pretesting could not be determined from the available literature. Radiologists in the United States probably first used such a diagnostic procedure in the 1930s.[48] In Germany, based on a suggestion by Jungmichel, attempts have been made since 1940 to identify patients at risk by intravenously administering a small amount of contrast medium.[49] In the following 2 decades, pretesting probably experienced its heyday. At the same time, undesirable CM reactions were observed despite a negative preliminary test[50-52] and even small test doses themselves resulted in severe reactions and death.[16,48,52-54] Based on these observations, Finby et al concluded that pretesting is of no proved value

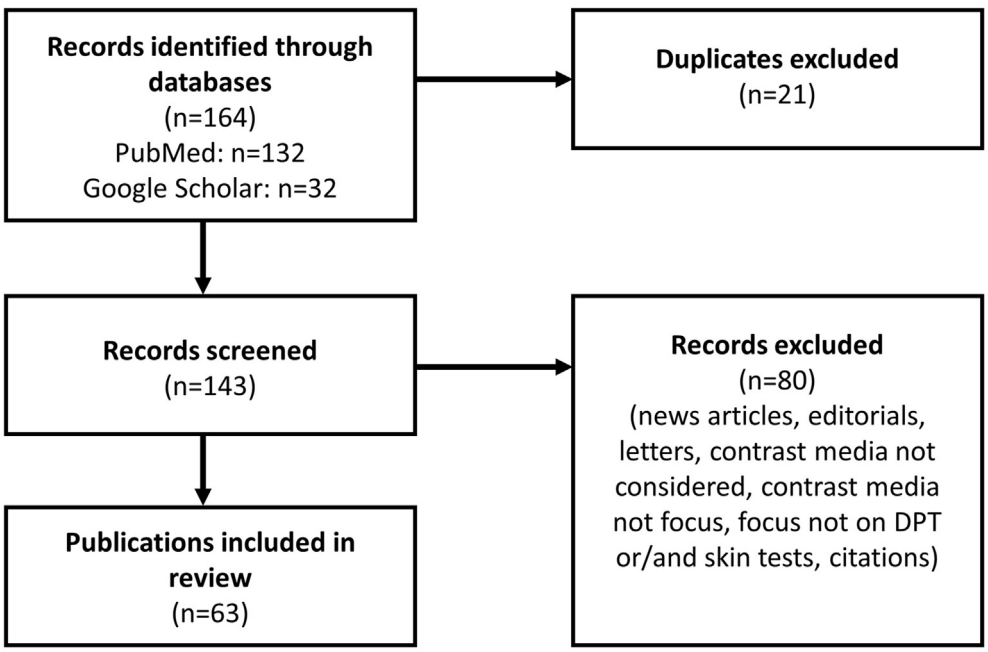

Fig. 1 Flowchart for selecting suitable publications

and recommended the pretesting as ultima ratio (ie, as final diagnostic option, when in doubt).[16]

At the beginning of the 1970s there were increasing reports showing that positive sensitivity tests correlated fairly well with mild or intermediate allergic-like reactions.[15] The expectations that came with the pretests were not fulfilled. Rather, it turned out that pretests were of no value in predicting death or severe reaction to the definitive intravenous dose.[15] Consequently, fewer and fewer pre-tests have been carried out since then. Shehadi mentioned in connection with a large study with 112,003 patients that the value of pre-testing is doubtful and routine pre-testing is not recommended.[14] In Japan only, radiologists did stick to pretesting until the 1990s.[55] During this period, Japan appears to be the only country in the world where the industry leaflets continue to recommend pre-testing.[56] Probably, pre-tests also ended in Japan this decade.

The transition from pretesting to DPTs was gradual. The preliminary tests that Yocum's group published already had characteristics of the DPTs.[13] They used graded challenge tests in patients with a history of immediate reactions to ICM. They injected 0.1 ml test doses starting with dilutions of 1:10 000 up to undiluted ICM in intervals of 15 min. Finally, the patients received 1 and 5 ml of the undiluted CM before the image-guided examination started. In 22%, positive reactions were documented; 50% of the patients with a positive pre-test received the full ICM-dose. The latter group reacted significantly more frequently than the group with a negative pre-test. However, the procedure could not be implemented at that time.

In the 1990s, pre-tests no longer played a clinical role (see also above) and were forgotten increasingly. At the same time, the literature contains provocation tests in individual cases that have now been carried out by allergists.[57,58] In 2009, Seitz et al published the first group of 4 patients who underwent a controlled provocation test.[59]

Unfortunately, after the discontinuation of the pre-testing the knowledge about relevant facts was lost. So that "the wheel has to be reinvented again and again". Interestingly, pretesting still has some clinical relevance today, as the package inserts for special contrast agents in use today indicate that pretesting should not be performed (see also under 3.5).

How did the pre-testing work? Patients with a history of CM hypersensitivity reaction received a small amount of the contrast agent as intravenous injection prior to the imaging. Then the radiologists observed what happened next. If the patient reacted, he/she received a premedication. If the patient did not respond, he/she received the diagnostically required CM dose. Although this procedure sounds logical, it turned out to be impractical. Some patients did not react to the low dose during the pre-testing, but afterwards to the diagnostically required CM dose. How is that possible? There are 2 possible explanations. On the one hand, there was no simultaneous exposure to X-rays in the pre-testing procedure (see below). On the other hand, the contrast agent dose is crucial for a reaction. Both low (eg, arthrography) and high (eg, angiography) doses of CM rarely induce an adverse reaction. CM doses used in CECT preferentially induce hypersensitivity reactions. Therefore, small CM-doses used for the pre-testing were often not able to induce an adverse reaction (further explanations see below under "3.3 Technique of DPT").

Technique of DPT

Standardization

Although a standardization would be useful, currently, no standardized procedure exists. This means that every allergy unit/clinic has its own concept of provocation. We found in the literature several different provocation tests as illustrated in Table 1. Some of which differ greatly from one another. Therefore, comparability of results from different publications should be done with great caution. Moreover, the statement that the DPT is the gold standard is problematic given the lack of standardization and is therefore not tenable. There are different protocols of provocation testing (Table 1). This fact also speaks against carrying out a DPT in its current form. There are different schedules and doses of CM administered to the patient. Which protocol is the optimal is currently unknown. Some protocols look very similar and others differ significantly from the majority. For example, there is a DPT

References	Precondition	Intravenous doses with ST-negative CM	Interval between doses	Total CM dose
Vernassiere 2004[20]	Negative ST	1/100 and 1/10 of dose required for radiol. examination.	2–24 h	
Torres 2012[10]	Negative ST	5, 10, 15 ml (1st day) 50, 50 ml (2nd day)	1 h	125 ml
Salas 2013[9]	Negative ST	5, 15, 30, 50 ml	45 min	100 ml
Lerondeau 2016[21]	Negative ST	1/100 and 1/10 of dose required for radiol. examination.	1 h	
Sesé 2016[22]	Negative ST	10 ml	1 dose	10 ml
Morales-Cabeza 2017[23]	Negative ST	5, 30, 60 ml (1st day) 120 ml (2nd day)	30 min	95 ml 120 ml
Trautmann 2019[7]	Negative ST	0.05, 0.5, 1.0, 5.0, 7.5, 10.0, 25.0 ml (IHR) 1.0, 5.0, 7.5, 10.0, 25.0 ml (NIHR)	30 min	49.05 ml 48.50 ml
Gracia-Bara 2019[24]	Negative ST	5, 20 ml (1st day) 50, 50 ml (2nd day the following week)	1 h	25 ml 100 ml
Soria 2019[25]	–	20, 30 ml 5, 15, 30 ml (with Grade 3 HSR)	2 h 1.5 h	50 ml
Doña 2020[5]	Negative ST	5, 15, 30, 50 ml (IHR) 5, 10, 15 ml (NIHR) 20, 30, 50 ml (NIHR 2nd run 7 days later if no reaction occurred)	45 min	100 ml 30 ml 100 ml
Meucci 2020[6]	Negative ST & characteristics of index reaction	5, 30, 60 ml (IHR) 5, 30 ml (NIHR) 30, 60 ml (NIHR 2nd run 7–14 days later if no reaction occurred)	30 min	95 ml 35 ml 90 ml

Table 1. Overview of the various DPT techniques in the literature showing the missing standardization. All analyzed papers reported about DPTs with iodinated contrast media (CM – contrast medium; DPTs – drug provocation tests; IHR – immediate hypersensitivity reaction; HSR – hypersensitivity reaction; NIHR – non-immediate hypersensitivity reaction; ST – skin test)

where day 2 of testing is carried out 1 week later.[20] We consider this delay as problematic.

Due to a missing standardization, the indications vary also. Some authors consider any negative CM skin test to be an indication for DPT. They call for this as definitive proof of tolerance, and also to identify safe alternative CMs for future radiological examinations.[5,7,8] Others, mainly older studies, describe DPTs for patients with CM-hypersensitivity generally as contraindicated[17] due to lack of predictive values,[18] or lower death rate and lower incidence of serous reactions in absence of intravenous pretesting.[19] Also, radiology guidelines such as these from the American College of Radiology (ACR) or the European Society of Urogenital Radiology (ESUR) do not recommend CM pretesting in general. Both societies propose prophylactic measures for managing patients at risk with an emphasis on

assessment of the initial reaction rather than on pre-exposure testing.

Iodinated contrast media and gadolinium-based contrast agents

Although hypersensitivity reactions to gadolinium-based contrast agents (GBCAs) are increasing due to the worldwide rise in nuclear magnetic resonance diagnostic techniques using GBCAs, during the past, GBCAs were tested only scarcely.[26,27] Only few studies about pretesting GBCAs have been conducted so far.[26–32] Therefore, data on this subject are limited, which can border the interpretation of the results. Several studies or reviews[26–32] report a high negative 166 predictive value (NPV) on GBCA-skin tests often referring to results of the studies by Chiriac 167 et al[33] and Seta et al[28] with random samples of 27 respectively 14 patients. Only few studies and reports[27,28,31] with small case series speak out cautiously for DPTs with GBCAs to confirm or exclude the diagnosis or find alternative GBCAs. Nevertheless, most allergists no longer perform DPTs with GBCAs. The reason for this is a possible deposition of GBCAs in the patients' organism (involved organs are brain, liver, spleen, kidneys, skin, and bone).[34] Currently, DPTs are exclusively performed with ICMs.

DPT as continuation of the intradermal test (IDT)

The low sensitivity from skin testing (SPT and intradermal test, IDT) is the reason why DPT was established. It should also be taken into account that the sensitivity of the skin tests is greater within the first 6 months following the occurrence of the immediate hypersensitivity reaction than afterwards.[46] The point that IDT should be carried out up to the undiluted level, is a specific feature of contrast agents,[42] and thereby it is quite different from immediate hypersensitivity to other allergens such as foods, penicillin, and venoms.[60]

Currently, the recommended method for hypersensitivity reactions is to begin with a skin prick (SPT) using undiluted CM. If the SPT yields negative result, an IDT is performed using progressively lower dilutions of CM (ie, 1:1000, 1:100, 1:10). Should a patient exhibit a positive reaction at any dilution, further testing with less diluted CM is not advised. Nonetheless, in the vast majority of studies and guidelines the IDT is carried out with a 1:10 dilution of CM only.[3,35] Additionally, some authors[5,8,10,36] suggest repeating the IDT with undiluted CM for higher sensitivity if the IDT is negative at the 1:10 dilution since IDTs apparently do not induce false positives in non-immediate hypersensitivity reactions and no adverse reactions were observed in doing so.[10,37]

Generally, the informative value of skin tests, including IDT with 1:10 dilution, is limited by low sensitivity.[38,39] The study of Goksel et al reported on a sensitivity of 20% and Kim et al. to 21.7% and for patients with severe reactions after all to a sensitivity of 57.1%. In summary, SPTs solely or combined with IDTs (up to 1:10 dilution) are incomplete diagnostic tools. The timeframe of the tests is also important. Tests performed more than 6 weeks after the acute event have a lower chance of a positive result.

We recommend a possible algorithm for the management of patients with reactions to contrast media (Fig. 2).

Test of culprit CM

Which contrast agents should be checked by using DPT? In general, negative tested CMs (by IDT) are used as test compounds. CMs that tested positive were rarely provoked in patients.[5,7,8,10,40] Regardless of the IDT result, both culprit and non-culprit CMs are tested.

DPT with the culprit CM is more than questionable. Exact documentation of the adverse drug reactions (ADRs), including the culprit CM, should be enough to inform the doctor about what has happened in the past.[41] Re-exposure to the culprit CM so that the allergist can satisfy himself that the radiologist's statement is correct means a high degree of stress for the patient. This stress itself can lead to an ADR. The clinical differentiation between allergy and stress-induced reaction can be difficult or impossible in individual cases. Moreover, such an approach is ethically unacceptable. Furthermore, the clinical relevance of a provocation with the culprit CM is low, and should be omitted.

Test of non-culprit CMs

DPT with a negatively tested non-culprit CM is used to confirm the IDT result and therefore

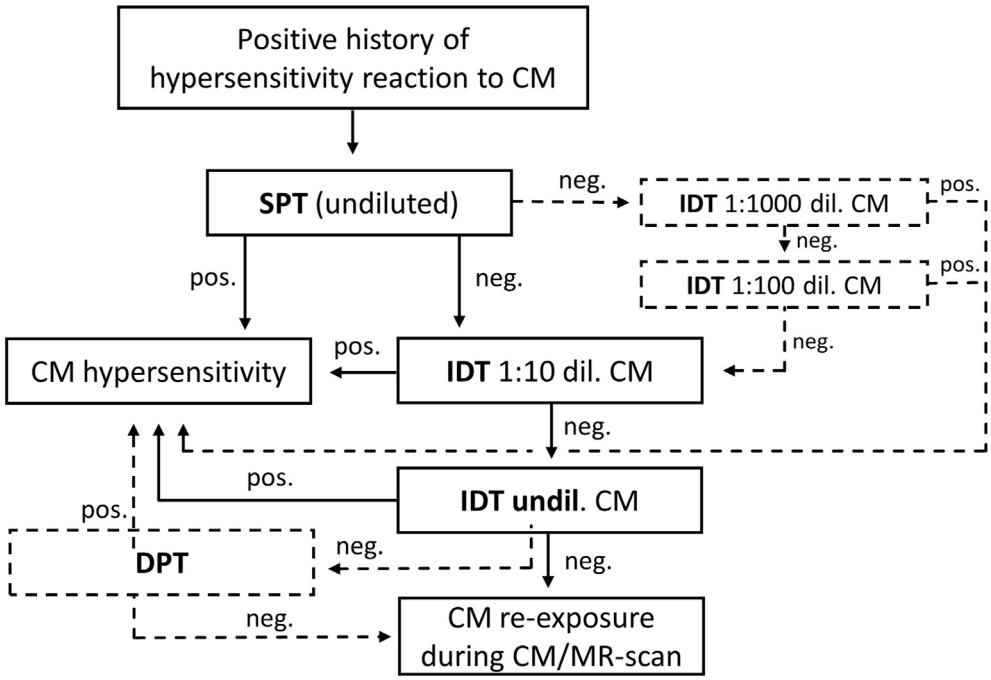

Fig. 2 Flowchart shows the proposed procedure for patients with suspected hypersensitivity reactions to contrast media. Dashed lines indicate additional options

provide an impression of safety. In particular, IDTs with diluted contrast agents are incomplete and therefore have low sensitivity and specificity.[42] In other words, the test result induces a feeling of uncertainty in the doctor. Instead of completing the IDT with undiluted contrast media and thus achieving significantly higher sensitivity and specificity,[43] provocation tests are carried out. Interestingly, the number of CMs and the number of patients tested is higher when IDT is performed with diluted CMs (it is significantly lower when IDTs are performed with undiluted CMs).[42]

Contrast media that tested negative are recommended as tolerable substances for future CECTs. According a study conducted by Meucci et al., following a negative DPT, an adverse reaction occurred in 7.7% (1 out of 13 re-exposed patients) of cases under routine radiological conditions.[6] Another study by Ahn et al. showed similar results with an overall sample of 106 cases that were intravenously challenged with challenge-negative CM. Eight (7.5%) out of 106 patients showed a breakthrough reaction (BTR) during the CT scans. The study also distinguishes between CT scan with challenge-negative low-dose CM (2, 5 and 10 ml = 17 ml) with n = 56 and CT scan with challenge-negative high-dose CM (5 and 30 ml = 37 ml) with n = 50. Out of 56 negative patients with low-dose challenge, 5 patients (8.9%) had BTRs and 4 out of 5 patients (7.1%) showed severe reactions (namely asymptomatic hypotension). On the other hand, there were relatively mild reactions within the high-dose challenge group and no severe reactions were observed. The BTR rate was with 6% (3/50) slightly lower than within the low-dose challenge group but not statistically significant.[44]

This fact is interpreted as "such a reaction can always happen". On the other hand, one should realize that DPTs only represent the pharmacological part, but not the physical one (ie, X-rays) (see below).

Exposure of X-rays seems to be also necessary

Serious hypersensitivity reactions are predominantly triggered by IgE-antibodies, while most mild to moderate reactions tend to be non-allergic in nature.[40] The discrepancy between the results of allergy tests and reaction under radiological conditions is usually explained by the fact that the reactions are pseudo-allergic in nature. There might be, however, another explanation for this phenomenon. This was published in 2019 by Park

et al[45] who were able to show that X-rays may also play a part in the induction of a reaction. They compared CT examinations with higher and lower voltage (120 kVp versus 100 kVp), and found that the rate of acute hypersensitivity reactions occurred in parallel to the voltage used (1.86% versus 1.42%). Due to simultaneously used higher injection speed as well as higher ICM-doses, the influences of single parameters remains to be elucidated.

Since exposure to X-rays is not possible during DPT, DPT should be performed in the form of a routine CECT.

Risks of DPTs

Contrast media are well-tolerated agents but can induce side effects (such as contrast-induced acute kidney injury, hypersensitivity reactions). Such adverse drug reactions (ADRs) can occur during both contrast-enhanced image-guided procedures, and during DPTs.

While radiologists are trained to comply with safety aspects of contrast media, in the context of DPT, allergists expect a hypersensitivity reaction, but do not consider other adverse reactions. We would therefore like to draw attention to important undesirable reactions caused by contrast media.

All CMs (ie, iodinated and gadolinium-based contrast agents (GBCAs) are nephrotoxic. If a provocation with CMs is carried out, the same precautionary measures must be taken as in radiology. This means, patients should be asked about existing kidney disease or nephrotoxic medications. In addition, one should ask when the last contrast-enhanced imaging was done.[3,46]

ICMs should be used with special precautions or not at all in patients with thyroid dysfunction such as hyperthyroidism. In the worst case, provocation with an ICM can trigger thyrotoxicosis. Therefore, before applying iodinated contrast media, one should make sure that there is no thyroid disease.[46]

In pregnancy and breast-feeding women, the indication for CMs is limited. Iodinated contrast agents should only be applied if the mother's life is at risk.[46] It is unclear whether the question of a possible pregnancy is asked in the context of a DPT with CMs, since the corresponding information is missing in the literature.

Due to the potential risks associated with DPTs, ethical considerations and safety aspects are valuable. Patients who should undergo DPT, especially in vulnerable populations, require a detailed doctor-patient communication. This is necessary to show the patient all possible risks and to involve the patient in the decision-making process. This means, among other things, that the patient must understand the test procedure in order to then be able to sign the informed consent. Monitoring of vital parameters during the test and emergency preparedness (standby of an anaesthesiologist) could also improve the safety during a DPT.

Industry recommendations

The industry recommendations were evaluated based on the package inserts for (FDA)-approved contrast media that are available on the market (see under Supplement). The consensus of manufacturers of contrast media is that pretesting with a low dose for hypersensitivity reactions is not recommended. This is a consistent stance across various products because of the lack of predictive value of such tests and the potential for pretesting to trigger serious or even fatal hypersensitivity reactions. Manufacturers of Ioversol (Optiray®), Iodixanol (Visipaque®), Iopromid (Ultravist®) and Iomeprol (Imeron®) all advise against pretesting, as it does not accurately indicate tolerance and poses a risk of inducing severe reactions. Instead of pretesting, the manufacturer of Iopamidol (Isovue®) emphasizes the importance of a detailed medical history focusing on allergy and hypersensitivity as a more accurate method for predicting potential ADRs.

For GBCAs, the recommendations are more specific to patient history. For Gadobutrol (Gadovist®) it is emphasized that in patients with a history of allergic reactions, the decision to use Gadovist® should be made after careful consideration of the benefit-risk ratio. No specific pretesting recommendations were provided for other GBCAs like Gadopentetate-dimeglumine (Magnevist®), Gadoteridol (ProHance®),

Gadodiamide (Omniscan®), and Gadoteric Acid (Dotarem®).

Overall, the industry advises against pretesting in general due to the potential risks involved. Instead, a thorough patient history is recommended to better predict and manage possible adverse reactions to CM administration. In addition, the exact documentation of previous hypersensitivity reactions is also very important.[41]

Pros and cons

As mentioned above, there are advantages (pros) and disadvantages (cons) to using the DPT, which are summarized in Table 2. Briefly, the counterpoints predominate. The most important of these are that 1) undesirable effects are possible in the context of a provocation (eg, renal insufficiency), 2) a negative DPT does not rule out a subsequent reaction with CECT, and 3) the DPT is not standardized and therefore, it is not a gold standard.

Pros	Cons
Diagnostic confirmation: DPTs can serve as a definitive step in diagnosing hypersensitivity reactions to CM. They can confirm or rule out an allergy when skin tests are inconclusive or negative.[10]	**Risks of DPT:** DPTs carry a risk for inducing severe hypersensitivity reactions[46] and other side effects (eg, renal complaints including CI-AKI) not to be neglected, as mentioned above.
Risk assessment: DPTs may offer a clearer assessment of the risk for future CM administration, which is crucial for patients requiring recurrent imaging.	**Breakthrough reactions despite negative DPT:** Despite the screening, a significant number of breakthrough reactions still occur despite using DPT-negative CMs, indicating that the method cannot eliminate the risk of reactions,[6,44] as mentioned above.
Identification of safe alternative: DPTs can help identify safe alternative CMs for patients with a history of reactions.[8,10,36]	**False results:** False positive or negative reactions.
	Potential for false security: Premedication protocols to prevent reactions are not foolproof and may give a false sense of security. Breakthrough reactions can still occur.[46]
	Potential for spontaneous desensitization: There is a possibility that a negative result might be due to a spontaneous desensitization rather than true tolerance.[47]
	No standardized protocols: No standardized procedure exists. Comparing results from different publications and health institutions is difficult, as mentioned above.
	Resource intensive: DPTs are time-consuming and resource-intensive procedures requiring careful monitoring and emergency readiness, which may not be practical in every healthcare situation and institution.[10,46]
	Low sensitivity: SPT and IDT have a low sensitivity. Moreover, the time frame of the test is also important (within the first 6 months following the acute event).[46]

Table 2. A non-exhaustive overview of the positive aspects and limitations associated with the use of DPTs in diagnosing hypersensitivity to CM

The lack of standardization, the potential risk to certain patient populations, and the inability of a negative DPT to rule out subsequent reactions are significant concerns. Several authors mention the lack of standardized protocols and indications[1,3,40,44,61]

Several authors are aware of the risk for certain patient groups and the inability of a negative DPT to effectively rule out subsequent reactions. Therefore, various studies generally state that a thorough check[3,62] of patients should be carried out before performing DPTs and that those with contraindications such as renal dysfunction, taking nephrotoxic drugs, pregnant or breastfeeding, and hyperthyroidism should be excluded. Some studies, such as Meucci et al or Ahn et al, report adverse or breakthrough reactions of 7–8% despite negative DPTs. But there are hardly any studies examining or quantifying the risk of DPTs to certain patient populations or the inability of a negative DPT to conclusively rule out subsequent reactions.

We identified 3 key studies that were either prospective[5,10] or retrospective studies.[44] Even in patients with negative IDT, there were some cases of positive responses to DPT. The problem here is that 1) the dose increase does not correspond to the situation in radiology and 2) that it is not known whether an injection in the context of CM-supported imaging was tolerated or not.

Doña et al investigated 101 patients with both immediate and non-immediate reactions who underwent intradermal testing followed by DPTs.[5] They performed a single-blind placebo controlled DPT with the culprit ICM in individuals with negative skin test. If skin test or DPT were positive, they assessed tolerance with an alternative skin test negative ICM. The main finding was that in patients with allergy to more than 1 ICM, DPT performed with skin test negative ICM was positive in more than 60% (24/36) of cases.[5] Thereby, they confirmed the notation that pretesting is of less sensitivity.

Ahn et al analyzed 85 patients with a history of ICM-anaphylaxis.[44] Patients with negative skin tests were challenged with 2 different protocols intravenous ICMs: low-dose and high-dose (maximum dose 10 and 30 ml, respectively). They found that 4 (3.6%) of the 110 challenge tests were positive challenges. Among 106 enhanced CT-scans performed in challenge-negative patients, breakthrough reactions occurred in 8 occasions (7.6%). The main disadvantage of this study is the fact that the investigation was done in individuals that were premedicated.[44] This means that a comparison with other non premedicated cohorts is not possible.

Recommendation for contrast re-exposure

The transition from pre-testing to DPT involved a change of location. While pre-tests took place in radiology, DPTs are done in allergology clinics/departments/units. The proposal to perform contrast re-exposures as part of contrast-enhanced imaging would mean that the diagnostics return to the original location. This would be an advantage for doctor and patient in terms of the logistical process of contrast-enhanced examinations because it could save time and resources. In particular, the fact that the CM exposure would only have to occur once instead of twice would be a benefit for the patient. Another advantage would be that the CM exposure takes place under investigational conditions (ie, CM plus X-radiation) and not under experimental conditions in allergy departments without simultaneous X-ray exposure. Another argument in favour of re-exposure carried out in radiology is that the high safety standards of CM application are applied. What risks does this approach have? In our opinion, no risks are to be expected. It could be disadvantageous if, for example, the radiologists do not precisely document the re-exposed CM or the adverse reactions that have occurred.[41] Important information would then be missing for future contrast-enhanced examinations.

Future research directions

Due to the problems described, it would make sense in the future if there were alternatives to DPT that were safer for the patient. Hence the question arises, are there novel diagnostic methods on the horizon that could address the limitations of DPTs? The basophil activation test (BAT)[63] could possibly replace the DPT in the future. The BAT is a provocation test carried out in vitro. This has the advantage of being safer. However, the procedure is not yet sufficiently developed to be used in clinical routine. Rather, it is an

experimental procedure that can only be carried out in special laboratories.

Artificial intelligence (AI) could also be helpful in diagnosing CM-induced hypersensitivity reactions in the future. What scenarios might be conceivable here? Based on a very large amount of data, it may be possible to use AI to determine compatible and incompatible contrast media in individual patients.

CONCLUSIONS

The comprehensive review of DPT for CM hypersensitivity reveals a complex interplay of benefits and risks. DPTs can provide definitive diagnostic confirmation in cases where skin tests are ambiguous or negative.

However, the application of DPT bears several significant risks. Taken together, it can be assumed that all contrast media are potentially dangerous. Main risks are hypersensitivity reactions, contrast-induced acute kidney-injury (potentially resulting in end-stage renal disease or even death), as well as thyrotoxic crisis and lactic acidosis. Moreover, the absence of standardization of protocols complicates the comparability of results and raises concerns about the reproducibility of findings. Breakthrough reactions occurring despite the negative DPT results underlines the limitations of current testing methodologies in completely obviating the risk of adverse reactions following CM exposure.

Furthermore, DPTs might not always be necessary, particularly when a negative IDT with 1:10 is followed by an undiluted IDT. All these factors necessitate a cautious approach, advocating for the minimization of DPT usage to scenarios where alternative diagnostic modalities are insufficient or inconclusive. Furthermore, we advocate for the development of unified, evidence-based guidelines that standardize DPT procedures with CM, enhance patient safety, and optimize diagnostic accuracy. There is also a need for ongoing research to explore the underlying mechanisms of CM hypersensitivity reactions and to develop new diagnostic agents with improved safety profiles.

In summary, DPTs in its current form should not be carried out due to the numerous disadvantages mentioned. Controlled provocation as part of contrast-enhanced imaging is an attractive alternative.

Abbreviations

ACR, American College of Radiology; ADR, adverse drug reaction; AI, artificial intelligence; BAT, basophil activation test; BTR, breakthrough reaction; CECT, contrast-enhanced computed tomography; CM, contrast medium; DPT(s), drug provocation test(s); EDTA, ethylene-diamine-tetraacetic acid; ESUR, European Society of Urogenital Radiology; GBCA, gadolinium-based contrast agent; HSR, hypersensitivity reaction; ICM, iodinated contrast medium; IDT, intradermal test; IHR, immediate hypersensitivity reaction; NIHR, non-immediate (delayed) hypersensitivity reaction; NPV, negative predictive value; SPT, skin prick test; ST, skin test.

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Availability of data and materials

All data are available in the manuscript or supplement; there are no further data.

Author contributions

Conception and design IBB; acquisition of data MD/IBB; analysis and interpretation of data MD/IBB; drafting the article MD/IBB; final approval of the version to be submitted MD/IBB.

Ethics statement

Not applicable, because it is a review article based on published papers.

Authors' consent for publication

Both authors gave their consent to publish the work.

Declaration of competing interest

The authors report no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2024.100946.

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