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FULL PAPER

Acute adverse reactions to iopromide vs iomeprol: a retrospective analysis of spontaneous reporting from a radiology department

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Objective: To compare the safety of iopromide and iomeprol use in a hospital that switched from the former to the latter and found an apparent increase in the number (and a different profile) of adverse reactions reported for iomeprol, putting the safety of its use into question.

Methods: This was a retrospective study of cases of acute reactions to iopromide and iomeprol reported in two successive time periods. Data from examinations using iopromide (62 539 CT scans and 10 348 urography scans) and iomeprol (34 308 CT scans and 2846 urography scans) were obtained from the computer system of the hospital.

Results: For each period, 154 cases of reactions were reported for iopromide and 86 for iomeprol, being severe in 10 (6.5%) patients for iopromide vs 17 (19.8%) patients for iomeprol; a statistically significant difference of $p < 0.003$ was recorded. The most frequent adverse reactions (%/%) for iopromide/iomeprol were urticaria

(29.1/17.2), pruritus (22.6/15.6), upper respiratory tract signs and symptoms (12.1/16.7), oedema (4.3/0), erythemas (3.4/5.0), nausea or vomiting (1.2/11.7) and chest pain (0/3.9) ($p < 0.0001$ for the global comparison). The distribution of the reactions (%/%) by System Organ Class for iopromide/iomeprol was skin (56.7/41.1), respiratory (19.2/26.7), vascular (6.8/2.2), general (5.3/7.2), gastrointestinal (4.6/15.0) and others (7.4/7.9) ($p < 0.0002$ for the global comparison).

Conclusion: Adverse reactions were more severe for iomeprol. Skin and vascular reactions with no chest pain were more frequent for iopromide, whereas gastrointestinal reactions were more frequent for iomeprol.

Advances in knowledge: Comparative studies of media contrast safety are scarce and summary information on product characteristics is insufficient. This study showed the differences in severity and profile of adverse reactions between iopromide and iomeprol.

The generalization of the use of non-ionic contrast media (CM) in recent decades in many hospitals has improved the safety of patients who are to be examined using CM, with 0.2–0.7% of patients reporting slight or moderate adverse reactions^{1–3} and 0.04% reporting reactions that endanger patients,³ and a mortality rate of 0.9 per 100 000 injections, according to a meta-analysis.⁴ Nevertheless, there are very few comparative studies of the efficacy and safety of CM, and the information about adverse reactions is similar in terms of the technical specifications of many of them.

When a change occurs in the CM that is to be used in a hospital, which is frequently not a decision made by the

radiology department, the new contrast can change the profile or incidence of adverse effects, which in turn can cause uncertainty among patients and radiologists, who had until then been used to a specific incidence and/or severity.

Our hospital recently began using the contrast iomeprol⁵ in indications where iopromide had been used previously, because of financial reasons. Coinciding with this switch, there was an apparent increase in the number and a different profile of adverse effects reported for iomeprol, putting the safety of its use into question. Moreover, the information available on the technical specifications of both contrasts does not provide data on the incidence or the severity of adverse effects for either of them.

Therefore, a comparative analysis of the adverse effects observed for both contrasts was conducted to determine differences regarding the incidence, severity and the type of adverse effects between iopromide and iomeprol, using spontaneously reported data. The absence of a reporting bias was assumed, given that they were conducted in the same hospital and in consecutive periods of time.

METHODS AND MATERIALS

Cases of suspected acute adverse effects to iopromide, which were spontaneously reported by the radiology department of a hospital to the Basque Country's Pharmacovigilance Unit between April 1997 and March 2006, were analysed, and they were compared with cases for iomeprol reported by the same department between January 2009 and April 2013.

The study was carried out in Galdakao-Usansolo Hospital, Galdakao, Spain, a tertiary hospital with 365 beds that provides all medical and surgical services except for obstetrics and paediatrics. Moreover, this hospital also houses the Basque Country Pharmacovigilance Unit.

The patient was considered a case when the diagnosis complied with the World Health Organization's definition of an adverse reaction: "any unexpected reaction that occurs when using a drug, at the usual dose for treatment, prevention, diagnosis or modification of a biological function".⁶

According to the protocol of the radiology department, when a patient had an adverse effect associated with radiological contrast administration, the doctor or nurse in charge of the patient filled out a reporting form. This form included patient data (name, sex, age and amount of medical history), the brand name of contrast used (dose and volume), the type of the radiological examination performed and the description of the adverse reactions and the outcome, and was sent to the Pharmacovigilance Unit.

The clinical records of each patient were consulted retrospectively case by case to complete (if necessary) the data collected by the doctor or nurse and to compare the homogeneity between the two groups and possible differences in pre-existing medical conditions that might increase the risk of adverse effects.⁷

Causality assessment of drug-adverse effect relation was made case by case. In each case, the first diagnosis was established by the doctor or nurse in charge of the patient, and their criteria were accepted by the research group. All patients who were initially categorized as having an adverse effect were assessed again by two of the authors (MG and CA), who met every week in an evaluation session so as to reach a consensus decision, using a sole algorithm (the Karch–Lasagna method, the official method used in the Spanish pharmacovigilance system).⁸ After evaluation, all cases were introduced into the Spanish pharmacovigilance database.

Data from computerized axial tomography and urography scans performed using intravenous (IV) iopromide and IV iomeprol within the indicated time intervals at the radiology department were taken from the administrative database of the hospital. The following variables were analysed: sex, age, severity of adverse

effects and type of adverse effects [by System Organ Class (SOC) and High-Level Terms (HLT) under the Medical Dictionary for Regulatory Activities classification].⁹

The severity of adverse effects was classified according to the European Medicines Agency (mild and severe).

ANALYSIS

An exploratory data analysis was initially performed using mean and standard deviations for continuous variables and using frequencies and percentages for categorical variables. The χ^2 test was used to assess the relationship between the dose of iodine (grams) or type of adverse effect (according to SOC and HLT) and the comparative groups. The relationship of sex, categorized age (<60 and ≥ 60 years), severity of adverse effect and risk factors between groups were assessed by means of the Fisher's exact test. For mean age differences between groups, the Wilcoxon non-parametric test for independent samples was used. All statistical analyses were performed using SAS system software (SAS Institute, Cary, NC). $p < 0.05$ was considered statistically significant. The study was approved by the institutional review board of the hospital.

RESULTS

In the interval between April 1997 and March 2006, 154 cases with adverse effects were reported for iopromide (323 symptoms) compared with 86 cases for iomeprol (180 symptoms) during the interval between January 2009 and April 2013. The description of patient characteristics, comorbidities, diagnostic procedures and contrast dose that were used are detailed in Table 1.

In the above-mentioned intervals, 62 539 CT scans with contrast and 10 348 urography scans ($n = 72\,887$ patients) were performed using iopromide, whereas 34 308 CT scans with contrast and 2846 urography scans ($n = 37\,154$) were performed using iomeprol. The incidence of adverse effects was 2.1 cases per 1000 patients for iopromide and 2.3 cases per 1000 patients for iomeprol.

There was no statistically significant difference in distribution by sex in the compared groups (males: iopromide, 48.7%; iomeprol, 48.8%). The distribution by age was not statistically significant when the average ages of 50.9 ± 17.9 years for iopromide and 55.4 ± 17.5 years for iomeprol were compared, nor was it statistically significant when the age was distributed with regard to the cut-off age of 60 years, where 96 (62.8%) patients were <60 years for iopromide compared with 50 (58.1%) patients for iomeprol.

When comorbidities (pre-existing medical conditions) in both groups were compared, no significant differences were found, except that there were more patients with an allergic history and benign prostatic hypertrophy in the iomeprol group ($p < 0.05$).

In the iopromide group, 10 (6.5%) cases had an allergic history [pollen (1), mites (1), non-steroidal anti-inflammatory drugs (NSAIDs) (1), contact dermatitis (1), salicylates (1), pyrazolones (1), sulphamides (1), pollen + mites (1), NSAIDs + sulphamides (1) and flu, cold and cough medicine (1)], whereas in the iomeprol group, 14 (16.3%) cases had an allergic record [mites (4), pyrazolones (1), acetylsalicylic acid (1), clavulanate/amoxicillin

Table 1. Description of the study population

Description	Iopromide	Iomeprol	<i>p</i> -value
Diagnostic procedures	<i>n</i> = 72 887	<i>n</i> = 37 154	
CT, <i>n</i>	62 539	34 308	
IV urography, <i>n</i>	10 348	2846	
Characteristics of patients suffering an adverse drug reaction	<i>n</i> = 154	<i>n</i> = 86	
Men	75 (48.7)	42 (48.8)	NS
Age (years), mean ($\pm$ SD)	50.9 ($\pm$ 17.9)	55.4 ($\pm$ 17.5)	NS
Age <60 years	96 (62.8)	50 (58.1)	NS
Risk factor/comorbidity			
Allergic history	10 (6.5%)	14 (16.3%)	0.0233 ^a
Asthma	10 (6.5%)	6 (6.9%)	NS
Prior CM reaction	6 (4.0%)	1 (1.2%)	NS
Renal failure	4 (2.6%)	1 (1.2%)	NS
Cardiac failure	5 (3.3%)	2 (2.3%)	NS
Hemorrhagic diathesis	1 (0.6%)	0	NS
Coronary disease	6 (4.0%)	4 (4.6%)	NS
Diabetes mellitus	7 (4.7%)	8 (9.3%)	NS
Autoimmune disease	3 (2.0%)	3 (3.5%)	NS
Dehydration	0	0	
Cancer	36 (23.4%)	27 (31.4%)	NS
COPD	11 (7.1%)	5 (5.8%)	NS
Asthma	10 (6.5%)	6 (6.9%)	NS
BPH	27 (17.5%)	25 (29.1%)	0.0494 ^a
Others	74 (48.5%)	48 (55.8%)	NS
Total patients with pre-medication	6 (4.0%)	1 (1.2%)	NS
Route of administration	IV	IV	
Dose of iodine (g)			<0.0001 ^a
<12	1 (0.6%)	0	
12.0–29.9	28 (18.2%)	42 (48.8%)	
30.0–37.4	43 (27.9%)	28 (32.6%)	
37.5–44.9	30 (19.5%)	2 (2.3%)	
$\geq$ 45	45 (29.2%)	1 (1.2%)	
Unknown	7 (4.5%)	13 (15.1%)	

BPH, benign prostatic hypertrophy; CM, contrast media; COPD, chronic obstructive pulmonary disease; IV, intravenous; SD, standard deviation.

Data are number (percentage) unless otherwise indicated.

^a*p* < 0.05.

(1), sulphamides (1), penicillins (4), phenylacetic acid derivatives (1) and unknown (1)].

In relation to prior allergy-like reactions, 6 (4.0%) patients in the iopromide group and 1 (1.2%) in the iomeprol group had a previous history of reaction to CM. No statistically significant differences were found. All cases took pre-medication (prednisone and dexchlorpheniramine) according to the guidelines of the

American College of Radiology.⁷ Moreover, the severity of these reactions was mild in all cases (iopromide and iomeprol) after the first and second CM administration.

The description of the most frequent adverse effects by HLT (%/%) for iopromide/iomeprol was urticarias (29.1/17.2) (*p* = 0.0035), pruritus (22.6/15.6) [*p* = not significant (NS)], upper respiratory tract signs and symptoms (12.1/16.7) (*p* = NS),

Table 2. Adverse effects classified by High-Level Terms (HLT) from the Medical Dictionary for Regulatory Activities terminology

Adverse effects	Iopromide	Iomeprol	<i>p</i> -value
HLT ^a	<i>n</i> (%)	<i>n</i> (%)	
Urticarias	94 (29.1)	31 (17.2)	0.0035 ^b
Pruritus	73 (22.6)	28 (15.6)	NS
Upper respiratory tract signs and symptoms (sneezing, throat irritation, rhinorrhoea)	39 (12.1)	30 (16.7)	NS
Oedema	14 (4.3)	0 (0.0)	0.0047 ^b
Erythemas	11 (3.4)	9 (5.0)	NS
Vascular hypotensive disorders	11 (3.4)	2 (1.1)	NS
Breathing abnormalities	10 (3.1)	8 (4.4)	NS
Peripheral vascular disorders (flushing, hot flush)	10 (3.1)	0 (0.0)	0.0175 ^b
Nasal congestion and inflammations	9 (2.8)	1 (0.6)	NS
Oral soft tissue swelling and oedema	8 (2.5)	2 (1.1)	NS
Rate and rhythm disorders	5 (1.5)	1 (0.6)	NS
Ocular disorders	5 (1.5)	5 (2.8)	NS
Nausea and vomiting symptoms	4 (1.2)	21 (11.7)	<0.0001 ^b
Rashes, eruptions and exanthems	3 (0.9)	2 (1.1)	NS
Feelings and sensations	3 (0.9)	4 (2.2)	NS
Coughing and associated symptoms	3 (0.9)	7 (3.9)	0.0220 ^b
Paraesthesias and dysaesthesias	3 (0.9)	1 (0.6)	NS
Gastrointestinal signs and symptoms (dysphagia)	2 (0.6)	3 (1.7)	NS
Pain and discomfort (chest pain)	0 (0.0)	7 (3.9)	0.0003 ^b
Other ≤2	18 (5.6)	18 (10.0)	NS
Total	323 (100)	180 (100)	

NS, not significant.

^a $p < 0.0001$, for the global comparison of adverse effects according to HLT between iopromide and iomeprol.

^b $p < 0.05$.

oedema (4.3/0) ($p = 0.0047$), erythemas (3.4/5.0) ($p = \text{NS}$), breathing abnormalities (3.1/4.4) ($p = \text{NS}$), peripheral vascular disorders (3.1/0) ($p = 0.0175$), nausea and vomiting symptoms (1.2/11.7) ($p < 0.0001$), coughing and associated symptoms (0.9/3.9) ($p = 0.0220$) and pain and discomfort (0/3.9) ($p = 0.0003$). The complete distribution of frequent (>2) adverse effects can be seen in Table 2, and the difference for the global comparison was statistically significant ($p < 0.0001$).

The distribution of adverse effects by organs (SOC) (%/%) for iopromide/iomeprol was skin and subcutaneous tissue disorders (56.7/41.1) ($p = 0.0008$); respiratory, thoracic and mediastinal disorders (19.2/26.7) ($p = \text{NS}$); vascular disorders (6.8/2.2) ($p = 0.0259$); general disorders and administration site conditions (5.3/7.2); gastrointestinal disorders (4.6/15.0) ($p < 0.0001$); and others (7.4/7.9). The distribution is shown in Figure 1, and the difference for the global comparison was statistically significant ($p = 0.0002$).

Finally, in relation to the severity of adverse effects, according to the European Medicines Agency classification, for iopromide, 10 (6.5%) cases were severe and 144 (93.5%) mild, whereas for

iomeprol, 17 (19.8%) were severe and 69 (80.2%) mild at a statistically significant difference of $p < 0.003$.

DISCUSSION

Our reported adverse effect rates, 0.21% for iopromide and 0.23% for iomeprol, were very rare in both, and lower than that reported by other investigators studying the safety of non-ionic CM: iomeprol,¹⁰ iopromide,^{10–13} iopentol¹³ and iobitridol.^{14,15} Although the incidence varies considerably between the different studies, the lower incidence observed in ours may be because of its retrospective nature and it being based on spontaneously reported adverse effects. As a result, under-reporting, particularly with regard to minor adverse effects, is likely to have occurred, in spite of the good co-operation of the radiology department.¹⁶ As for the direct comparison of iomeprol vs iopromide, there is little published data on the incidence of acute adverse effects. Our results are consistent with Gomi *et al*¹⁰ on iomeprol vs iopromide, but differ from those of Lapi *et al*.¹⁷

In our study, there is a significant difference in the severity of the adverse effects reported: 6.5% for iopromide vs 19.8 for

Figure 1. Adverse effects (AEs) classified by System Organ Class (SOC) level from the Medical Dictionary for Regulatory Activities. *indicates significance to the level of $p < 0.05$, and **to the level of $p < 0.001$. NS, not significant.

iomeprol. In published studies, the severity of the adverse effects is classified according to three categories (mild, moderate and severe), whereas drug regulatory agencies distinguish only two categories (mild and severe). This study has used the latter classification, which adds some difficulty to the comparison. However, other studies do not describe differences in the incidence of severity between various compared CMs.^{10,17,18} The studies referring to a single contrast describe 4.6% severe effects for iobitridol,¹⁴ while another study reports 3.3%.¹⁵ Even if the incidence of adverse effects classified as moderate is added to those in the severe category, the frequency described is lower than that for iomeprol in our study. This occurs in the case of iopromide, with 11% (moderate plus severe effects) in the study by Mortelé et al.¹²

In relation to the Weber effect (a transient increase in adverse event reporting that tends to peak in the second year after a new agent is introduced), in our opinion, it has been 4 years since the introduction of the new contrast and, therefore, the peak of notifications should have fallen. Our study did not find differences in adverse effects between the two contrasts in relation to gender. This is consistent with another study;¹⁰ however, in others, the adverse effects were more frequent among females.^{11–15}

No differences with regard to age were found, both in terms of the average age and when it was compared establishing the age of

60 years as the cut-off point. This is consistent with some studies^{10,12} but differs from others,^{11,14} which find differences (greater frequency in patients aged <60 years).

Our data do not show significant differences in comorbidities between iopromide and iomeprol, except the incidence of patient allergic history and benign prostatic hypertrophy, but not in medical records of prior reaction to CM or asthma. In this issue, an increased likelihood of a contrast reaction in patients with asthma or a history of a prior allergy-like reaction to CM has been pointed out,¹⁹ and most forms of atopy result in a two- to three-times likelihood of contrast reaction compared with non-atopic patients.²⁰

In our comparison, the profile of adverse reactions classified by organs/systems for both CM differs. For iopromide, skin and vascular adverse effects are more frequent, whereas adverse effects more frequently affected the gastrointestinal tracts in the case of iomeprol. An organ-by-organ comparison with other published studies is difficult, as most of these do not provide this information, classifying reactions only according to severity. When the results were compared with those described for iobitridol¹⁵ (one of the few studies that classifies the adverse reactions by organs), differences were observed with regard to distribution; gastrointestinal effects prevail (32.6% of the total 1437 symptoms), whereas in our study, they were 4.6% (iopromide) and 15.0% (iomeprol).

As for the most common adverse reactions, once again, comparison with other studies is difficult because no standardized classification is used, many of them lack percentage results, and there is a disparity in the denominator used (in general, number of patients rather than symptoms observed). Even so, it is striking that no thoracic pain was reported for iopromide, and no oedema or flushing were reported for iomeprol in our study, which are very common adverse effects for many CM.

Preliminary results of this study were presented to the Spanish Committee on Safety of Medicines for Human Use (CSMUH) in April 2010 as a potential signal, ahead of the possible regulatory action by the Spanish Agency of Medicines and Medical Devices, but the CSMUH found insufficient existing data so far to recommend regulatory action.

Limitations

The lack of comparative studies of different CM hinders the comparison of the results. Moreover, the spontaneous nature of the analysed data, as opposed to those obtained by other

prospective studies, may influence the number and severity of the effects reported. Although the source of cases for both contrasts is the same radiology department, the possibility of a reporting bias cannot be entirely ruled out.

CONCLUSION

In spite of the limitations, it can be concluded that the incidence of adverse effects for iomeprol is similar overall, but it differs in severity and frequency from iopromide. New studies would be needed to confirm this finding and improve the scarce information provided by the technical specifications and published data.

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REFERENCES

1. Cochran ST, Bomyea K, Sayre JW. Trends in adverse events after IV administration of contrast media. *AJR Am J Roentgenol* 2001; **176**: 1385–8. doi: [10.2214/ajr.176.6.1761385](https://doi.org/10.2214/ajr.176.6.1761385)
2. Wang CL, Cohan RH, Ellis JH, Caoili EM, Wang G, Francis IR. Frequency, outcome, and appropriateness of treatment of nonionic iodinated contrast media reactions. *AJR Am J Roentgenol* 2008; **191**: 409–15. doi: [10.2214/AJR.07.3421](https://doi.org/10.2214/AJR.07.3421)
3. Thomsen HS, Bush WH Jr. Adverse effects of contrast media: incidence, prevention and management. *Drug Saf* 1998; **19**: 313–24.
4. Caro JJ, Trindade E, McGregor M. The risks of death and of severe nonfatal reactions with high- vs low-osmolality contrast media: a meta-analysis. *AJR Am J Roentgenol* 1991; **156**: 825–32. doi: [10.2214/ajr.156.4.1825900](https://doi.org/10.2214/ajr.156.4.1825900)
5. Dooley M, Jarvis B. Iomeprol: a review of its use as a contrast medium. *Drugs* 2000; **59**: 1169–86.
6. World Health Organization. International drug monitoring: the role of national centres. Tech Rep Ser WHO 1972; no 498 [cited 11 November 2013]. Available from: <http://www.who-umc.org/graphics/24756.pdf>
7. ACR manual on contrast media—Version 9. 2013. ACR Committee on Drugs and Contrast Media—American College of Radiology. [cited October 2013]. Available from: <http://www.acr.org/Quality-Safety/Resources/Contrast-Manual>
8. Aguirre C, Haramburu F. Official systems of pharmacovigilance in France and in Spain. Comparison of spontaneous reporting in two regional centers: Pays Basque and Bordeaux. [in French.] *Therapie* 1995; **50**: 563–9.
9. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (Med-DRA). *Drug Saf* 1999; **20**: 109–17.
10. Gomi T, Nagamoto M, Hasegawa M, Katoh A, Sugiyama M, Murata N, et al. Are there any differences in acute adverse reactions among five low-osmolar non-ionic iodinated contrast media?. *Eur Radiol* 2010; **20**: 1631–5. doi: [10.1007/s00330-009-1698-6](https://doi.org/10.1007/s00330-009-1698-6)
11. Kopp AE, Mortelé KJ, Cho YD, Palkowitsch P, Bettmann MA, Claussen CD. Prevalence of acute reactions to iopromide: postmarketing surveillance study of 74,717 patients. *Acta Radiol* 2008; **49**: 902–11. doi: [10.1080/02841850802282811](https://doi.org/10.1080/02841850802282811)
12. Mortelé KJ, Oliva MR, Ondategui S, Ros PR, Silverman SG. Universal use of nonionic iodinated contrast medium for CT: evaluation of safety in a large urban teaching hospital. *AJR Am J Roentgenol* 2005; **184**: 31–4. doi: [10.2214/ajr.184.1.01840031](https://doi.org/10.2214/ajr.184.1.01840031)
13. Encina JL, Martí-Bonmati L, Ronchera-Oms CL, Rodríguez V. Iopentol (Imagopaque 300) compared with iopromide (Ultravist 300) in abdominal CT. A multi-centre monitoring trial assessing adverse events and diagnostic information—results from 518 patients in Spain. *Eur Radiol* 1997; **7**(Suppl. 4): S115–19.
14. Vogl TJ, Honold E, Wolf M, Mohajeri H, Hammerstingl R. Safety of iobitridol in the general population and at-risk patients. *Eur Radiol* 2006; **16**: 1288–97. doi: [10.1007/s00330-005-0061-9](https://doi.org/10.1007/s00330-005-0061-9)
15. Maurer M, Heine O, Wolf M, Freyhardt P, Schnapauff D, Hamm B. Safety and tolerability of iobitridol in general and in patients with risk factors: results in more than 160,000 patients. *Eur J Radiol* 2011; **80**: 357–62. doi: [10.1016/j.ejrad.2010.03.018](https://doi.org/10.1016/j.ejrad.2010.03.018)
16. Alvarez-Requejo A, Carvajal A, Bégaud B, Moride Y, Vega T, Arias LH. Under-reporting of adverse drug reactions. Estimate based on a spontaneous reporting scheme and a sentinel system. *Eur J Clin Pharmacol* 1998; **54**: 483–8.
17. Lapi F, Cecchi E, Pedone C, Attanasio F, Banchelli G, Vannacci A, et al. Safety aspects of iodinated contrast media related to their physicochemical properties: a pharmacoepidemiology study in two Tuscany hospitals. *Eur J Clin Pharmacol* 2008; **64**: 723–37. doi: [10.1007/s00228-008-0477-7](https://doi.org/10.1007/s00228-008-0477-7)
18. Harding JR, Bertazzoli M, Spinazzi A. A randomized, double-blind, parallel group trial of iomeprol, iohexol and iopamidol in intravenous urography. *Br J Radiol* 1995; **68**: 712–5.
19. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez 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.
20. Coakley FV, Panicek DM. Iodine allergy: an oyster without a pearl?. *AJR Am J Roentgenol* 1997; **169**: 951–2. doi: [10.2214/ajr.169.4.9308442](https://doi.org/10.2214/ajr.169.4.9308442)