the sympathetic opinion of the medical social workers is the result of a predominantly "behavioural" training.

We wish to thank all those who participated in the study. We thank the members of the medical division of the Western Infirmary for allowing the students to study their patients.

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Hospital Topics

Acute Reactions to Urographic Contrast Media

P. DAVIES, M. B. ROBERTS, J. ROYLANCE

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Summary

A prospective study of 3509 consecutive patients examined by excretion urography has been conducted to assess the incidence and significance of the untoward effects of urographic contrast media. Four compounds were used in doses containing 160 to 500 mg iodine/kg body weight. Toxic effects, arm pain, and allergic reactions were assessed separately, while the remainder were classified according to the influence of each reaction on the investigation and the need for treatment. From the results and a review of the literature we conclude that when there is a clear clinical indication for excretion urography a dose of contrast medium containing up to 600 mg iodine/kg body weight should be injected rapidly. Prophylactic antihistamine treatment and pretesting should be abandoned. Special care is needed for small infants and the elderly and for patients with renal or hepatic failure, myeloma, heart disease, or a history of previous major reaction. Full resuscitation facilities must always be available.

Introduction

Almost everyone suspected of urinary tract disease will undergo excretion urography.[1] During the past decade studies of film quality and urinary concentrations of excreted contrast medium have established that the use of higher doses of contrast media results in an improvement in the radiographic visualization of the whole urinary tract.[2] High doses have been recommended for the investigation of almost all urinary tract disorders, including acute and chronic renal failure,[3 4] congenital abnormalities,[5] obstructive uropathy,[6] inflammatory disease,[7-9] calculus disease,[10 11] trauma,[12 13] and renal masses,[14 15] and as a preliminary to renal puncture[16] and needle nephrostomy.[17] Acute reactions to the injection of urographic contrast media, however, are well known, and anxiety has been expressed about the safety of high-dose urography.[18] A prospective study has been undertaken to assess the incidence of untoward effects and their influence on the investigation.

Department of Radiodiagnosis, Bristol Royal Infirmary, Bristol BS2 8HW
P. DAVIES, D.M.R.D., F.F.R., Senior Registrar (Now Consultant Radiologist, City Hospital, Nottingham)
M. B. ROBERTS, D.M.R.D., F.F.R., Senior Registrar
J. ROYLANCE, D.M.R.D., F.F.R., Consultant

Patients and Materials

A consecutive series of 3509 patients referred to this department for excretion urography were included in the study, which was carried out over 23 months. Altogether 2008 were male and 1501 female and their ages ranged from 9 to 94 years (fig. 1). Out of 355 patients with a history of asthma, eczema, hay fever, or drug hypersensitivity 147 were given prophylactic chlorpheniramine (Piriton). Doses of contrast medium ranged from 160 to 500 mg iodine/kg body weight. An infusion of 25% sodium diatrizoate (Hypaque) was used for 444 examinations, a mixture of sodium and meglumine diatrizoate (Urovison) was injected in 713, sodium iothalamate (Conray 420) was used for 1022, and 45% sodium diatrizoate (Hypaque) was used for the remaining 1330. A further 755 patients were examined to assess the cause of arm pain.

Method

Immediately before the investigation the patient's age, sex, menstrual state, and allergic history were recorded. The type and quantity of the contrast medium used and the speed of injection were documented during the examination. The presence and nature of any untoward

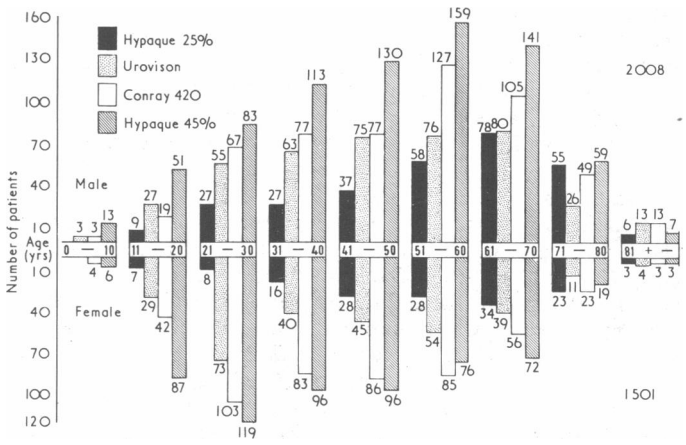

FIG. 1—Frequency with which each contrast medium was used in each age group. Figures at top and bottom of columns are numbers of patients.

effects were elicited by direct questioning and by observations during the examination. The information was recorded on special survey sheets, transferred to punch cards, and analysed on a computer. The results were assessed for statistical significance, a level of $P < 0.05$ being regarded as significant.

Results

The urographic appearances were normal in 2041 patients. In the remainder the major abnormality (673 patients) was bladder outflow obstruction (table I).

There were no deaths after urography in this series, and no side effects occurred in 1287 (37%) of the patients (table II). Ureteric compression caused discomfort in virtually all cases and in 133 (4%) it was removed prematurely because it became intolerable or caused hypotension.

TABLE I—*Urographic Findings in 3509 Patients*

	No. of Patients
Normal	2041
Bladder outflow obstruction	673
Calculi	165
Secondary hydronephrosis	105
Chronic pyelonephritis	78
Bladder carcinoma	62
Primary pelvic hydronephrosis	57
Renal masses	48
Other	280
Total	3509

TABLE II—*Reactions in 3509 Patients during Excretion Urography. (Some Patients Experienced More than One Reaction)*

	No. (%) of Patients
No side effects	1287 (37)
Toxic effects (heart failure)	4(0·1)
Allergic effects	52(1·5)
Urticaria	37
Angioneurotic oedema	5
Asthma	5
Conjunctivitis	4
Rhinitis	1
Major reactions	4(0·1)
Hypotension	1
Bronchospasm	1
Vomiting	1
Dyspnoea and urticaria	1
Minor reactions	286 (8)
Nausea	196
Nausea and vomiting	90
Trivial reactions	2060 (59)
Warmth	1726
Metallic taste	379
Visceral sensations	206
Tingling	199
Flushing	191
Cough and sneeze	72
Miscellaneous	138

REACTIONS (TABLE II)

Toxic effects, defined as those due to an excess of contrast medium, occurred in four patients (0·1%), who developed acute heart failure. All had pre-existing heart disease and recovered promptly after treatment.

Allergic effects were experienced by 52 patients (1·5%). Most (37 cases) were urticarial eruptions but examples of angioneurotic oedema (5 cases), asthma (5), conjunctivitis (4), and rhinitis (1) were also seen. Thirteen of these patients had a history of asthma, eczema, or drug hypersensitivity.

Major reactions, defined as those which both interfered with the investigation and required treatment, were recorded in four patients (0·1%). One developed marked hypotension which persisted for half an hour, another developed acute bronchospasm, one had severe vomiting, and the fourth became dyspnoeic and suffered from widespread urticarial eruptions. All four recovered promptly with treatment and successful examinations were completed.

Minor reactions, defined as those which interfered with the examination but did not require treatment, were nausea and vomiting. Nausea was experienced by 286 patients (8%), 90 of whom vomited.

Trivial reactions were defined as those which did not interfere with the examination and required only reassurance; 2911 such reactions were experienced by 2060 patients (59%). They included a wide variety of sensations, the most common of which was warmth (1726 cases; 49%). Others were a metallic taste (379 cases; 11%); visceral sensations (206; 6%), usually an unpleasant feeling in the epigastrium but sometimes a more diffuse sense of unease within the abdomen; tingling in the skin (199; 6%); widespread flushing (191; 5%); and coughing and sneezing (72; 2%). A further group (138 patients; 4%) had a number of interesting but individually rare reactions. These included tinnitus and sensations of disorientation, drunkenness, burning in the throat, formication, hot water running over the trunk, and floating or falling backwards, but the most common was unpleasant sensations in the perineum; these included burning, wetness, or a desire to empty the rectum or bladder, sometimes accompanied by a spurious sensation of having done so.

EVALUATION

A correlation was sought between each type of reaction and all other data. No significant difference in the incidence of type of reaction was found between the sexes. With increasing age there was a decreasing incidence of a metallic taste. The incidence of warmth increased with the concentration of the contrast medium, the speed of the injection, and the dose used (table III).

Among the 355 patients with a history of allergy there was no difference in the incidence or type of non-allergic reactions. These patients, however, exhibited a threefold increase in allergic reactions when compared with patients without such a history (13 out of 355 patients (3·7%) compared with 39 out of 3154 (1·2%)). The use of prophylactic antihistamines in patients with an allergic history caused no reduction in the incidence or severity of allergic reactions and was followed by a threefold increase in the incidence of flushing (table IV).

TABLE III—*Incidence of Warmth with Increasing Doses of Contrast Media*

Dose (mg iodine/kg body weight)	160	240	360
Incidence of warmth	21%	44%	70%

TABLE IV—*Use of Prophylactic Antihistamine Treatment in 355 Patients with History of Allergy and Incidence of Allergic Reaction and Flushing*

	Patients Given Antihistamine (n = 147)	Patients not Given Antihistamine (n = 208)
No. (%) with allergic reactions	6 (4·1)	7 (3·4)
No. (%) with flushing	18 (12·2)	9 (4·3)

ARM PAIN

Arm pain was inadequately classified during the major series as simple venepuncture may be slightly painful. Some patients complained of severe pain at the site of the injection and others complained of pain proximal to the injection site. To evaluate the incidence of this and investigate the cause a further 755 patients were studied. In each case a plain film of the site of the injection was taken immediately after the nephrogram and the appearances were correlated with an independent record of the site and nature of any arm pain and the contrast medium injected. In most cases pain at the injection site was found to be associated with a perivenous injection of contrast medium (fig. 2) though this was not clinically apparent. Perivenous injections were equally frequent with the three agents used and were almost always associated with persistent pain at the site of the injection when Conray 420 was used, less frequently when Urovison was used, and rarely when Hypaque was injected (table V). In 18 patients given Conray 420 and in 10 given Urovison pain extending up the arm was experienced. In these the post-injection radiograph of the injection site usually showed stasis of contrast medium in the vein (fig. 3).

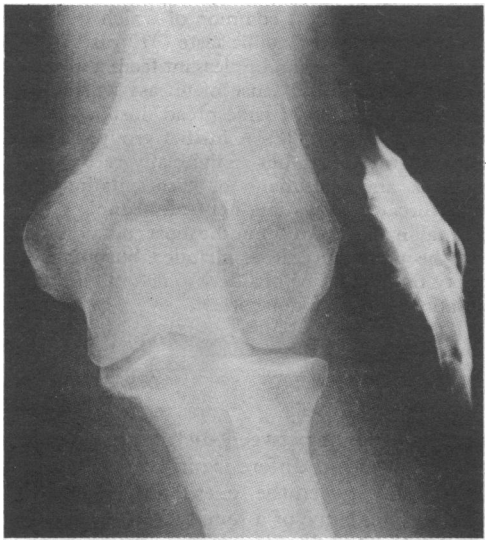

FIG. 2—Plain x-ray film of injection site in patient with arm pain showing perivenous deposit of contrast medium.

TABLE V—*Incidence of Arm Pain, Extravasation, and Venous Stasis with Three Contrast Media in 755 Patients*

	Conray 420		Urovison		Hypaque 45%	
	No.	%	No.	%	No.	%
No extravasation and no pain ..	239	78·4	248	80·0	119	85·0
Extravasation and pain	43	14·1	35	11·3	2	1·4
Pain without extravasation	4	1·3	5	1·6	3	2·1
Extravasation without pain	1	0·3	12	3·9	16	11·4
Stasis in vein with pain	18	5·9	10	3·2	0	0
Total	305	100·0	310	100·0	140	100·0

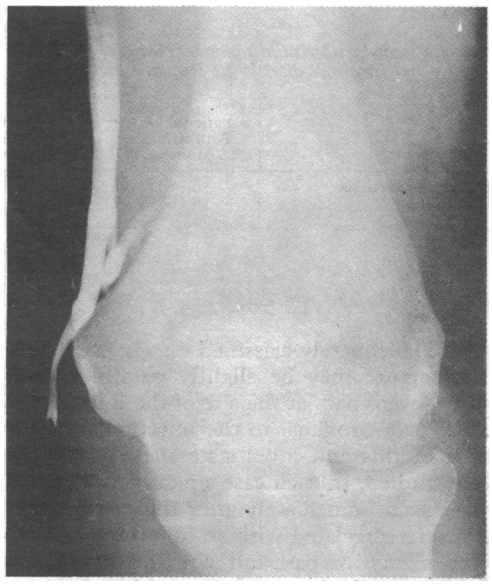

FIG. 3—Post-injection radiograph from patient with arm pain showing stasis of contrast medium in vein.

Discussion

Reactions to urographic contrast media vary widely in both nature and severity. No interrelationship between each type of reaction has been shown. No universally accepted classification has so far emerged and summation of other published results is not possible. As toxic effects, arm pain, and allergic reactions are thought to be due to excess dosage, perivenous injection, and hypersentivity respectively these have been classified separately in this series. The mechanisms responsible for all other types of side effects remain obscure, and fear inherent in the patient or engendered by the radiologist appears to be the most important factor in so-called idiosyncratic reactions.[19] A classification which depends on the influence of each reaction on the examination and the need for treatment has been employed. Trivial reactions have been said to be unimportant[20] but are often unpleasant and may alarm the patient. These factors are of increasing significance as safer agents are introduced.[21] Nausea and vomiting have been classified as minor side effects as retching and the associated accumulation of gas in the bowel hamper radiography.

From our results and a review of the literature it is possible to reappraise the problems posed by modern, high-dose urography.

Is Excretion Urography Dangerous?

Estimates of the mortality from excretion urography include 1 in 116 000,[22] 1 in 61 000,[23] 1 in 85 000,[24] 1 in 100 000,[2] 1 in 40 000,[18] and 1 in 52 000.[25] Thus most radiologists will not meet such a tragedy throughout their careers. These mortality rates are likely to include patients who have suffered from frank overdosage of contrast medium, those who have succumbed to inappropriate resuscitation, and those for whom resuscitation facilities were not available. In addition, deaths from causes other than excretion urography may well be included. A fatal haemorrhage from multiple hepatic metastases, for example, has been reported to have been indistinguishable clinically from a reaction to contrast medium.[26] Thus while deaths due to excretion urography are rare, unavoidable deaths directly due to the intravenous injection of contrast medium are extemely rare. Other methods of management are not without risk. The death rate from nephrectomy is 1·8%[27] and from exploration of a kidney 1·6%.[28 29]

Does an Increase in Dose Increase the Risk?

There is no evidence that increases in dose increase the incidence of major, minor, or allergic reactions, but they are associated with an increase in trivial reactions. In animal experiments the acute toxicity (LD_{50}) of diatrizoates is about 25 ml/kg for a 50% solution[30] and is comparable in magnitude to that of glucose used for intravenous feeding.[31] Despite the fact that these compounds are given by rapid intravenous injection of strongly hypertonic solutions to patients who are usually ill their use is associated with surprisingly few serious reactions.[30] Toxic effects should not be a problem in excretion urography for doses up to 600 mg iodine/kg body weight.[2]

These doses are, however, close to the safety margin[32] and there are occasions when there is a risk of overdosage. The kidneys of small infants concentrate and excrete contrast medium less well than the mature kidney. Thus infants are more susceptible to the toxic effect of contrast medium, and large doses have caused death. In one instance the dose exceeded the LD_{50} for the contrast medium.[32] Patients with pre-existing cardiac disease may develop heart failure after the injection of large volumes of contrast medium,[33] and this occurred in four patients in our series. Meglumine salts should be employed preferably when examining patients with hypertension or heart disease to reduce the sodium load.[2] Patients with combined hepatic and renal failure are also more susceptible to the toxic effects of contrast medium.[34]

What is the Significance of a History of Allergy?

No significant difference was found in the incidence of non-allergic types of reactions in patients with an allergic history.[21] There was, however, a threefold increase in the incidence of

allergic reactions,[35] though still affecting less than 4% of such patients. Prophylactic antihistamine treatment has been recommended when a history of allergy is present,[36-39] but as in the present series such prophylaxis does not reduce the incidence of side effects.[21 40] Indeed, it has been associated with an increased incidence of flushing. Thus while prophylactic antihistamine treatment may reduce the radiologist's anxiety[41] it is otherwise ineffective and undersirable.

What Other Patients Present Special Risks?

While there is an overall reduction in side effects with increasing age[42] the mortality rate and severity of reactions increase. Apart from instances of gross excess of contrast medium given to small infants nearly all deaths have occurred in patients over 50 years old.[18] Patients suffering from myelomatosis may tolerate excretion urography badly[43] but it appears that the preliminary dehydration and not the contrast medium is the major cause of ill effects.[44-47] The presence of renal failure presents similar problems, when dehydration is dangerous.[4]

Should the Patient be Pretested?

The present series provides no information on the value of pretesting, which was abandoned in the United Bristol Hospitals 10 years ago. All forms of pretesting have been shown repeatedly over the past 20 years to be of no value.[22 48-50] Nevertheless, a review of nearly four million examinations in the U.S.A. showed that pretesting is still used for all patients in some departments and for selected patients in others.[25] A lower death rate and a lower incidence of serious reactions were reported in those departments which had abandoned all forms of pretesting. In the other departments 23 deaths and more than 700 serious reactions occurred despite negative pretesting results. Two deaths and 59 serious reactions were caused by the tests. In the presence of overwhelming evidence that test doses are not only useless in the prediction of reactions but also potentially hazardous there can be no medical indication and therefore no medicolegal indication for their use.[35]

Should the Contrast Medium be Injected Rapidly?

The diagnostic value of the nephrogram is now well recognized. Under normal circumstances the intensity of the nephrogram is at a maximum immediately after a rapid injection.[51] It has been suggested that theoretically slower injections should be safer than those given rapidly,[18] but experience has shown no increase in mortality after rapid injections,[24] and, as in our series, apart from an increased incidence of warmth the rate of all reactions is strikingly similar at all injection speeds.

What is the Importance of Major Reactions?

While major reactions are rare they are unpredictable, currently unavoidable, and may threaten life. They require prompt recognition and treatment. The very rarity of such reactions presents problems since full resuscitation facilities must not only be provided but must also be regularly reviewed. All staff must be trained in their use and a high level of efficiency maintained by constant practice.[52 53] An efficient communication system to summon aid without delay is essential. When a major reaction does occur a complete record must be kept. Though subsequent exposure to the same contrast medium may cause no reaction it is prudent to avoid further excretion urography. When another examination is unavoidable prophylactic intravenous steroid treatment some 30 minutes before the injection of an alternative contrast medium, an indwelling intravenous catheter, and careful supervision are indicated.[2]

Conclusions

Though excretion urography is safe it should be undertaken only when there is a clear clinical indication and should be performed in a manner designed to reduce the patient's anxiety. A dose of contrast medium containing up to 600 mg iodine/kg body weight should be injected rapidly intravenously. Special care is needed for small infants, and the elderly and for patients with renal or hepatic failure, myloma, heart disease, or a previous major reaction to contrast medium. As 96% of patients with an allergic history will not suffer an allergic reaction it is unreasonable to deprive such patients of the benefit of excretion urography when this is indicated. Both prophylactic antihistamine treatment and pretesting with a small dose of contrast medium are unhelpful and should be abandoned. Excretion urography should be performed only when full resuscitation facilities are available.

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