Renal Injury Associated with Intravenous Pyelography in Nondiabetic and Diabetic Patients

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We studied 23 patients with renal functional deterioration after intravenous pyelography; 16 were nondiabetic. Nondiabetic patients at risk are often elderly and have pre-existing renal disease. The course of acute renal failure is fairly characteristic; most patients recover, but some do not. Estimates suggest that the syndrome is not uncommon in susceptible nondiabetic subjects. Pyelography cannot be considered absolutely safe for this group, and alternative diagnostic procedures or caution with contrast dosage and patient preparation may be wise.

REPORTS OF acute renal failure after angiography or pyelography suggest that currently used radiographic contrast agents may be nephrotoxic for diabetic persons (1-4). There is conflicting information, however, about their danger when used for pyelography in nondiabetic subjects. Studies of more than 100 000 pyelograms by Diaz-Buxo and colleagues (2) and more than 3 800 000 pyelograms by Pendergrass and associates (5) revealed no cases of acute renal failure in patients without diabetes, whereas Ansari and Baldwin (6) identified nine cases, all in patients who had pre-existing renal disease or pre-renal azotemia.

We summarize here our recent experience with pyelography-associated renal failure in nondiabetic as well as diabetic subjects and describe the clinical course.

Materials and Methods

Four patients were referred to the inpatient nephrology consultation service between March 1976 and June 1976 for acute renal failure apparently associated with intravenous pyelography. Because they aroused our interest, random auditing was undertaken to determine the full spectrum of the phenomenon. A computer search of the billing records of Strong Memorial Hospital was undertaken for a 10-month period (1 July 1976 to 30 April 1977) to identify all inpatients who had had intravenous pyelography (IVP) and on whom serum creatinine (sCr) levels had been measured $\leq$ 7 days before and $\leq$ 7 days after IVP. During the survey period, 2360 pyelograms were done at this hospital, of which 1135 were on inpatients. Four hundred fifty inpatient charts met our criteria, and 395 were available for review. Records of patients with > 1.0 mg/dl increment in sCr after IVP were scrutinized closely. Pyelography-associated renal dysfunction was diagnosed when an abrupt increase in sCr of more than 1.0 mg/dl, with or without oliguria, occurred after an IVP and no other nephrotoxic factors could be invoked. In most cases sCr was stable before examination, but in six cases pre-existing deterioration in renal function accelerated or oliguria occurred abruptly after IVP. Eighteen patients with IVP-associated renal functional deterioration were excluded from this study because hypotension (systolic < 100 mm Hg), sepsis, significant amounts of nephrotoxic antibiotics, or other factors were present, and the precise cause of their acute renal failure could not be ascertained.

Patients were considered to have no renal disease if there was no previous evidence of renal abnormalities and if sCr was < 1.5 mg/dl before pyelography. This group included patients with unrecognized renal disease with normal and mildly reduced renal function. Nondiabetic renal disease was diagnosed on the basis of clinical and laboratory evidence or if sCr was > 1.5 mg/dl before preparation for pyelography in patients without clinical evidence of diabetes in whom random blood sugars or a glucose tolerance test had been normal. Hypertensive renal disease was diagnosed in patients with a long history of uncontrolled systolic and diastolic hypertension without another obvious cause for renal insufficiency. Diabetes was diagnosed by previous clinical evidence and abnormal glucose tolerance tests.

Dehydration was diagnosed when suggested by the clinical history and by one or more of these findings before IVP: orthostatic drop in systolic or diastolic blood pressure > 10 mm Hg; urinary sodium concentration pre-IVP < 15 meq/litre; negative fluid balance of > 1 litre or loss of > 1 kg of body weight in the previous 2 to 3 days; or blood urea nitrogen to sCr ratio > 20. Congestive heart failure (CHF) was identified when diagnosed by the attending staff and when at least two of these conditions were present: radiographic cardiomegaly; radiographic pulmonary vascular congestion; S_3 gallop; and peripheral edema. Patients were considered hypertensive if blood pressures were consistently > 150/100 mm Hg in hospital or if they had a history of hypertension and were taking antihypertensive drugs.

Intravenous pyelography was done with 300 ml of Reno-M-Dip (30% diatrizoate meglumine; E.R. Squibb, Princeton, New Jersey) by infusion (42.3 grams of iodine per examination). Inpatients were given a mild purgative but were not fluid-restricted before examination.

Results

INCIDENCE OF IVP-ASSOCIATED RENAL INJURY IN SURVEYED GROUP

Four patients and five instances of renal functional deterioration associated with IVP were identified before the formal review. Eighteen additional cases were found among the 377 charts included in the review. Table 1 shows an occurrence in patients "without renal disease" of one in 169, in patients with nondiabetic renal disease of 10 in 177, and in diabetics of seven in 31. The incidence rose as renal failure became more severe in both groups, to 31% in nondiabetic subjects and to 100% in

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Table 1. Occurrence of Renal Dysfunction Associated with Pyelography in Surveyed Population

Group	sCr* < 1.5 mg/dl	sCr 1.5 to 4.5 mg/dl	sCr > 4.5 mg/dl	Total
	no. %	*no.* %	*no.* %	*no.* %
No preceding renal disease or dysfunction	1/169 (0.6)			1/169 (0.6)
Nondiabetic renal disease or dysfunction	3/95 (3.2)	2/66 (3.0)	5/16 (31)	10/177 (5.6)
Diabetic	0/19 (0)	5/10 (50)	2/2 (100)	7/31 (23)
All patients surveyed	4/283 (1.4)	7/76 (9.2)	7/18 (39)	18/377 (4.8)

* sCr = serum creatinine.

diabetic subjects with pre-IVP sCr > 4.5 mg/dl. Three of four nondiabetic patients with hypertensive renal disease and sCr > 4.5 mg/dl sustained IVP-associated renal injury, while the occurrence in nondiabetic patients with renal disease due to factors other than hypertension with sCr > 4.5 mg/dl was two in 12. This difference is not significant, however (chi-square analysis, $p = 0.12$).

The occurrence of this phenomenon in the total population surveyed was 18 of 377, or 4.8%. If we assume that no other cases occurred among inpatients or outpatients not included in the survey, the occurrence in the 2360 IVP done over that 10-month period was 18 of 2360, or 0.8%.

CHARACTERISTICS OF PATIENTS WITH IVP-ASSOCIATED RENAL INJURY

Table 2 characterizes patients who developed renal failure after pyelography. Fifteen nondiabetic patients were identified. The first four came to our attention before the chart survey; renal failure occurred on two occasions after IVP in Patient 4. The remaining 11 patients were identified through the survey. Fourteen of these 15 patients had recognized renal disease, due to hypertension in five, glomerulonephritis in three, hydronephrosis in three, and polycystic disease, gouty nephropathy, and questionable mild transplant rejection in one each. Patient 8 had urinary retention due to benign prostatic hypertrophy, but there was no hydronephrosis and sCr was 1.0 mg/dl before his pyelogram. He represents the single patient "without pre-existing renal disease" who sustained renal injury, yet he clearly had urologic abnormalities. Most of these patients had renal insufficiency, with a mean sCr of 4.1 mg/dl. Four of 15, however, had sCr < 1.5 mg/dl, which suggests that markedly reduced renal function is not a prerequisite for development of renal failure. Only two patients had proteinuria in the nephrotic range. Most patients were elderly (mean age, 61 years), 10 were hypertensive, four were in CHF, and only two were dehydrated by our criteria at the time of pyelography, although more subtle degrees of dehydration may have been overlooked. Mean serum uric acid before pyelography was 8.5 mg/dl, albumin 3.4 g/dl, and hematocrit 36.4%. Nine patients were receiving diuretics and eight, antibiotics. No patient was hypotensive or septic, and antibiotics were generally given for urinary infections or pneumonia in appropriate doses. The abrupt development of excretory dysfunction after pyelography and the subsequent recovery, often with continued administration of antibiotics, indicated that these drugs were unlikely to be the major cause of renal injury, although an additive or sensitizing role cannot be excluded.

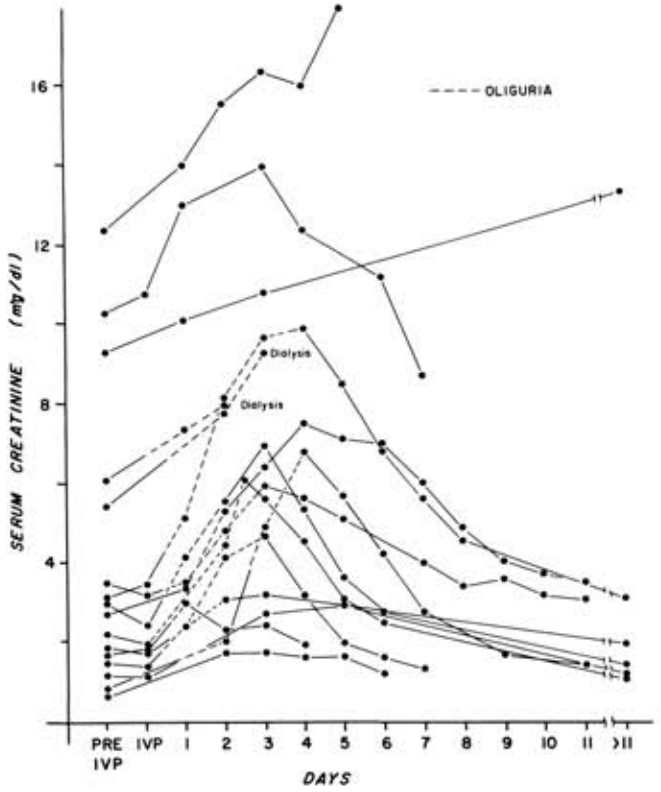

Figure 1. Course of acute renal failure associated with intravenous pyelography (*IVP*) in nondiabetics subjects.

Seven cases of renal failure associated with IVP were identified in diabetic patients. Mean baseline sCr was 4.3 mg/dl; none had sCr < 1.5 mg/dl. Mean age was 65.8 years. Only two with long histories of diabetes needed insulin. Hypertension was present in five, CHF in three, and dehydration in five. Two were receiving antibiotics and six, diuretics. Mean serum uric acid was 8.9 mg/dl, albumin 3.7 g/dl, and hematocrit 28%.

COURSE OF RENAL FAILURE ASSOCIATED WITH PYELOGRAPHY

Figure 1 shows the course of this phenomenon in nondiabetic patients. Eleven of 16 episodes were accompanied by oliguria within 24 h of pyelography. Oliguria was refractory to volume expansion or diuretics when administered but was of short duration, averaging between 24 and 48 h and never lasting more than 72 h. Serum creatinine peaked in a mean of 3.3 days. Urinary sodium concentrations obtained while renal function was deteriorat-

ing in patients not taking diuretics ranged from 1 to 47 meq/litre, with five of nine concentrations being < 30 meq/litre. Two patients had structural changes of acute tubular necrosis on renal biopsies done 1 and 14 days after IVP. Their urine sodium concentrations on Days 1 and 2 after IVP, however, were low (1 meq/litre and 13 meq/litre, respectively). Complete recovery occurred in nine instances within a mean period of 14.8 days, and most improvement occurred within 6 days. In three episodes, however, recovery was only partial by Day 11 or later. Two patients underwent chronic hemodialysis within a few days of IVP and two within a few weeks. The course of renal failure in the seven diabetic patients was similar. Three patients were oliguric for a mean of 3.5 days after IVP. Serum creatinine peaked between the 2nd and 5th days. Urinary sodium concentration during the period of deterioration in five patients not taking diuretics was less than 30 meq/litre in three. Three patients, two of whom had been oliguric, began to recover by Days 4 to 6 and reached their baseline sCr in a mean of 9.3 days. Two patients had only partly regained their baseline renal function by Day 11, and one patient with severe renal insufficiency underwent chronic dialysis on Day 9. The fate of one patient is unknown.

Discussion

We have described 23 cases of decreased renal function probably due to intravenous pyelography. Seven occurred in diabetic patients, but 16 occurred in nondiabetic patients, 11 of whom were identified by a restricted chart review over a 10-month period.

Susceptible nondiabetic and diabetic patients were usually elderly and had pre-existing renal disease and often reduced excretory function. Hypertension was present before IVP in 67% and 71% of nondiabetic and diabetic patients, respectively; congestive failure in 27% and 43%; and mild dehydration in 13% and 71%. Sixty percent of nondiabetic and 85% of diabetic patients were receiving diuretics before IVP, and 50% of nondiabetic and 30% of diabetic patients were receiving antibiotics. Some of these factors may have contributed to the decline in renal function, but the development and resolution of the syndrome was chronologically related to the pyelography procedure.

The course of this phenomenon was relatively uniform. Renal functional deterioration was immediate, oliguria was frequent but of short duration, and recovery was usual but not invariable, began fairly promptly, and was sometimes incomplete at 11 or more days. Three patients required dialysis shortly after IVP, and one began chronic dialysis within a few weeks. Pyelography probably only hastened the initiation of dialysis in these patients, all of whom had previous severe progressive renal disease. Morbidity due to IVP was reflected mainly in extended hospital stays—with more vigorous monitoring during the period of renal failure, added discomfort, expense,

Table 2. Characteristics of Patients who Developed Renal Failure after Intravenous Pyelography

Patient	Age	Diagnosis*	Dehydration	CHF	Diuretics	Antibiotics	Serum Creatinine
	yrs						*mg/dl*
Nondiabetic							
1	77	BPH, chronic UTI, hypertension	−	−	+	+	2.4
2	64	Hypertension	−	−	−	−	3.5
3	36	Membranous GN with nephrotic syndrome	+	−	+	−	1.7
4	83	Prostatic carcinoma, unilateral hydronephrosis	−	−	−	+	2.5/3.5†
5	72	Unilateral prohydronephrosis, hypertension	−	+	+	+	1.3
6	68	Hypertension, nephrosclerosis, pneumonia	−	+	+	+	6.1
7	72	Hypertension, CHF, atheroembolic renal disease	−	+	+	+	5.4
8	75	BPH, urinary retention	−	−	−	+	1.0
9	42	Polycystic kidneys, hypertension	?	−	−	+	12.4
10	89	Nephrolithiasis with obstruction, UTI	−	−	−	+	1.1
11	70	Cerebrovascular disease, carotid endarterectomy, ? gouty nephropathy	−	−	−	−	1.7
12	32	Chronic GN, hypertension, UTI	−	+	+	−	9.3
13	48	Hypertension	?+	−	+	−	10.8
14	52	Cadaver renal transplant recipient	−	−	+	−	1.9
15	32	Lupus nephritis, hypertension	−	−	+	−	0.7
Diabetic							
1	32	JDM, hypertension	−	+	+	−	14.8
2	83	AODM, nephrolithiasis, hydronephrosis	?	−	+	+	2.7
3	87	AODM, hypertension, arteriosclerotic cardiovascular disease	+	?+	+	−	2.4
4	63	AODM, hypertension, arteriosclerotic cardiovascular disease	+	+	+	−	4.4
5	67	AODM, hypertension, nephrolithiasis, unilateral obstruction, metastatic tumor	+	−	+	−	1.8
6	48	AODM, hypertension, past history of acute interstitial nephritis	+	−	−	−	2.2
7	81	AODM, BPH with retention	+	−	+	+	1.5

* BPH = benign prostatic hypertrophy; UTI = urinary tract infection; GN = glomerulonephritis; CHF = congestive heart failure; JDM = juvenile-onset diabetes mellitus; AODM = adult-onset diabetes mellitus.
† This patient had two intravenous pyelograms, both of which were followed by acute renal failure.

and risk—and in shortened time to dialysis in those with antecedent progressive azotemia. No deaths occurred.

Pyelography-associated renal injury may occur by several mechanisms. Dehydration from the preparation and the contrast-induced osmotic diuresis in nonoliguric patients may contribute. Contrast media may have direct vascular toxicity (suggested by renal vasoconstriction and cortical ischemia observed during renal angiography [7,8]), and, although contrast is diluted by peripheral blood during pyelography, vascular toxicity could be of significance to an already hypoperfused kidney. Our impression that patients with primary hypertensive renal disease were at higher risk than other nondiabetic patients with similar impairment of renal function suggests that occlusive disease of small renal vessels in diabetic patients and in patients with nephrosclerosis could predispose to contrast-induced renal failure. Tubular epithelial cell toxicity from contrast agents might be more severe in compromised kidneys than in healthy ones, for although intratubular contrast concentrations may be less than normal, the period of exposure is prolonged and each surviving nephron handles a larger fraction of the administered dose.

The high incidence of renal failure that we observed might be partly explained by the relatively large standard dose of contrast agent used. There is clinical and experimental evidence that renal damage is more likely to occur with larger or repeated doses of contrast (4, 9, 10). In earlier series demonstrating the safety of pyelography (11-14) doses of contrast were often, although not invariably, lower than those administered to our patients and to the patients who sustained renal failure after pyelography in the series of Ansari and Baldwin (6).

The incidence of this phenomenon was 4.8% in our surveyed high-risk group of hospitalized patients. However, 18 additional cases of renal dysfunction after IVP were discarded from the 395 charts originally in the study because too many nephrotoxic factors were present. If some of these were in fact due to contrast, the incidence in this high-risk group may be greater than stated. If we assume no additional cases went undetected among the entire 2360 IVP done during the 10-month period, we have a minimum incidence of 0.8%. If undetected transient episodes of renal dysfunction short of florid acute renal failure occurred in nonsurveyed inpatients and in outpatients having IVP, the incidence in the entire group exceeds 0.8%. Hence, contrast-induced renal damage appears to occur in high-risk groups and in the total population having pyelograms more frequently than previously reported (2, 5) and is certainly not confined to diabetic subjects. Ansari and Baldwin (6), who recognized this phenomenon in nondiabetic subjects, could not estimate its prevalence. We found that the risk is negligible in persons with no renal disease or impairment, rises as renal failure progresses, is prohibitive in diabetic patients with sCr > 1.5 mg/dl, but is also significant in those with nondiabetic renal disease, especially those with advanced renal failure (31% incidence when sCr > 4.5 mg/dl). Because this group is much larger than the diabetic group, these patients comprise most of the cases.

Prevention of pyelography-induced renal failure is a desirable goal, and prior identification of susceptible patients is the first step. If the desired information can be so obtained, we now advocate initial use of radioisotope or ultrasound studies, or both, rather than pyelography in some high-risk patients. If pyelography is necessary, care should be taken with preparation and contrast dose, and the patient should be monitored for renal dysfunction afterwards.

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