DRUG-ASSOCIATED ACUTE RENAL FAILURE.  
A PROSPECTIVE MULTICENTRE REPORT

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Summary

During a one-year period, drug-associated acute renal failure was prospectively recorded in 398 patients, registered in 58 Nephrology Units. Drugs involved were primarily antibiotics, mainly aminoglycosides, glafenin, non-steroidal anti-inflammatory drugs and contrast media administration. Predisposing factors such as decreased renal perfusion, sodium depletion and/or congestive heart failure were present in one half of the patients. Fifty patients died, and in 92 permanent renal damage remained. Age, oliguria and severity of renal insufficiency were poor prognostic indicators. We conclude that prevention of drug-associated acute renal failure should be especially directed to high risk patients.

Introduction

The incidence of drug-induced acute renal failure has been changing over the past two decades, increasing from five per cent [1] to 20 per cent and 25 per cent of total patients admitted with acute renal failure in recent publications [2–4]. In order to delineate the spectrum of drug-induced acute renal failure, we conducted a prospective study of patients admitted to French Nephrology Units during a one-year period (April 1983 — April, 1984).

Patients and methods

Fifty-eight Units collaborated in the study. Acute renal failure was defined as a rapid increase in serum creatinine from normal to more than 200μmol/L, or of 50 per cent or more above baseline values for patients with previous chronic renal failure (initial serum creatinine > 150μmol/L). Patients with advanced chronic renal failure were excluded (initial serum creatinine > 300 μmol/L). Oliguria was defined as a urine volume of less than 500ml per day. Fractional excretion of sodium and renal failure index were used in differentiating patients with acute tubular necrosis from those with pre-renal failure [5].
All relevant data were recorded on a standardized inquiry form containing the following information: a) timing of events, drug concentrations, evidence of overdose, effect of stopping and rechallenge; b) renal and extrarenal symptoms and signs of the intoxication; c) biological signs suggesting a hypersensitivity reaction; d) predisposing factors to acute renal failure; e) clinical outcome, including serum creatinine at six months and one-year in patients who did not recover promptly. Using the algorithm of Dangoumou et al [6], only cases with probable or possible side effects to the drug(s) were considered in this study; doubtful cases were excluded.

Results

Drug-associated acute renal failure was recorded in 398 patients (male: 222, female: 176; mean age 56.9±19.9 years), registered in 58 Nephrology Units. This figure represents 18.3 per cent of total patients with acute renal failure hospitalized during the same period. Acute renal failure occurred in a medical setting in 358 patients (89.9%), and in surgical setting in 40 patients.

Drugs

Drugs involved were primarily antibiotics (136 patients, 34.2%). Among these, aminoglycosides accounted for 107 cases, including gentamicin (59), sisomycin (16), netilmicin (11), dibekacin (7), amikacin (4), tobramycin (2), and a combination of two aminoglycosides (8). A cephalosporin was associated in 27 instances, including cephalothin in 12, but it is likely that the aminoglycoside was the main offending agent: excessive or prolonged doses were given in 59 patients, high serum aminoglycoside concentrations were found in 13 patients, and 16 patients developed signs of cochlear and/or vestibular toxicity. More rarely, acute renal failure was related to penicillins (8) with ampicillin in four patients, cephalosporins (7) mainly cephaloridine in four. Other drugs (14) included cotrimoxazole (5), rifampicin (4) and tetracyclines (2). The reason for therapy was septicaeemia (24), acute pneumonitis (24), cutaneous infection (16), pyuria (14), acute bronchitis (8), acute pyelonephritis (6), bacterial endocarditis (5) and various infections. Seventy patients had evidence of sodium depletion, twenty-six had previous chronic renal failure and fifteen had hepatocellular insufficiency.

Glafenin and its derivatives (antrafenin and floctafenin) accounted for 79 cases (19.8%), including 76 for glafenin alone. Acute intoxication was responsible for 52 cases, but acute renal failure followed therapeutic doses of glafenin in 25 cases. Twelve patients took 400 to 4000mg (two to twenty tablets) of glafenin within one to three days; two or more tablets were often taken within a few hours.

Non-steroidal anti-inflammatory drugs were involved in 62 cases (15.6%). The most frequently responsible drugs were clomecin (13), diclofenac (7), indomethacin (6), ketoprofen (5), piroprofen (4), fenoprofen (3), ibuprofen (2) and other non-steroidal anti-inflammatory drugs (6). In 15 instances, two or more non-steroidal anti-inflammatory drugs appeared to be involved.
Contrast media administration accounted for 50 cases (12.6%), following twelve intravenous pyelographies, eleven aortic or renal angiograms, ten non-renal angiograms, six caval or femoral phlebographies, two cholecystographies and nine computed tomographic scans with contrast enhancement or multiple radiological procedures performed over a few days. Thirty-one patients were sodium depleted, twenty patients had diabetes mellitus, nineteen had previous chronic renal failure, five had hepatocellular insufficiency, and two had myeloma.

Diuretic-associated acute renal failure was present in 18 patients (4.5%). Several episodes developed in patients treated with a combination of a thiazide with triamterene (7) and of a thiazide with amiloride (4), or with tienilic acid [3]. Fourteen cases were secondary to chemotherapy administration, including cisplatinum (4) cyclophosphamide (4) and mitomycin (3) alone or in combination. Other drugs involved were captopril with functional acute renal failure (9), paracetamol (5), low molecular weight-dextran (3), colchicine (2), piperazine salts (2), amoxapine (2), allopurinol, pirodoxilate, phenindione + tienilic acid, fenofibrate, chlorpropamide and other drugs, in individual cases.

On the whole, two or more drugs were given in 128 patients (32.2%), and in 33 instances it was not possible to recognize the main responsible agent.

Symptoms and signs

Acute renal failure was oliguric in 175 patients (44.8%), and non-oliguric in 216 patients (55.2%). Non-oliguric acute renal failure was more frequent in glafenin (60.3%) and antibiotic-induced (59.1%) than in contrast-media associated (38.8%). Macroscopic haematuria occurred in 7.3 per cent and heavy proteinuria in 4.6 per cent of total patients, mainly with non-steroidal anti-inflammatory drug-induced acute renal failure (11 of 15 patients). According to clinical, biological and pathological findings acute renal failure could be classified as pre-renal azotaemia (14.5%), acute tubular necrosis (55.8%), acute interstitial nephritis (4.6%) all biopsy-proven, tubular obstruction (1.7%), and vascular nephropathy (1.0%). The type of acute renal failure could not be determined in 22.4 per cent of total patients.

Renal biopsy was done in 81 patients. Renal pathological findings were acute tubular necrosis (42 cases, i.e. 18.9% of total patients with acute tubular necrosis), acute interstitial nephritis (20 cases), minimal changes (3 cases), and thrombotic microangiopathy, vasculitis and tubular obstruction (one case each). Signs of chronic nephropathy were found in 21 patients, associated to acute tubular necrosis or acute interstitial nephritis in eight patients.

Clinical signs, i.e. fever, arthralgias, skin rash and/or hepatocellular damage, biological and/or pathological signs suggestive of a hypersensitivity reaction, were reported in 69 patients, including 20 with biopsy-proven acute interstitial nephritis and six with biopsy-proven acute tubular necrosis. Hypotension was documented in 20, haemolysis in 12 and rhabdomyolysis in 11 patients. A positive basophil degranulation test was found in seven of 12 patients (58.3%), an increase in serum IgE in 38 of 167 (22.8%), a blood eosinophilia in 58 of 344 (16.9%), and circulating immune-complexes in 18 of 163 patients (11%).
Eosinophiluria was found in five of 172 patients (2.9%), none of them having antibiotic-induced acute renal failure. Circulating antibodies to the drug were found in only two of 90 patients.

Predisposing factors

Factors predisposing to acute renal failure included previous diuretic therapy (133), sodium depletion (96), congestive heart failure (85), underlying chronic renal failure (74), diabetes (60), hepatocellular insufficiency (26), hypotension, i.e. blood pressure less than 90/60mmHg (18), and myeloma (6 patients). Decreased renal perfusion, i.e. dehydration, sodium depletion and/or congestive heart failure, was documented in 198 patients. Two or more predisposing factors were present in 255 patients (66%).

Clinical outcome

Haemodialysis and/or peritoneal dialysis was required in 114 patients (28.6%). Further outcome was known in 395 patients. Fifty patients (12.7%) died, 190 recovered fully, 61 with underlying chronic renal failure regained previous renal function, in 92 permanent renal damage remained (23.3%), and two required chronic dialysis.

The mortality rate was higher in patients aged over 60 (17.1%, \(p<0.01\)) than in younger patients, and in patients with a maximum increase in serum creatinine equal to or more than 500\(\mu\)mol/L (16.7%, \(p<0.01\)). Death was more frequently observed in oliguric compared to non-oliguric patients (18%, \(p<0.01\)). The mortality rate was not affected by the presence or the absence of previous chronic renal failure.

Discussion

In our series, the incidence of drug-induced acute renal failure (18.3%) was lower than that found in recent studies, in which the percentage ranged from 20 to 25 per cent [2–4]. In the English literature, the responsible drugs are mainly antibiotics and contrast media, the incidence of the latter being two to six times that registered in French reports [2].

The aminoglycosides are widely used in the treatment of severe infections, and there is no accurate predictive test for nephrotoxicity of these drugs [7]. Aminoglycoside-associated acute renal failure occurred in 107 of our patients, and in 50 per cent of cases, this occurrence seemed not predictable. Close monitoring of aminoglycoside serum concentrations do not avoid an approximately 10 per cent incidence of renal damage in double-blind controlled studies [7]. Considering this pitfall, and the additive risk of ototoxicity, it seems safe to avoid the use of aminoglycoside in patients at high risk, or to correct any predisposing factor before their use; the recommended dosing schedule should then be followed with treatments not exceeding ten to twelve days.
The high incidence of glafenin-induced acute renal failure observed in our series is unknown in the English literature. One-third of cases followed therapeutic (or nearly therapeutic) doses, sometimes in pre-sensitized patients. There is a relatively narrow range between toxic and therapeutic doses, and some cases of acute renal failure would probably be avoided by dividing the intake of glafenin tablets without exceeding an intake of four to six tablets a day.

It is likely that any non-steroidal anti-inflammatory drug may be responsible for acute renal failure, and the number of cases is growing during the past few years [8]. In our series, most patients had taken therapeutic doses of non-steroidal anti-inflammatory drugs. In 26 of 62 instances two to five different drugs were taken, non-steroidal anti-inflammatory drugs included. The interval between the intake of the drug and the onset of renal symptoms ranged from one day to several months, as has already been reported [9]. Two-thirds of our cases had acute tubular necrosis, the remaining patients had acute interstitial nephritis or pre-renal failure.

In many instances, we could hardly decide whether patients had acute tubular necrosis or pre-renal failure, and eight patients with a FENa index below one per cent had a biopsy-proven acute tubular necrosis. In biopsied patients, there was a continuous spectrum between true acute interstitial nephritis and predominant acute tubular necrosis, and in eight patients with acute tubular necrosis the clinical picture suggested an hypersensitivity reaction. It is now known that a given drug may induce either acute interstitial nephritis or acute tubular necrosis, as has been described for rifampicin, cephalosporins or glafenin.

The mortality rate in our series (12.7%) was lower than that reported in other types of acute renal failure [1,3,4], However, the high incidence of renal sequalae (23.3%) was unsuspected, and suggests that drug-induced acute renal failure is an underestimated cause of chronic renal failure. Aged, sodium depleted, and renal hypoperfused patients seem at particularly high risk, and our efforts to prevent drug-induced acute renal failure should be especially directed at these patients.

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References