

A Fatal Case of Triple Whammy in an Elderly Patient

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Abstract

Triple whammy is a drug-induced renal failure which in patients treated with ACE-inhibitors or angiotensin II receptor blockers, diuretics and non-steroidal anti-inflammatory drugs.

We report a case of a 79-year-old woman affected with hypertension, depression and arthritis that was hospitalized for abdominal pain and discharged with normal renal function and with poly-treatment: furosemide, aspirin, carvedilol, omeprazole and ramipril. Few days later she was visited for depressive symptoms, pain in the right shoulder and cystitis and treatment with oral ketoprofen and ciprofloxacin was prescribed.

One week later she experienced loss of appetite, asthenia and swelling of the face. Blood analyses showed acute renal failure, whereas clinical examination showed heart failure and pleural effusion. She was again hospitalized in a geriatric ward for metabolic acidosis. Drug treatments and hemodialysis did not improve clinical conditions and she died thirteen days after her hospitalization.

History suggested the onset of drug-related acute renal failure probably due to the combination of furosemide, ketoprofen and ramipril, defined as triple whammy.

Keywords: Acute renal failure; Diuretic; ACE-inhibitor; NSAID; Drug-interaction

Introduction

Adverse drug reactions (ADRs) represent a common problem during drug treatment [1,2] and may induce organ failure, particularly in the elderly [3,4].

In the elderly, poly-treatment is common in patients with heart failure and hypertension [5] and these drugs may induce the development of pharmacokinetic as well as pharmacodynamic drug-drug interactions [6,7].

Moreover, elderly patients may have chronic inflammatory diseases or chronic non cancer pain, so a treatment with a non-steroidal anti-inflammatory drug (NSAID) might be indicated [8-11].

The combination of an angiotensin converting enzyme-inhibitor (ACEI) or an angiotensin II receptor blocker (ARB), a diuretic and a NSAID may increase the risk of acute kidney injury, called triple whammy, because each drug is able to affect kidney function through different mechanisms [12,13]. In particular, diuretics can lead to hypovolaemia, ACE-inhibitors/ARBs cause haemodynamic decrease

of glomerular filtration rate due to efferent arteriolar vasodilation, and NSAIDs inhibit prostacyclin synthesis (thus leading to renal afferent arteriolar vasoconstriction) [14-16].

In this paper we report a case of fatal acute kidney injury in an elderly poly-treated woman.

Case Report

A 79-year-old woman with history of hypertension, depression and arthritis was hospitalized for abdominal pain and discharged with normal renal function (serum creatinine=0.82 mg/dL, normal values 0.7-1.2 mg/dL; Chronic Kidney Disease Epidemiology Collaboration: 84.1 mL/min, normal values >60 mL/min) and with the following pharmacological treatment: furosemide (25 mg/day), aspirin (100 mg/day), carvedilol (12.5 mg/day), omeprazole (20 mg/day) and ramipril (5 mg/day). Few days later she was visited at home for the worsening of depressive symptoms, pain in the right shoulder and cystitis and treatment with oral ketoprofen (160 mg/day) and ciprofloxacin (250 mg bid) was prescribed.

About one week later she experienced loss of appetite, asthenia and swelling of the face, therefore she was hospitalized. Clinical examination showed heart failure and pleural effusion while blood

chemical analyses showed acute renal failure (creatinine 5.6 mg/dL) and metabolic acidosis (pH=6.1, normal values: 7.35-7.45; PaCO₂=39 mmHg, normal values: 35-45; HCO₃=18 mEq/L, normal range: 22-26). Bicarbonate administration and hemodialysis did not improve the clinical conditions and the patient died thirteen days later.

Discussion

We described a case of drug-related acute renal failure, defined as *triple whammy*, in an elderly woman, related to drug drug-interaction induced by inappropriate prescription.

Inappropriate prescription is the use of drugs with risks greater than the possible benefits, inappropriate dosing duration, prescriptions that lead to clinically significant drug-drug and drug-disease interactions, and the underuse of potentially beneficial medications [17-19].

In particular, inappropriate prescription seems to be common in the elderly with a prevalence of 40%-50% among nursing home residents [20], and 19%-28% among community dwelling patients [21,22].

In our case report, the patient was treated with ramipril (ACE-inhibitor) and furosemide (diuretic) for hypertension with a good control of symptoms and without the development of renal failure.

Recently, Lapi et al. [13] documented an overall increased risk of acute kidney injury with a triple therapy combination but not with a double therapy combination in a retrospective study evaluating 487,372 patients. In fact, during the treatment with diuretics and NSAIDs (without an ACEI or an ARB), despite a reduction in renal blood flow (caused by diuretics) and the presence of renal afferent arteriolar constriction, glomerular filtration is probably maintained as a result of the effect of angiotensin II mediated efferent arteriolar vasoconstriction and sodium retention [23-25]. On the other hand, among patients taking ACEIs or ARBs and NSAIDs (without a diuretic), the afferent vaso constrictive stimulus induced by the NSAIDs through the inhibition of prostacyclin synthesis is probably insufficient to substantially increase the risk of acute kidney injury in the presence of a normal extracellular fluid volume and preserved renal blood flow.

In our case report, the development of pain induced a new clinical evaluation and a prescription of ketoprofen (NSAID). NSAIDs are very dangerous and potentially harmful when co-administered with ACEIs or diuretics; in fact, the patient developed fatal acute renal failure about one week after the NSAID administration.

The mechanisms of renal failure could be related to an early and severe deteriorating effect of the NSAID in our patient, concomitantly treated with ACEI and furosemide; as above reported it is also dependent on the blockade of prostacyclin synthesis, which play a crucial role for maintaining renal function. In fact, acute renal failure or acute kidney injury can occur in patients with underlying volume depletion or ineffective blood volume, in those with preexisting renal insufficiency, and of course, in the elderly [26].

A cross-sectional study involving patients admitted to a teaching hospital general medical ward has specifically documented an increased risk of acute kidney injury associated with the concomitant use of diuretics, ACE inhibitors and NSAIDs [12].

However, must be remembering that at home the patient received a treatment with ciprofloxacin and we can't exclude a role of

ciprofloxacin in the severe worsening of symptoms. In fact several papers have documented an association between ciprofloxacin and nephrotoxicity [27,28], therefore in our patient ciprofloxacin treatment may have played a role in the fatal impairment of clinical conditions.

Furthermore, it is conceivable that this serious impairment of clinical function has induced a cardiorenal syndrome, with the development of severe heart failure responsible for the death.

Take together these data, we think that drug-drug interaction induced a clinical impairment that, precipitated by ciprofloxacin administration, induced a severe cardio renal syndrome with severe severe heart failure and death.

However, we have not able to demonstrate this because we have not data of heart function at the time of clinical impairment (before the exacerbation: ejection fraction 68%).

Conclusions

In conclusion, our case report shows that doctors may take attention during the treatment of elderly patients. An accurate pharmacological analysis needs to be always performed before the prescription of a new drug, in order to avoid the development of potentially fatal drug interactions. Finally, we must emphasize the need for increased clinical monitoring of poly-treated patients, in order to perform an early recognition and treatment of adverse reactions.

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