Case Report

Beware of Triple Whammy

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Article Info

Received date: 18 Nov 2021
Accepted date: 10 May 2022
Published date: 30 Jun 2022

Keywords: Acute renal failure; diuretic; RAAS; NSAID; triple whammy.

ABSTRACT

The term “triple whammy” refers to a drug interaction following the concurrent use of angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers, diuretics and non-steroidal anti-inflammatory drugs, the combination of which greatly increases the odds of acute kidney injury. Here, we report a case of a 66-year-old gentleman who was admitted into a tertiary care hospital for elective orthopaedic intervention. He had previously been prescribed sacubitril/valsartan and frusemide and had newly been started on celecoxib during hospitalisation. Upon the initiation of celecoxib, a mild increase in his serum creatinine was immediately observed, and this occurrence is believed to be due to the “triple whammy” combination. The combination of perindopril, frusemide and celecoxib continued to be overlooked throughout his hospitalisation. He was subsequently planned to be discharged with celecoxib on top of his existing chronic medications. However, upon discharge, the dispensing pharmacist took notice of the drug interaction and successfully intervened to withhold celecoxib.

INTRODUCTION

“Triple whammy” refers to a drug interaction following the concurrent use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-II receptor blockers (ARB), diuretics and non-steroidal anti-inflammatory drugs (NSAID). Individually, they pose a relatively small risk of acute kidney injury (AKI), but in combination, the risk increases substantially [1].

The combined use of NSAID, diuretics and ACEIs or ARBs can potentiate AKI due to their compounding effects on reduced renal blood flow and glomerular filtration rate. Individually, ACEIs and ARBs inhibit angiotensin II-mediated efferent arteriolar vasoconstriction, whilst NSAID inhibits prostaglandin-mediated afferent arteriolar vasodilation, both of which are capable of reducing blood flow to the kidney. Diuretics act by increasing the excretion of water and sodium from the body, decreasing the plasma volume. This plasma volume reduction, when occurring in tandem with a reduced blood flow through the use of both ACEIs or ARBs and NSAIDs in combination, could increase the risk of AKI [1,2].

In this paper, we report a case of an overlooked triple whammy in an inpatient setting.

CASE DESCRIPTION

A 66-year-old gentleman was referred for hospital admission from an orthopaedic clinic for wound debridement and ray amputation of the big toe and third toe of his left leg. Foot examination in the clinic revealed a non-infected wound of the left foot with dry gangrene at the big and third toes.

The baseline laboratory investigations at the clinic were as follows: white blood cell count 7.1 x 10⁹ / L, haemoglobin 14 g / dL, platelet 342 x 10⁹ / L, urea 7.4 mmol / L, sodium 138 mmol / L, potassium 5.42 mmol / L, chloride 106 mmol / L and creatinine 105 μmol / L. The patient’s coagulation profile was normal, and his body temperature reading was normal at 37°C. In terms of cardiovascular parameters, his systolic blood pressure was 107 mmHg, with a diastolic blood pressure of 65 mmHg, and a pulse rate of 59 beats per minute. His respiratory rate was 20 breaths per minute, with SpO2 of 100% under room air. Furthermore, he had a pain score of 1 out of 10, a capillary

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blood glucose level of 9.6 mmol/L and a mean arterial pressure of 79.

He had a documented medical history of type 2 diabetes mellitus, hypertension, bronchial asthma, myocardial infarction, and bilateral peripheral vascular disease. Meanwhile, his medication history included dual anti-platelets, simvastatin, sacubitril/valsartan, trimetazidine, frusemide, bisoprolol, isosorbide mononitrate, empagliflozin, sublingual glyceryl trinitrate and insulins. However, the prescriber had been unaware of his medication history and only continued aspirin (100mg, once daily), frusemide (40mg, once daily), insulin (short-acting, 16IU, three times daily), insulin (intermediate-acting, 16IU, at night), perindopril (2mg, once daily) and atorvastatin (40mg, once daily) in the ward. Meanwhile, intravenous amoxicillin plus clavulanate (1200mg, three times daily), paracetamol (1000mg, four times daily) and celecoxib (200mg, when required) were also started as prophylactic antibiotic and analgesics. Wound debridement and ray amputation were performed on the second day of admission with no complications.

On the first day of admission, he developed hyperkalaemia (potassium 6.31 mmol/L) along with a mild increase in serum creatinine from 105 to 121 µmol/L after just a single dose of celecoxib. A lytic cocktail was given, and consequently, his potassium was reduced to 4.43 mmol/L.

The mild AKI had gone unnoticed until the third day of admission during a morning review by the specialist. The specialist reportedly ordered that an urgent renal profile be obtained, which came back with the following results: urea 8.4 mmol/L, sodium 135 mmol/L, potassium 4.29 mmol/L, chloride 102 mmol/L and creatinine 108 µmol/L. A total of three doses of celecoxib had been given throughout the hospitalisation.

During his admission, he had also developed episodes of hypertension urgency, with recorded systolic blood pressure readings being in the range of 190 to 195 mmHg. To alleviate this issue, short-acting antihypertensives were given immediately. In the process, the inadvertent omission of the patient’s antihypertensives (bisoprolol, sacubitril / valsartan, isosorbide mononitrate) remained unnoticed. On the third day of admission, it was noted that the patient had one episode of hypoglycaemia due to a missed meal after the insulin injection at night. Insulin was then withheld in the morning that followed but restarted at a lower dose at midday since the patient’s glucose level rose to 12.8 mmol/L before lunch.

The patient was discharged on the fourth day of admission in an afibrile state with the following oral medications: amoxicillin plus clavulanate, celecoxib and paracetamol. The dispensing pharmacist noticed the triple whammy combination and intervened. The intervention was agreed upon by the prescriber, and celecoxib was withheld.

**DISCUSSION**

The term “triple whammy” was first coined by Merlin C Thomas in 2000 following the observation that two patients demonstrated signs of kidney injury following the concurrent use of ACEIs or ARB, diuretics and NSAID. In a literal sense, “triple whammy” bears the meaning of three simultaneous, deleterious blows with a compounded effect [2]. Since the establishment of the term, similar reports of “triple whammy” had appeared worldwide involving a reduced creatinine clearance in patients taking the three medicines together [3,4,5,6], with fatality rates allegedly being as high as 10%, as reported by the Australian Adverse Drug Reactions Advisory Committee (ADRAC) [6]. Several risk factors for renal failure in “triple whammy” cases were identified, including old age, chronic kidney disease, dehydration, digoxin toxicity, acute illness and the recent addition of an NSAID to the existing ACEI/ARB and diuretics regimen [7].

The prevalence of detected “triple whammy” occurrences in Malaysia is 0.5% [8], which is a figure that corresponds to findings from New Zealand (0.2%) [9] and Japan (0.3%) [10]. Despite the relatively low prevalence, “triple whammy” drugs (when used individually or in combination) are involved in over 50% of cases involving iatrogenic AKI reported to the ADRAC [6]. Moreover, a previous survey conducted at a government-funded district hospital located in the central part of Klang Valley, Malaysia found that 40.1% of outpatient prescriptions contained both ACEIs and diuretics [8]. This suggests the possibility that undetected “triple whammy” cases may be higher than anticipated, especially since the availability and widespread use of NSAIDs for pain or fever, particularly without appropriate screening, can potentially place patients who are on antihypertensives such as ACEi, ARB and diuretics at risk of AKI following its use.

At the point of writing, available evidence does not suggest that a particular NSAID is more beneficial than another in terms of posing a lesser risk for AKI. All NSAIDs pose a risk to renal failure following both short-term (adjusted odds ratio, OR 1.82; 95% CI 1.68 - 1.98) and long-term usage (adjusted OR 1.86; 95% CI 1.72 - 2.01) [11]. Of all the NSAIDs, ibuprofen (adjusted OR 1.69; 95% CI 1.35 - 2.11), indomethacin (adjusted OR 2.15; 95% CI 1.66 - 2.78) and sulindac (adjusted OR 1.85; 95% CI 1.06 - 3.24) are found to be more likely to result in AKI as compared to celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor [12]. Although several observational studies had concluded that celecoxib outperformed non-selective NSAIDs [11,12,13,14] with regards to AKI risks, the risk difference across NSAIDs was not statistically significant, and with overlapping confidence
Cheah H.M. and Islahudin F.H.

In intervals. In fact, compared to non-NSAID users, a celecoxib-user is associated with adjusted odds 1.54 (95% CI 1.14 - 2.09), meloxicam-user with adjusted odds 2.5 (95% CI 1.73 - 3.08), naproxen-user with adjusted odds 2.42 (95% CI 1.52 - 3.85), rofecoxib-user with adjusted odds 2.31 (95% CI 1.73 - 3.08) and users of other non-selective COX inhibitors with adjusted odds 2.3 (95% CI 1.6 - 3.32). [13]. In addition, care should also be exercised when interpreting the results as misclassification bias might follow with the use of prescription database analysis since the usage of over-the-counter medications cannot be identified. Therefore, there is no conclusive evidence pointing towards the superiority of one NSAID over the other class in terms of selectivity or duration of action.

With regards to the case reported in this study, the patient showed an acute increase in creatinine level, but the increment did not fulfil the requisite level to be defined as an incident of AKI, with respect to definitions set by the Risk, Injury, Failure, Loss, End-Stage (RIFLE) criteria, the Acute Kidney Injury Network (AKIN) or the Kidney Disease Improving Global Outcomes (KDIGO). The 15.2% increase in serum creatinine was probably attributed to the ingestion of “triple whammy” combination, which may have been exacerbated by his underlying heart failure as another risk factor for AKI. Fortunately, however, his serum creatinine readings recovered to his baseline serum creatinine after two days, coinciding with the withdrawal of celecoxib from the regime. Despite this, it cannot be doubted that the combination of “triple whammy” drugs presents an independent risk factor for AKI [2,3,5,10]. Therefore, in more unfortunate situations as far as the currently reported case is concerned, such as if a slight change in haemodynamic parameters were to occur (such as in hypoperfusion), a full-blown lethal complication could have ensued. In fact, Lapi et al. demonstrated that a “triple whammy” combination could increase the risk of AKI by 31%, with the highest risk of AKI occurrence being within 30 days after the commencement of the combination therapy [15].

Patients above 65 years of age, such as in this case, are especially susceptible to this drug interaction. In fact, it has been found that, of all the outpatient prescriptions with a combination of ACEI and diuretics, 21.7% of them consist of elderly patients. [8]. Moreover, common chronic medical illnesses such as chronic kidney disease, type 2 diabetes mellitus, hypertension, heart failure and arthritis are more prevalent with increasing age. Unsurprisingly, people with one or more of the above medical conditions are more likely to take one or all the “triple whammy” medicines. Elderly patients are also noted to have less-than-sufficient renal function, which could also predispose them to an increased risk of AKI [16].

In this case, the patient is treated with ACEIs or ARB for their renal and cardio-protective effects, likely on account of his diabetes and prior history of myocardial infarction. Steps should be taken to review the use of furosemide and celecoxib. Since the patient’s reported pain score at discharge was 1 to 2 (from a scale of 10), which was by no means high, the use of celecoxib was brought into question for this case, prompting the pharmacist to suggest paracetamol as a maintenance therapy to replace celecoxib. Meanwhile, furosemide was left intact until his next visit to the cardiologist to reassess its necessity.

A few other steps could have been taken to improve pharmaceutical care in this case. Firstly, the hypertensive episodes observed in this patient could have been avoided if his pre-admission antihypertensives were reinstated in a timely manner. Furthermore, pharmacists should record the medication history of patients within 24 hours of admission. The complete medication history should also be made available for all healthcare professionals to ensure a smooth transition of care. The “triple whammy” combination, as it occurs in this case, could have been avoided if more careful attention is given by pharmacists on the patient’s medical records. Finally, the patient’s insulin therapy should be given more emphasis, and his meals should be given more attention in order to avoid hypoglycaemia following a reduction in oral intake during hospitalisation.

CONCLUSION

In conclusion, pharmacists play a significant role in patient care as medication experts and the guardian of medication safety. Pharmacists should always pay attention to ensure that medications are screened on admission, during hospitalisation and on discharge to ascertain the appropriateness of medications in each stage. This could aid in reducing drug interactions and adverse reactions, while also allowing for the provision of appropriate advice to prescribers in order to reduce risk of potential pitfalls and prevent medication misadventure.

ACKNOWLEDGEMENT

We would like to thank the Director General of Health Malaysia for the permission to publish this article.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare. This research did not receive any specific grant from funding agencies in public, commercial or not-for-profit sectors.

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Cheah H.M. and Islahudin F.H.

Mal J Pharm 8 (1) 2022, 38-41


