

ADVERSE DRUG INTERACTION BETWEEN ASPIRIN AND FUROSEMIDE: A CASE REPORT

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ABSTRACT

Drug–drug interaction between two drugs leads to a serious adverse drug reaction which is an adverse drug interaction. A 60-year-old female patient came with complaints of chest pain since 6 pm on the day of admission which is a burning type of pain and also a history of breathlessness. She was a known case of hypertension and diabetes mellitus since 5 years on medications, i.e. tablet atenolol-5 mg - 1-0-0, tablet amlodipine - 5 mg - 1-0-0, and tablet metformin - 500 mg - 1-0-1; the patient's appetite was reduced and sleep was disturbed. On examination, blood pressure was 120/100 mmHg, pulse rate: 80 bpm, SpO₂: 94% with room air, respiratory system: B/L coarse crepitation (+), and pallor (+) remaining systemic examination showing no any deformities. Laboratory reports show microcytic hypochromic with neutrophilia and thrombocytosis and ultrasonography (USG): B/L Grade I renal parenchymal disease. The patient treated with the following mentioned medication during his hospital stay. both the drugs injection calcium gluconate and asthalin nebulization were given on 3rd day of admission. The patient diagnosed as chronic kidney disease in the middle of the treatment which was adverse reaction interaction between aspirin and furosemide.

Keywords: Hypertension, Diabetes mellitus, Microcytic, Hypochromic, Neutrophilia, Thrombocytosis, Renal parenchymal disease, Nephrotoxicity, Interactions.

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INTRODUCTION

Aspirin may reduce the diuretic effect of bumetanide, furosemide, or piretanide and reduce the venodilation produced by furosemide. The combination of aspirin and furosemide may increase the risk of acute renal failure and salicylate toxicity. The risk of ototoxicity with high doses of salicylates may theoretically be increased by loop diuretics [1]. Furosemide is a strong diuretic but a weaker antihypertensive than thiazides: Fall in blood pressure (BP) is entirely dependent on reduction in plasma volume and cardiac output (C.O). The natriuretic action lasting only 4-6 hours after the conventional morning dose is followed by compensatory increase in proximal tubular reabsorption of Na⁺. Intravenous furosemide causes a prompt increase in systemic venous capacitance and decreases left ventricular (LV) filling pressure, even before the saluretic response is apparent. This action also appears to be PG mediated and is responsible for the quick relief it affords in LV failure and pulmonary edema. Moreover, the high ceiling diuretics are more liable to cause fluid and electrolyte imbalance, weakness, and other side effects.

Aspirin is the first drug to be used in all cases; other drugs are added or substituted only when it fails or in severe cases. Aspirin is a weaker analgesic (had lower maximal efficacy) than morphine type drugs: aspirin 600 mg~codeine 60 mg. However, it effectively relieves inflammatory, tissue injury-related, connective tissue, and integumental pain but is relatively ineffective in severe visceral and ischemic pain. Anti-inflammatory action is exerted at high doses (3–6 g/day or 100 mg/kg/day). Aspirin has no direct effect on the heart or blood vessels in therapeutic doses. Larger doses increase cardiac output to meet the increased peripheral O₂ demand and cause direct vasodilatation. Toxic doses depress vasomotor center: BP may fall. Because of increased cardiac work as well as Na⁺ and water retention, congestive heart failure may be precipitated in patients with low cardiac reserve. The plasma t_{1/2} of aspirin as such is 15–20 min, but taken together with that of released salicylic acid, it is 3-5 hours. However, t_{1/2} of anti-inflammatory doses may be 8-12 hours while that during poisoning may be as high as 30 hours.

Adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs)

- Renal: Na⁺ and water retention, chronic renal failure, nephropathy, and papillary necrosis (rare)
- Hematological bleeding, thrombocytopenia, hemolytic anemia, and agranulocytosis [2].

CASE REPORT

A 60-year-old female patient admitted to the female general medicine ward with the complaints of chest pain since 6 pm, and she was apparently well 1 day back then given a history of chest pain since 6 pm which is a burning type of pain and also a history of breathlessness since 6 pm. The patient's appetite was reduced and sleep was disturbed. She is known case of (k/c/o) hypertension and diabetes mellitus since 5 years on medications, i.e., tablet atenolol - 5 mg (1-0-0), tablet amlodipine - 5 mg (1-0-0), and tablet metformin - 500 mg (1-0-1).

On examination, the patient was conscious and oriented, the patient consent was received, and the patient's BP was 120/100 mmHg, pulse - 80 bpm, SpO₂ - 94% under room air, and RS-B/L coarse crepitation (+). The laboratory data are as follows:

- Electrocardiogram: ST depression in II, V₄, V₅, and V₆ with T-wave inversion suspected in the same lead, left ventricular strain pattern
- USG: B/L Grade I renal parenchymal disease
- Peripheral smear report: Normocytic hypochromic to microcytic picture with neutrophilia and thrombocytosis (Table 1).

On the assessment of both subjective and objective evidence, the patient was diagnosed as "acute left ventricular failure, ischemic heart disease with old hypertension, and type 2 diabetes mellitus."

The patient was treated with the following medications, It is the treatment when patient admitted in the hospital. Continuous BP was monitored on the 1st, 2nd, and 3rd days (Table 2). Day 2 examination shows pulse rate (PR) - 93 bpm, BP - 136/80 mmHg, and SpO₂ - 96% under room air; day 3 examination shows PR - 94 bpm, BP - 100/70 mmHg, and SpO₂ - 97% under room air; day 4 examination shows PR - 80 bpm and BP - 126/70 mmHg; day 5 examination shows PR - 76 bpm and BP - 118/70 mmHg.

Table 1: Laboratory data

Parameter	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
WBC	36,300	33,300		26,500	24,400	11,000
Polymorphs	60%	89%		88%	88%	75%
Lymphocytes	38%	06%		11%	12%	25%
Platelets	7.58 L/cumm	6.74 L/cumm		6.46 L/cumm	6.21 L/cumm	6 L/cumm
MCV	74 fl	83.7 fl		75 fl	74 fl	74.2 fl
MCH	26 pg/cells	26.7 pg/cells		25.6 pg/cells	25.4 pg/cells	25.2 pg/c
MCHC	35 g/dl	34.9 g/dl		34.1 g/dl	34.0 g/dl	33.2 g/dl
Sodium	133 mEq/L	108 mEq/L	138 mEq/L	116 mEq/L	113 mEq/L	
Potassium	3.6 mEq/L	6.0 mEq/L	3.5 mEq/L	5.8 mEq/L	5.3 mEq/L	
Chloride	100 mEq/L	81 mEq/L	102 mEq/L	84 mEq/L	87 mEq/L	
Serum creatinine	1.6 mg/dl	1.7 mg/dl	1.7 mg/dl	1.6 mg/dl	1.6 mg/dl	1.6 mg/dl
Serum urea	55 mg/dl	64 mg/dl	67 mg/dl	55 mg/dl	32 mg/dl	50 mg/dl

WBC: White blood cell, MCH: Mean corpuscular hemoglobin, MCV: Mean corpuscular volume, MCHC: Mean corpuscular hemoglobin concentration

DISCUSSION

Various large epidemiological studies and meta-analyses of clinical studies have been conducted to assess the effects of NSAIDs on BP in patients taking antihypertensive. A cross-sectional cohort study (1993) conducted in 2800 elderly patients those taking both NSAIDs and antihypertensive has shown 29% increased risk of hypertension than those taking antihypertensives [1]. Furosemide has been used as an effort to try to minimize the risk of contrast-induced nephropathy. Although the results for the studies showing that furosemide use for the prevention of acute kidney injury (AKI) is inconclusive [3], Marenzi *et al.* in a prospective randomized trial showed a significantly lower incidence of AKI in patients treated with hydration and furosemide versus those treated with hydration alone [4]. In our study, the patient was diagnosed with "acute LV failure, ischemic heart disease with old hypertension, and type 2 diabetes mellitus." She had been treated with aspirin, clopidogrel, atorvastatin, furosemide, nitroglycerin, pantoprazole, heparin, insulin R, enalapril, amlodipine, and calcium gluconate and nebulizer asthalin. There are 6 major interactions, of which 4 moderate interactions have been found among the prescribed drugs using Micromedex software.

Major interactions

- Amlodipine ⇌ Clopidogrel: Concurrent use of amlodipine and clopidogrel may result in decreased antiplatelet effect and increased risk of thrombotic events.
- Aspirin ⇌ Furosemide: Concurrent use of loop diuretics and NSAIDs may result in reduced diuretic effectiveness and possible nephrotoxicity.
- Clopidogrel ⇌ Aspirin: Concurrent use of aspirin and clopidogrel may result in an increased risk of bleeding.
- Clopidogrel ⇌ Heparin: Concurrent use of anticoagulants and antiplatelet agents may result in increased risk of bleeding.
- Heparin ⇌ Aspirin: Concurrent use of anticoagulants and antiplatelet agents may result in increased risk of bleeding.
- Nitroglycerin ⇌ Heparin: Concurrent use of heparin and nitroglycerin may result in a decreased partial thromboplastin time.

Moderate interactions

- Nitroglycerin ⇌ Aspirin: Concurrent use of aspirin and nitroglycerin may result in an increased in nitroglycerin concentrations and additive platelet function depression.
- Aspirin ⇌ Insulin R: Concurrent use of insulin/pramlintide and salicylates may result in increased risk of hypoglycemia.
- Enalapril ⇌ Insulin: Concurrent use of ACE inhibitors and antidiabetic agents may result in increased risk of hypoglycemia.
- Enalapril ⇌ Furosemide: Concurrent use of ACE inhibitors and loop diuretics may result in postural hypotension [5].

The patient was taking aspirin and furosemide all the 6 days of the treatment, and the concurrent use of these two drugs causes possible nephrotoxicity where the patient was diagnosed as Grade I

Table 2: Blood pressure monitoring chart

Date	Time	Blood pressure	Pulse rate
September 02, 18 (day 1)	8:45 pm	180/90 mmHg	86 bpm
	10:00 pm	190/100 mmHg	80 bpm
	2:00 am	170/90 mmHg	84 bpm
September 03, 18 (day 2)	5:00 am	140/86 mmHg	84 bpm
	8:00 am	130/86 mmHg	82 bpm
	9:00 am	140/80 mmHg	82 bpm
	11:00 am	130/86 mmHg	86 bpm
September 04, 18 (day 3)	2:00 pm	140/80 mmHg	86 bpm
	9:00 pm	100/70 mmHg	
	10:00 pm	106/70 mmHg	
	11:00 pm	110/70 mmHg	
	12:00 am	110/68 mmHg	
	1:00 am	106/70 mmHg	
	2:00 am	110/70 mmHg	
	3:00 am	106/70 mmHg	
	4:00 am	110/70 mmHg	
	5:00 am	100/70 mmHg	
	6:00 am	98/70 mmHg	
	7:00 am	98/66 mmHg	
	8:00 am	100/68 mmHg	

renal parenchymal disease in the middle of the treatment, which was a suspected adverse drug interaction between the drugs. In addition, the progression of CKD may lead to the increased number of medications taken by patients to manage the complications and the comorbidities and subsequently increase the prevalence of Drug Related Problems (DRPs). DRP is defined as "an event occurring, as a result, the drug therapy that actually or potentially interferes with desired health outcomes" [6]. The leading factors of kidney failure are undiagnosed or uncontrolled BP, diabetes mellitus, irrational use of painkillers, improper diet, and environmental stress. According to recently carried out clinical studies, earlier diagnosis and treatment of hypertensive patients with incipient renal failure could result in more effective control of BP and therefore earlier detection and treatment of atheromatous progression toward end-stage renal disease [7]. Even the patient was given tablet enalapril 2.5 mg orally for two times, i.e., on the 2nd and 3rd days and stopped on the 4th day due to decrease of BP, and after stopping the drug, the patient's BP (5th day) has improved to 126/70 mmHg from 98/66 mmHg and 100/68 mmHg. A study in healthy subjects given single doses of enalapril and furosemide found no evidence of any pharmacokinetic interaction between these drugs. The risk of first-dose hypotension can be reduced by starting low dose of ACE inhibitors. In a study, 8 patients with hypertension who had been taking a diuretic (mainly furosemide or hydrochlorothiazide) for at least 4 weeks, captopril was started in small, increasing doses, from 6.25 mg. Symptomatic postural hypotension was seen in 2 of the 8 patients, but it was mild and transient [1].

CONCLUSION

Aspirin may compete with furosemide for a common secretory mechanism in the proximal tubule. In addition, aspirin may also inhibit renal prostaglandins which appear to mediate the increased renal blood flow induced by loop diuretics in cirrhotic with ascites. An interaction between aspirin and loop diuretics, which results in an attenuation of the diuretic effect, is established; however, the clinical relevance of this effect does not appear to have been studied. Nevertheless, the reduction in diuretic effects seen in the studies might reasonably be expected to lead to a worsening of the condition being treated with the loop diuretic. The UK manufacturer of furosemide warns that aspirin may attenuate the action of furosemide and may cause acute renal failure in cases of pre-existing hypovolemia or dehydration. It would, therefore, seem prudent to avoid the use of high-dose salicylates in those taking loop diuretics, giving an alternative non-NSAID analgesic wherever possible. Close monitoring of signs of reduced diuretic effect and signs of renal impairment is necessary in case of concurrent administration of aspirin and furosemide. In such cases, either reconsidering use of salicylate or diuretic dose adjustment is suggested [1].

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AUTHORS' CONTRIBUTIONS

Gundeti Kavya Reddy: Concept, informed consent, laboratory investigations, laboratory report interpretation, patient evaluation,

examination of patients on follow-up, drafting final report, and publication.

Nisi Grace Kuriakose: Concept, design, master file of project and evaluating patients' file, laboratory investigations, laboratory report interpretation, drafting final report, and publication.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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