## **Case Report**

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20211277

# Acute kidney injury and severe septicemia: toll of over-the-counter availability of drugs

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Received: 22 January 2021 Accepted: 02 March 2021

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### **ABSTRACT**

Non-steroidal anti-inflammatory drugs (NSAIDs) act mainly on peripheral pain mechanisms and on the central nervous system to raise the pain threshold. Their usage is widespread and many of these drugs are available over-the-counter (OTC) and hence self-medicated and abused. Drugs and Cosmetics Act is quiescent on this issue. Literature review has shown that, nimesulide, a preferential COX-2 inhibitor group of NSAID is notorious to produce hepatic and renal damage besides gastric mucosal injury which surpass its benefits. Here a case has been reported on life-threatening condition faced on cumulative over-consumption of this OTC drug. A young female was admitted with sudden onset of abdominal pain, fever and vomiting. On examination, findings were almost within normal limit whether laboratory investigation over 2 successive days of admission revealed hyponatraemia, hypokalaemia, severe anaemia, deranged renal and liver function tests, nephrolithiasis in USG and sepsis without detection of any septic foci. The patient was managed conservatively with broad spectrum antibiotics besides supportive management. Nephrological and surgical consultation was taken alongwith. Upon being ambulatory and parameters on reaching to normal value, the patient was discharged following fortnight of hospitalization. Easy accessibility of OTC drugs even at online pharmacy is increasing the burden of iatrogenic ill-health to a great extent. If necessary steps are implemented for appropriate self-medication by Central Drugs Standard Control Organization (CDSCO) that might save Disability Adjusted Life Years (DALYs), health resources and thousands of lives.

Keywords: Case report, NSAID, Nimesulide, Over-the-counter, Self-medication

#### **INTRODUCTION**

India Today reported on 15th of February 2011 that, GOI has banned the use of Nimesulide, which is very commonly used for treatment of fever and pain in almost all the age groups. The decision was taken by Union health ministry after experts on the Drug Technical Advisory Board as the said drug causes hepatic failure. At that time, the drug was strictly prohibited from sale, distribution and manufacture of its pediatric formulation and there were demands for banning of its adult preparation also like as for the different developed countries. But to a great

despair, the drug is still available as over-the-counter besides being ordered in different online drug procurement systems.

Nimesulide, a NSAID, sub-categorized as a preferential COX-2 inhibitor. The reported adverse effects of this drug are gastrointestinal, dermatological and central besides fulminant liver failure among children.<sup>1</sup>

This drug is extensively metabolized and excreted mainly in urine with its t ½ being 2-5 hours. On literature review, acute kidney injury (AKI) have been reported following

this drug abuse but no case have been found to report on this drug induced nephrolithiasis, and/or septicaemia.

#### **CASE REPORT**

A 37-year old female patient was admitted in the hospital with complaint of sudden onset of upper abdominal pain associated with fever, on and off for one day. The fever showed no periodicity, high in nature (temperature was not recorded at home), remitted on intake of paracetamol 650 mg on s.o.s. basis without any medical consultation. She started vomiting, which was projectile in nature since the morning of day of admission. Neither any significant past medical or surgical history nor any epidemiological

context was found. She stated to develop anorexia and easy fatigability for last 3-5 days. In personal history, she stated herself as non-smoker and non-alcoholic. One striking thing in her statement was that she was taking tablet nimesulide for chronic body ache for last few years without any prescription at no fixed dose, and number of tablets varying from 4 tablets on regular basis and, 16 tablets at its maximum in a day. She stated, "one day I took one entire strip containing 15 tablets and also 1 tablet from next strip throughout the day". She was extensively investigated for collagen vascular diseases years back without any positive findings. No significant family history could be elicited except for her mother, who was a hypertensive died from myocardial infarction years back.

Table 1: Investigations done for the patient serially.

Days of investigation (s)	At presentation 1 <sup>st</sup> day	Nimesulide stopped 3 <sup>rd</sup> day	5 <sup>th</sup> day	8 <sup>th</sup> day	11 <sup>th</sup> day	14 <sup>th</sup> day	16 <sup>th</sup> day
BUN (mg/dl)	43.8	41.1	40.1	40.6	33.15	16.8	8.87
Serum creatinine (mg/dl)	7.8	5.71	4.76	4.14	3.17	1.84	1.23
Serum Na (mmol/l)	129	132	133	136	137	136	136
Serum K (mmol/l)	2.9	2.9	3.0	2.9	3.0	3.1	3.3
C-reactive protein (mg/l)	194	132	72	64	50	34	12

On admission, patient was hemodynamically stable, pulse 100/minute, B.P. 110/70, temperature 102 degree Fahrenheit, CBG 82 mg/dl, some dehydration was present, no systemic abnormality was elicited except for mild tenderness over the epigastric region on palpation.

Laboratory result initially was as follows: Hb was 6.9 g/dl, RBC count 3.76 million/cmm, PCV 27.6%, MCV 73.4 fl, MCH 25.5 pg, TLC 12,000/cmm, ESR 110 mm/1st hour, C-reactive protein 194 mg/l, BUN 43.8 mg/dl, Na 129 mmol/L, K 2.9 mmol/l, Creatinine 7.8 mg/dl, creatinine clearance (CrCl) as 52 ml/min, estimated GFR (eGFR) was calculated as 5.6 ml/min./1.73m², serum Bilirubin 1.51 mg/dl (direct-1.19 mg/dl), total protein 4.5 g/dl, albumin 2.2 g/dl. Resting ECG showed RBBB, LVH and anterior wall ischaemia and ABG showed metabolic acidosis with respiratory compensation going into alkalosis (Table 1 shows laboratory parameters over time).

Blood testing for Malaria antigens, dengue, serological testing for hepatitis and chest X-ray did not show any abnormality. Urine and stool routine examination were also within normal limits.

On the next day following admission, ultrasonography of whole abdomen was done and it was found to detect hepatomegaly, sludge in gall bladder and left sided nephrolithiasis. (Figure 1)

The blood culture detected growth of Escherichia coli after 48 hours of incubation in Fluorescence detection method

with help of the BD BACTEC culture vials (BACTEC FX40).

From the CrCl, on calculation of GFR, patient was provisionally diagnosed to have chronic kidney disease stage IIIa. Following AKIN classification for Acute Kidney Injury (AKI), the patient was diagnosed to have AKI stage 2. So, the final diagnosis was arrived at AKI in a long-standing case of CKD stage IIIa with septecaemia (qSOFA score: 2).

On assumption of bacterial infection patient was started on supportive management and intravenous antibiotics from the beginning. Following the blood culture sensitivity report, the broad spectrum antibiotics covering both gram positive and negative organisms were added accordingly. Patient received 2 units of packed red blood cell (PRBC) transfusion started 4 days following admission when fever began to remit. Nephrological consultation was taken; based on age and clinical status, conservative management was advised to be continued. Laboratory parameters started to improve gradually and patient was also recovering clinically. On 11th day following admission, she became afebrile. From the next morning, she was shifted to all oral medications and at ambulatory condition and having all the laboratory parameters reached at baseline values, the patient was discharged on 16th day following admission. She was followed up after 7 days of discharge with the repeat reports of HB%, TLC, BUN, Urea, Creatinine, CrCl, Na, K, total protein and all these were found to reach normal range. But the etiology behind

the event remained presumed to be analgesic abuse in absence of any other circumstantial evidence behind it.



Figure 1: Ultrasonography of whole abdomen of the patient.

#### **DISCUSSION**

4%). Non-steroidal anti-inflammatory drugs (NSAIDs) have analgesic, antipyretic and anti-inflammatory actions in varied contexts. Neither they depress CNS, nor do they produce any physical dependence and abuse liability because of their mild analgesic property. But the development of psychological dependence out of cumulative drug abuse may be a concern. Relative gastric toxicity by mucosal damage dictates choice of analgesic to a large extent. NSAIDs induced renal damage by varied mechanisms have been well documented but they are found most often among people with existing comorbidities like as CHF, cirrhosis of liver, renal insufficiency and those who are on diuretics and antihypertensive drugs. I

In our current context, the patient did not have any of these co-morbidities. The only positive history was that of excessive use of analgesic for relief of body pain the etiology of which could not be elicited. After investigations on hospitalization, no infective foci could be detected while the blood culture showed load of pathogenic microorganisms the source of which remained in dearth. Kwon et al reported statistically significant increased risk (fixed effects RR 2.43, 95% CI 1.82-3.26). On disproportionality analysis in their systematic review and meta analysis, from pharmacovigilance database they showed significantly higher propensity towards hepatic damage by nimesulide compared to the other NSAIDS.<sup>2</sup> Even excluding notoriety bias, drug-induced liver injury (DILI) out of NSAIDs usage has been reported in case reports and case series.3 Fulminant hepatic failure and death have been reported even following EMA approved duration of nimesulide intake.<sup>4</sup> Schattner A also reported fatal hepatitis and renal failure while treating with nimesulide.<sup>5</sup> Acute kidney injury may be attributed to drug-induced severe hepatic toxicity or renal arteriolar constriction by vasodilatory prostaglandins which in the current case have been reflected by increased BUN, creatinine, CrCl etc. Gupta et al reported similar case finding from Punjab in a 6-year old child.<sup>6</sup> Sozer et al in his randomized control trial on Wister albino rats have shown kupffer cell proliferation, congestion and hydropic degeneration as well as congestion of renal tissues among those on nimesulide administration even at adjusted therapeutic doses.<sup>7</sup>

Analgesic nephropathy was reported long back by Spuhler in 1953; Zaki also reported a case of nimesulide-induced acute renal failure and recommended for supportive management which was also followed in the current case besides management of septicemia. Niepen reported calcium oxalate crystals in histological examination of renal biopsy and tubular casts of IgA, IgG and Kappa and mesangial deposits of C3 in immunofluoroscence study in a 40 years old male patient presenting with complaints similar to our current patient with history of 5600 mg of nimesulide over one week. Nimesulide have been claimed by Warrington SJ to produce renal intolerability even among normal individuals on repeated dosing.

Over-the-counter (OTC) availability of drugs and inappropriate self-medication with them is an important public health problem globally. India, being itself a developing country is not an exception. OTC poses multipronged perils like as of non-measurability of extent of problem, no level telling the usage of the medicine, its active and inactive ingredients, potential side effects, drug interactions etc. Another surprising fact is that, the term OTC doesn't exist as per Indian law. Neither the Drugs and Cosmetics Act, 1940 nor the Drugs and Cosmetics Rules, 1945 (D and C) define OTC, so the OTC drugs lack legal recognition in India. Business research predicts for India as an emerging market for OTC drugs offering significant growth potential for the industry; the risk of it is obvious. Cooper, Tesfamariam et al from their various studies have pointed towards this risky practice and its predictors. 12,13 Pileggi et al. marked non-prescription drugs (NPDs), OTC drugs and complementary alternative medicines (CAMs) among children and their grim outcomes.14

In our current context, the patient faced this catastrophic kidney insult and septicemia presumably out of self-medication, which could be avoided on prior medical consultation for her existing complaints.

#### **CONCLUSION**

On cumulative intake of approximately 2.8 gm. of nimesulide over one week of time and continued for long as before, brought a serious acute kidney injury, hepatic damage, cardiac abnormality and septicemia in an apparently healthy woman. This, along with many other instances, remind repeatedly the need of a comprehensive drug policy addressing NPDs, CAMs and specially OTC

drugs and implement that in reality to avoid future harm out of drug abuse.

Funding: No funding sources Conflict of interest: None declared Ethical approval: Not required

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**Cite this article as:** Mitra S. Acute kidney injury and severe septicemia: toll of over-the-counter availability of drugs. Int J Community Med Public Health 2021:8:2038-41.