

## CASE REPORT

# Dexamethasone and diclofenac intramuscular mixture injection and risk of death: A case series study

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## Abstract

Diclofenac and dexamethasone injection mixture could be associated with fatal cardiovascular events, further studies are warranted to explore the safety of this injection mixture and explore the genetic role of it.

## KEYWORDS

cardiovascular, dexamethasone, diclofenac, mixture, safety

## 1 | CASES PRESENTATION

Steroidal and nonsteroidal anti-inflammatory medications are associated with adverse events including hematobiochemical and immunological changes, and cardiovascular events. Three patients died after being given an intramuscular injection of a mixed diclofenac sodium and dexamethasone. We hypothesized that this combination may be fatal in some cases.

Data were extracted from the medical records at Baiji General Hospital, Ministry of Health, Salah ad Din, Iraq. The three patients were males who aged from 28 to 60 years. Two of the patients had comorbidities (diabetes mellitus, hypertension, and dyslipidemia) and they were on treatments while the third was not complaining of previous diseases. Two patients were smokers; none of them were alcoholic or allergic to any medication. In the 24 hours prior to their death, the patients complained of various symptoms such as abdominal pain, headache, and loss of appetite. However, immediately prior to their death, the patients' main complaints were chest pain, shortness of breath, severe vomiting, and hyperthermia.

The only common thing in between them is that they have received diclofenac and dexamethasone injection mixture in the 24 hours prior to their death (Table 1).

## 2 | DISCUSSION

Anti-inflammatory drugs alleviate inflammation by decreasing the plasma concentration of the inflammatory mediators that are released during the inflammatory response.<sup>1,2</sup> Steroidal anti-inflammatory drugs (SAIDs) and nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used anti-inflammatory drugs for pain management. SAIDs inhibit the release of arachidonic acid, the precursor of prostaglandins, whereas NSAIDs inhibit the cyclooxygenase-1 or cyclooxygenase-2 (COX-1 or COX-2) enzyme. Both classes have proven a high efficacy in relieving pain, reducing inflammation, and fever.<sup>3</sup> Anti-inflammatory medications are associated with adverse reactions including hematobiochemical and immunological changes, and cardiovascular and gastrointestinal adverse effects.<sup>4</sup> In a study comprising a large

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database in the UK, it has been reported that extensive use of diclofenac substantially increases the risk of acute myocardial infarction (AMI).<sup>5</sup> Similarly, previous studies reported a relationship between the use of diclofenac and the development of cardiovascular problems including myocardial infarction.<sup>5-8</sup> Preclinical studies have shown that diclofenac treatment caused significant molecular and histological alterations in mouse hearts after repeated-dose administration.<sup>9</sup> On the other hand, it has been revealed that diclofenac can cause a significant increase in plasma cardiac markers at single-dose treatment in ram.<sup>10</sup> Recently, a Danish review of a series of 252 nationwide cohort studies compared the adverse cardiovascular events related to diclofenac therapy. The study has found that diclofenac initiators were at increased risk of major adverse cardiovascular events (atrial fibrillation or flutter, ischemic stroke, heart failure, acute myocardial infarction, and cardiac death) when compared to initiators with other NSAIDs or paracetamol.<sup>7</sup> The study has also found that the risk of a first cardiovascular event is significantly greater for 30-day use of diclofenac than for a 30-day use of other NSAIDs or paracetamol. Diclofenac sodium cause marked increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT), urea, and creatinine levels.<sup>11</sup> These disturbances of liver and kidney function tests may be due to its serious side effects (such as gastrointestinal ulceration or bleeding, kidney and liver damage, myocardial infarction, and cardiac sudden death<sup>12,13</sup>) as well as increase in ALP and AST may be attributed to cardiovascular side effects of diclofenac, which may induce myocardial damage or infarction that are related to the inhibition of Cox synthesis.<sup>10</sup> Additionally, the change in the balance between COX-1 and COX-2 activities in the body has been suggested to have a role in triggering multiple adverse effects including GI complications, bleeding disorder, and cardiogenic events.<sup>14</sup>

Dexamethasone cause marked decrease in total protein, gamma globulin, and total globulin beside insignificant decrease in albumin.<sup>4</sup> Dexamethasone can also cause cardiovascular effects including alterations in heart-pressure measurement.<sup>15</sup> Sholter et al<sup>16</sup> have also reported adverse cardiovascular events associated with the long-term use of corticosteroids. The main reported side effects were dyslipidemia, hypertension, and left ventricular wall rupture after myocardial infarction. It has been concluded that these effects may predispose treated patients to coronary artery disease when high doses and prolonged courses of treatment are used.<sup>16</sup> The separate use of members of both steroidal and nonsteroidal classes have been well established for the management of acute as well as chronic inflammatory conditions.<sup>2,17-20</sup> However, the combined use of both steroidal and nonsteroidal anti-inflammatory drugs (mixed in the same injection) is not commonly explored and has less clear-cut outcomes. In the Middle East region, mixing dexamethasone and diclofenac sodium in the same syringe,

**TABLE 1** Characteristics of the patients

Age (years)	Gender	Comorbidities	Treatment received before death	Cause of death	Medication use history	Symptoms presented 24 h before death	Symptoms presented immediately before death	Smoking history
40	Male	Hypertension and dyslipidemia	Diclofenac, dexamethasone, and Ampiclox (ampicillin + cloxacillin)	Myocardial infarction	Enalapril, thiazide, spironolactone, statin, and vitamin E	Headache	Chest pain and shortness of breath	Yes
60	Male	Hypertension, type 2 diabetes mellitus, and dyslipidemia	Diclofenac and dexamethasone	Myocardial infarction	Metformin, metoprolol, valsartan, and diuretics	None	Chest pain and shortness of breath	No
28	Male	None	Diclofenac, dexamethasone, congestal (chlorpheniramine, dextromethorphan, acetaminophen, and pseudoephedrine), and paracetamol.	Heart attack	None	Loss of appetite and abdominal pain	Abdominal pain, hyperthermia, and severe vomiting	Yes

and administering the mixture intramuscularly to patients complaining of severe pain, is a common practice. However, there is a scarcity in the research concerning the safety of the parenteral combination of corticosteroids and NSAIDs in the same syringe.

In this article, we report the clinical characteristics of three patients who died due to heart attack or MI. However, the only common thing we have found among the deceased subjects is that they have been administered a combined injection of dexamethasone and diclofenac mixed in the same syringe and injected intramuscularly to alleviate certain type of pain or inflammation. Having in mind the possibility of gastrointestinal and cardiovascular side effects induced by anti-inflammatory drugs, we tend to think about the combination as being the culprit in these cases.

Bamgbose et al<sup>21</sup> reported that coadministration of dexamethasone and different NSAIDs have shown to provide synergistic anti-inflammatory activity. Park et al,<sup>22</sup> 2019 suggested that coadministration of NSAID with dexamethasone in a low dose can reduce the dose of both drugs, consequently decreasing the potential side effects of monotherapies in which each drug is separately administered. However, in the abovementioned studies, dexamethasone and different NSAIDs were given separately but at the same time.

To benefit from the superior therapeutic efficacy and the reduced side effects of diclofenac/dexamethasone combination, both drugs were incorporated in several novel formulations which have been investigated. Elron-Gross et al have injected a novel combination of the two drugs into mice, which have demonstrated a full biological activity. This formulation has been recommended for the treatment of the most severe cases of osteoarthritis.<sup>23</sup> In a more advanced research, Assali et al<sup>24</sup> have found that a nano-formulation of the twin-drug has a sustained release profile with an excellent anti-inflammatory activity in vivo.

It has been reported that concomitant therapy of corticosteroids and anticoagulant significantly increase the gastrointestinal complications and bleeding side effects.<sup>25</sup> Hence, coadministration of dexamethasone, a corticosteroid drug, and diclofenac which is an NSAID drug can elevate the risk of GIT ulceration, perforation, and hemorrhagic event induced by NSAID.<sup>26</sup> Moreover, there is a strong evidence that cardiovascular events including stroke and myocardial infarction are associated with diclofenac sodium administration.<sup>27</sup> Additionally, diclofenac potassium and dexamethasone reported to be associated with causing several hematobiochemical and immunological changes.<sup>4</sup> In light of that, an increase in the risk of death due to dexamethasone/diclofenac coadministration could be explained.

This may suggest that cardiovascular side effects are exacerbated by the coadministration of diclofenac and dexamethasone injection mixture. Inter-individual variation in this cardiovascular response among the patients with

coadministered drugs may be attributed to many factors such as genetic polymorphisms, health status, and drug-drug interaction. Thus, further studies including histological investigation are proposed in order to investigate the risk factors involved in the development of cardiovascular effects induced by the coadministration of diclofenac and dexamethasone.

### 3 | CONCLUSION

There is no clear evidence in the literature on the safety of diclofenac and dexamethasone injection mixture.

Despite that there is no documented fatal effect associated with the use of this mixture; we suggest that mixing them together in the same syringe maybe associated with increased risk of death due to cardiovascular events. Hence, healthcare professionals should be aware of the possibility of fatal cardiovascular events when using this mixture.

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### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### AUTHOR CONTRIBUTIONS

AN, SQ, and QJ: performed conceptualization, methodology, formal analysis, data curation, validation, writing the original draft, writing-review and editing, project administration, and funding acquisition. RATiyah and AA: collected the data. SQ, HA, QJ, RAYoub, and AJ: involved in interpretation, writing the original draft, and writing-review and editing. AN: provided resources and supervised the study. All authors agreed to be accountable for the content of the work.

### ETHICAL APPROVAL

Ethical approval for this study was obtained from the research ethics committee (REC) at the faculty of pharmacy at Isra University (PH – 2021 - 03)).

### DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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