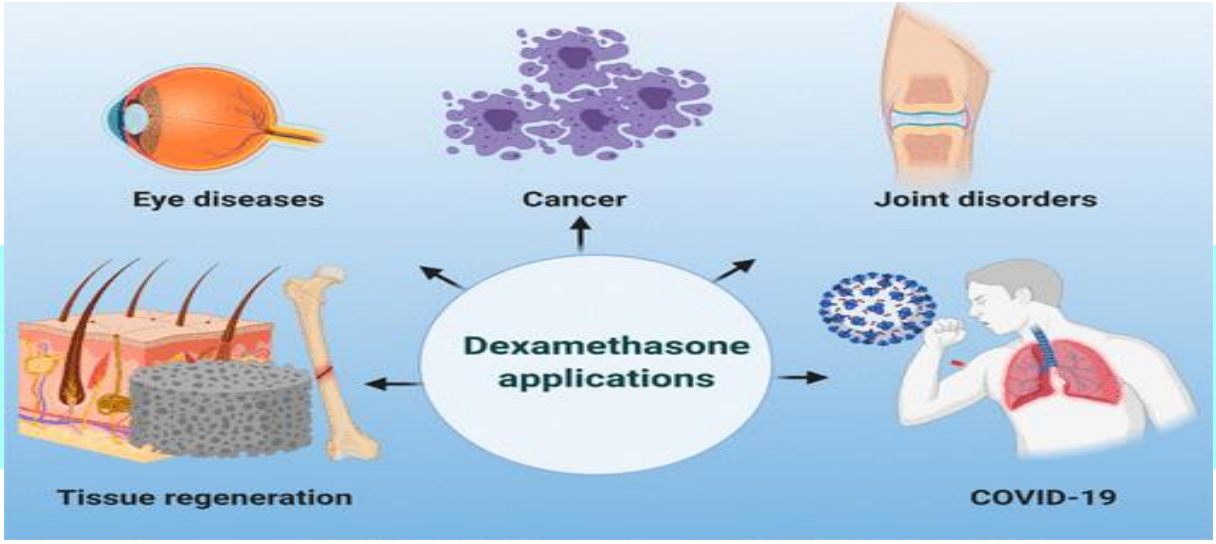
Safety Concerns Over Concurrent Use of Diclofenac & Dexamethasone

Dexamethasone: is a potent, synthetic member of the glucocorticoid class of steroid drugs. It has pleiotropic effects on multiple signaling pathways that result in a broad range of activities, the anti-inflammatory & immunosuppressant being the best known. It works on the immune system to help relieve swelling, redness, itching, and allergic reactions. It regulates the expression of many target genes that affect inflammatory responses, cellular proliferation and differentiation in target tissues

Indications of Dexamethasone

- Inflammation, allergies, asthma, and cerebral edema.
- Rheumatoid arthritis, lupus, and multiple sclerosis.
- Patients with COVID-19, atopic and contact dermatitis.



Adverse Effects

- Blurred vision, Swelling, Insomnia, Mood changes
- Slow wound healing
- Increased sweating
- Headache, dizziness, nausea
- Stomach pain

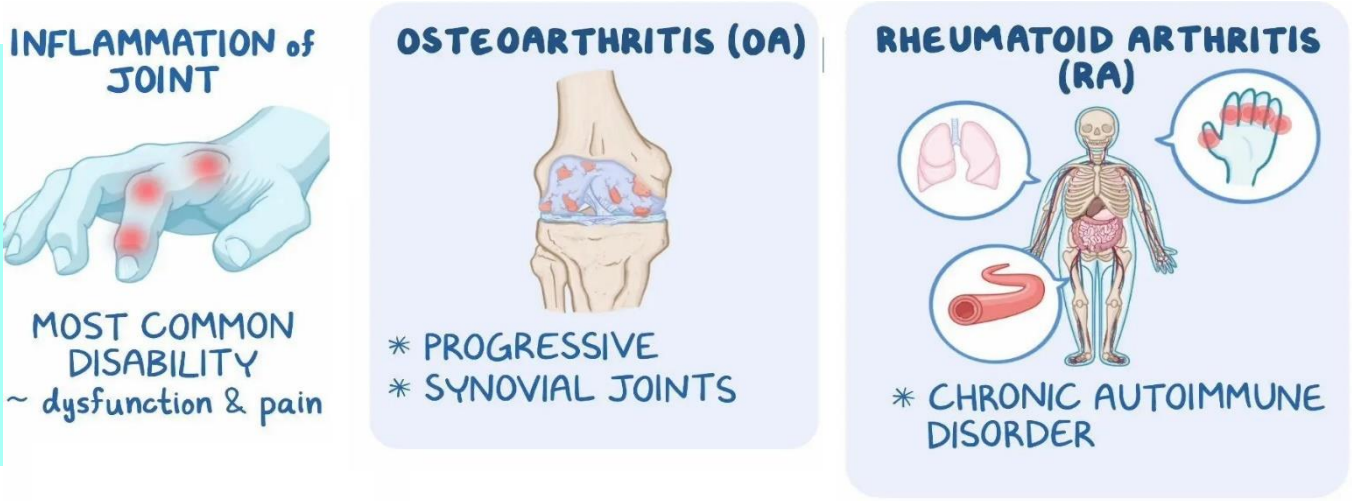
Diclofenac

Diclofenac is a phenylacetic acid derivative and non-steroidal anti-inflammatory drug (NSAID). NSAIDs inhibit cyclooxygenase (COX)-1 and-2 which are the enzyme responsible for producing prostaglandins (PGs). PGs contribute to inflammation and pain signaling. Diclofenac, like other NSAIDs, is often used as first line therapy for acute and chronic pain and inflammation.

Indications

Inflammatory conditions such as:

- Osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis.
- Injury-related inflammation due to surgery and physical trauma.
- Often used in combination with misoprostol as a gastro-protective agent in patients with high risk of developing NSAID-induced ulcers.



Growing Threat

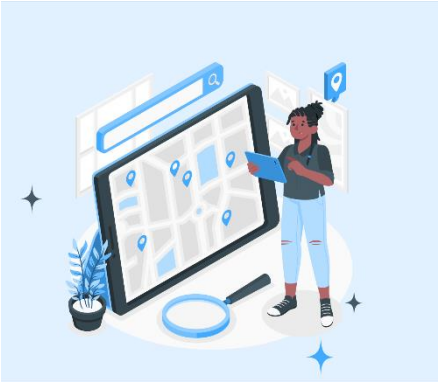
Despite evidence supporting the synergistic anti-inflammatory effects of dexamethasone and diclofenac, no studies have evaluated the safety of mixing them in the same syringe for injection. This lack of data raises concerns about the advisability of such combinations. Notably, three patients reportedly died from heart-related issues within 24 hours of receiving an injection of both medications, suggesting a potential interaction may have contributed to these fatalities.

Case Series study

Recent case reports have highlighted serious safety concerns regarding the simultaneous use of diclofenac and dexamethasone, especially when administered through intramuscular injections. Tragically, three patients died within 24 hours of receiving the injection, with acute myocardial infarction being determined as the cause of death.

Patient demographics

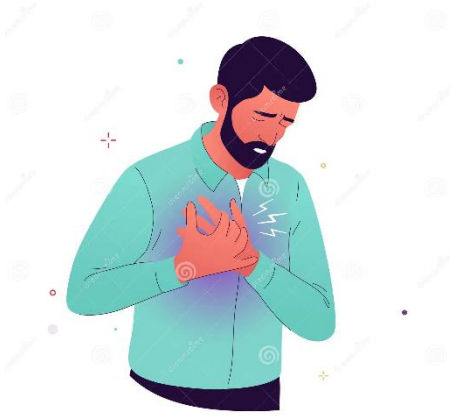
The study examined three male patients aged 28 to 60 years who died following the administration of a diclofenac and dexamethasone mixture. The patients exhibited various comorbidities and symptoms leading to their deaths.



Patient Profiles

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 (chloropheniramine, dextromethorphan, acetaminophen, and pseudoephedrine), and paracetamol.	Heart attack	None	Loss of appetite and abdominal pain	Abdominal pain, hyperthermia, and severe vomiting	Yes

Symptoms



In the 24 hours leading up to their deaths, patients reported abdominal pain, headache, and loss of appetite. Just before death, they experienced chest pain, shortness of breath, severe vomiting, and hyperthermia.

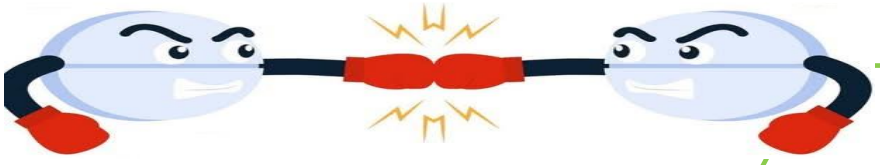
Potential Mechanisms:

Steroidal anti-inflammatory drugs (SAIDs) and nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for pain management, with SAIDs inhibiting arachidonic acid release and NSAIDs blocking cyclooxygenase enzymes (COX-1 and COX-2). Both classes effectively relieve pain, inflammation, and fever but are associated with adverse effects, including cardiovascular and gastrointestinal complications.

- **Diclofenac** inhibits the COX enzyme, particularly COX-2, leading to reduced prostaglandin production, which in turn can cause vasoconstriction and increase the risk of coronary artery narrowing, making the patient susceptible to myocardial infarction. Notably, NSAIDs carry a boxed warning regarding these cardiovascular risks. Extensive use of diclofenac has been linked to a significantly increased risk of acute myocardial infarction and other cardiovascular issues, as shown in various studies. Diclofenac treatment has also been associated with notable changes in cardiac markers and liver and kidney function tests. The alteration of COX-1 and COX-2 activity balance may contribute to these adverse effects, including gastrointestinal complications and cardiovascular events.

- **Dexamethasone** prevents prostaglandin formation and contributes similar cardiovascular risks. Additionally, prolonged use of dexamethasone is known to affect blood pressure, glucose levels, and lipid profiles.

- **Synergistic effect:**
- The critical point here is that the combination of dexamethasone and diclofenac can create a **synergistic effect**, leading to greater risks than the sum of their individual effects. Furthermore, various drug interaction databases indicate that dexamethasone can exacerbate the side effects associated with NSAIDs, including increased susceptibility to bleeding, while both drugs carry boxed warnings for thrombosis and myocardial infarction.



- Using diclofenac and dexamethasone separately is generally acceptable; however, mixing them and administering them in the same syringe has not been thoroughly tested although it is a common practice in the middle east region.

- While it is possible to use dexamethasone and diclofenac together, they should be administered separately. Their combined effects can be beneficial, but healthcare providers must consider the potential for increased harm and adjust dosages accordingly to mitigate risks.
- To benefit from the superior therapeutic efficacy of this combination, scientists have made specialized formulations for treating osteoarthritis that incorporate both medications in a liposomal delivery system, allowing for slow release and minimizing the risks associated with their combination while maximizing therapeutic benefits.

Recommendations for Healthcare Providers

- **Assess Patient Risk**: Evaluate individual patient health status and comorbidities before prescribing this combination.
- **Monitor Patients Closely**: Implement vigilant monitoring for signs of cardiovascular distress in patients receiving the mixture.
- **Educate Patients**: Inform patients about potential symptoms that may indicate serious side effects. By prioritizing patient safety and adhering to best practices, healthcare professionals can mitigate the risks associated with this medication combination.

Conclusion

While the combination of diclofenac and dexamethasone may offer enhanced anti-inflammatory effects, emerging evidence suggests a potential association with fatal cardiovascular events. Until more definitive data are available, it is prudent to carefully assess the risk-benefit profile for each patient and consider alternative therapeutic strategies when appropriate.

References:

- **Mayoclinic**

- **https://pmc.ncbi.nlm.nih.gov/articles/PMC8077341/#:~:text=Dexamethasone%20and%20diclofenac%20are%20commonly,the%20same%20syringe%20for%20injection.**
- **https://www.drugs.com/drug-interactions/dexasone-with-diclofenac-810-3297-869-0.html**
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- **https://go.drugbank.com/drugs/DB00586**