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CASE REPORT

Topical Diclofenac-Induced Hepatotoxicity

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Abstract

The hepatotoxic potential of diclofenac, a commonly used non-steroidal anti-inflammatory agent, is well established in literature. However, cases of diclofenac-induced liver disease have occurred almost exclusively with the oral formulation of this medication. We report the case of an elderly man with Paget's disease and osteoarthritis who developed acute hepatotoxicity, as evidenced by laboratory diagnostics, four months after use of topical diclofenac 1% gel. Once diclofenac gel was discontinued, repeat blood work three weeks after discharge demonstrated return of liver function tests to baseline. Given the temporal relationship between the initiation and escalation of topical diclofenac and the changes in liver function tests, the likelihood of diclofenac-induced liver injury was deemed possible using a well-recognized causality assessment tool. Further research on topically administered non-steroidal anti-inflammatory agents is needed to identify monitoring intervals for early detection and avoidance of adverse effects in patients using topical diclofenac.

Keywords: Non-steroidal anti-inflammatory drugs, Diclofenac, Topical, Drug-induced liver injury, Acute liver injury, Hepatotoxicity, Adverse drug reaction

1. Introduction

Drug-induced liver injury (DILI) refers to unexpected, adverse effects of medications on the liver. Incidence has been reported as 1 in 10,000 to 1 in 100,000 − a wide range owing to underreporting, diagnostic challenges, and underpowered clinical trials.[1] In patients that present with jaundice and elevated serum aminotransferases (>3 times upper limit of normal), there is an approximate 14% risk of mortality secondary to acute liver failure.[2-6] The mechanism of hepatotoxicity includes an intrinsic dose-dependent pathway by which a drug may reach a predictable toxic threshold.[2,7] More specifically, when dose threshold is exceeded, further drug metabolism results in production of reactive metabolites that can inhibit mitochondrial function, reducing ATP-dependent bile acid export and increasing production of reactive oxygen species, culminating in hepatocyte death.[8] The net effect is therefore 'intrinsic' to the metabolic capacity of the liver. Alternatively, idiosyncratic hepatotoxicity results from incidental interaction between drug properties, the environment, and host genetics, leading to reduced detoxification and increased bioactivation pathways.[9] The latter mechanism accounts for 10−15% of acute liver failure in the United States.[7,10,11] Diclofenac, a commonly prescribed non-steroidal anti-inflammatory and analgesic agent, may lead to idiosyncratic hepatotoxicity.[4,10,12] Yet, incidence of this adverse reaction remains rare, and seemingly limited to the oral formulation of the drug, occurring at a rate of 6 per 100,000 users.[4] Indeed, there is lack of evidence for causality between topical forms of diclofenac and liver enzyme derangements, with only two reported cases in literature.[13,14] We report another case of a patient who developed acute hepatotoxicity shortly after treatment with topical diclofenac.

2. Case

A 94-year-old man presented to hospital after being found on the ground approximately 1 h following an unwitnessed fall. There was no history

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of prodromal features, palpitations, or loss of consciousness before the fall. The family reported reduced oral intake and poor appetite over the past day. Medical history was notable for Paget's disease of the bone and arthritis. His only new medication was diclofenac 1% topical gel, which was applied liberally to all his joints and lateral legs. More specifically, the gel was started around 4 months prior, and amount applied progressively increased to about half a tube (50 g) a day by time of admission. Other chronic medications included acetaminophen 650 mg daily, aspirin 81 mg daily, atorvastatin 10 mg daily, ibuprofen 200 mg as needed, and metoprolol succinate 25 mg daily.

On presentation to the hospital, the patient was vitally stable. Physical exam was remarkable for warmth and tenderness to palpation of the left hip. Laboratory diagnostics demonstrated mild anemia (hemoglobin, 11.1 g/dL (reference range 12.5–16.5 g/dL)) and thrombocytopenia (79×10^9/L (reference range $145–400 \times 10^9$/L)). Creatinine phosphokinase level (CPK) was elevated (5549 units/L (reference range 46–171 units/L)). Coagulation panel showed an elevated PT (20.4 s (11.8–14.6 s)) and INR (1.8 (0.8–1.2)). Furthermore, liver function tests (LFTs) revealed an elevated total bilirubin (4.9 mg/dL (reference range 0.2–0.9 mg/dL)) that was predominantly direct (3.84 mg/dL (reference range 0.00–0.3 mg/dL)), aspartate aminotransferase (AST; 426 U/L (reference range 0–33 U/L)), alanine aminotransferase (ALT; 239 U/L (reference range 10–49 U/L)), and alkaline phosphatase (ALP; 368 U/L (reference range 46–116 U/L)). The R factor,[15] a diagnostic tool to differentiate hepatocellular versus cholestatic patterns of hepatic injury (AST/alkaline phosphatase; $R \geq 5$ is hepatocellular, $R < 2$ is cholestatic and $2 < R < 5$ is mixed DILI), was noted to be 3.2, suggestive of a mixed DILI pattern of injury. Of note, LFTs were within normal range about three months prior barring his ALP (226 U/L), which showed persistent elevation since 2014, consistent with established Paget's disease.

The patient was admitted to the medicine ward for further evaluation and management. Orthostatic vital signs were notably positive. The patient received IV crystalloid with subsequent improvement in his pressures and CPK levels. Investigation of the noted transaminitis demonstrated an unremarkable acetaminophen level and negative hepatitis viral panel. There was little concern for an autoimmune etiology. Erythrocyte sedimentation rate remained low (16 mm/h (reference range 0–20 mm/h)). Diagnostic imaging included Computed Tomography of the abdomen that failed to demonstrate biliary obstruction. The atorvastatin, acetaminophen, ibuprofen, and diclofenac were held, with gradual improvement in all LFTs.

The patient was discharged home with advice to stop potential hepatotoxic agents such as atorvastatin, acetaminophen, diclofenac, and ibuprofen. On follow-up three weeks after discharge, LFTs normalized except for chronic elevation of the ALP (Fig. 1).

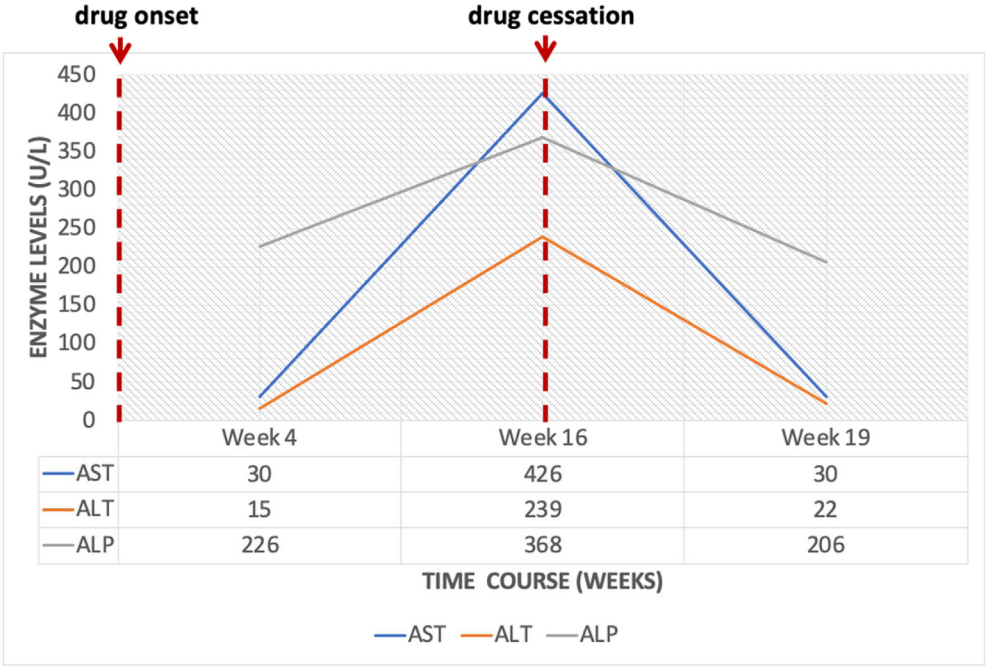

Fig. 1. Timeline of hepatic enzymatic derangements with topical diclofenac use.

3. Discussion

Diclofenac is one of the most frequently prescribed and over-the-counter supplied NSAIDs worldwide.[10,16] Diclofenac sodium 1% gel formulation is available over-the-counter for managing osteoarthritis (up to 32 g per day).[17] Evidence of DILI, as defined by an international expert panel (Table 1),[18] has been reported in approximately 15% of diclofenac users.[19] Liver enzyme elevations greater than three times the upper limit of normal, have been reported in only 3.5% of cases,[20] but almost exclusively with the oral formulation of diclofenac. The pattern of liver damage, as interpreted from liver biochemistry, is largely hepatocellular.[21] However, based on the DILI Network prospective study,[22] there can be shift of LFTs with disease progression; calculation of the R ratio characterized 57% of cases as hepatocellular based on early lab values versus the 45% identified at a later time point. Unfortunately, our patient did not have frequent lab monitoring and DILI recognition may have been at a time where ALT relative to ALP favoured a more mixed pattern. Nevertheless, cases of mixed injury with diclofenac use have also been reported.[23] These enzyme derangements are typically evident within six months of drug exposure.[24,25] While clinically significant, most patients remain asymptomatic.[10] Cases of diclofenac-induced symptomatic liver disease requiring hospitalization have only been reported in 23 persons per 100,000 exposed.[25] Risk factors commonly linked to diclofenac-induced hepatotoxicity include female sex, increased dose and duration of treatment, and osteoarthritis.[26] In one study, use of 48 g of diclofenac sodium 1% gel formulation per day as compared to 16 g, almost quadrupled systemic absorption after 7 days of treatment, with measurable levels persisting in circulation after a 14-day washout period.[27] The same study showed that diclofenac levels spiked after oral administration, whereas levels from diclofenac sodium gel 1% remained relatively constant throughout the day suggesting accumulation and slow release from skin and underlying tissues potentially reaching concentrations that exceed liver drug metabolism capacity.[27] Additional factors increasing absorption of diclofenac can include skin hydration or age, method of application, and use of topical vehicles which alter barrier function.[28] The proposed idiosyncratic mechanisms by which the drug harms the liver at the cellular level include individual allelic variants of UGT2B7, CYP2C8, and ABCC2, which can lead to accumulation of reactive metabolites (diclofenac acyl glucuronides), resulting in formation of unstable adducts and inappropriate immune responses.[4,7,21,29]

The connection between diclofenac use and liver injury can be validated using international consensus criteria for suspected DILI (Table 2).[30] Based on this clinical diagnostic scale (CDS), the likelihood of diclofenac-induced liver injury for our patient is possible (score 11). The causal relationship can be further corroborated by ruling out other differentials for acute liver injury, specifically his multiple contributing medications. Acetaminophen use (650 mg once daily) remained stable, without dose escalation, and his levels remained undetectable. Similarly, ibuprofen, a medication rarely associated with liver injury, remained stable without a change in dose or frequency of use over the past year. Atorvastatin, in contrast, is a medication known for DILI at any time during therapy.[31] In

Table 1. Laboratory diagnostics.

Liver Function Component	Threshold
AST or ALT	≥5-fold x ULN
ALP	≥2-fold x ULN
TBILI + ALT	TBILI>2-fold x ULN + ALT ≥3-fold x ULN[a]

[a] Criterion constituting Hy's Law which suggest risk of liver transplantation and/or mortality ~10%[2].

Table 2. Clinical diagnostic scale as adapted from[26].

Component	Score
Chronological Criteria	
4-56 days of initiation to onset	2
<4 or >58 days of initiation to onset	1
<7 days of drug withdrawal to onset	3
8-15 days of drug withdrawal to onset	0
>15 of drug withdrawal to onset	-3
De-challenge	
<6 months of withdrawal to normalization of labs	3
>6 months of withdrawal to normalization of labs	0
Alternative causes	
Full exclusion	3
Partial exclusion	0
Alternative likely	-1
Extrahepatic manifestations	
>4	3
2-3	2
1	1
Rechallenge	
Positive rechallenge test	3
Negative/absent rechallenge test	0
Evidence in Literature	
Yes	2
No (drug marketed <5 years)	0
No (drug marketed >5 years)	3
Total Score	
Definite	>17
Probable	14–17
Possible	10–13
Unlikely	6–9
Excluded	≤6

most cases however, atorvastatin-associated DILI occurs within 6 months of onset or dose escalation and usually assumes a hepatocellular injury.[31] Our patient had remained on a stable dose of atorvastatin for over 20 years; the noted CDS score was 5 (excluded). Intriguingly, the patient was noted to have an asymptomatic elevation of the CPK, a finding potentially consistent with statin-induced muscle injury,[32] however, in the absence of myalgia or muscle weakness (common findings in cases of statin toxicity) it is more plausible that the elevated CPK resulted more acutely from dehydration secondary to poor oral intake and trauma from the fall, in combination with long-term statin use.[33] Moreover, while elevated AST levels have been observed in rhabdomyolysis cases,[34] the downtrend of CPK in our patient was not in parallel with either AST or ALT (73.8% versus fall of mean AST by 42.6% and ALT by 19.7%), therefore making rhabdomyolysis less likely. While it is not entirely possible to rule out a contributory effect of all medications, the acute nature of the liver injury and the fact that the topical diclofenac gel was the only relatively new medication and furthermore applied in escalating doses, diclofenac-induced liver injury remains high on the differential. Other possible conditions leading to acute hepatitis, including viral etiologies were negative and autoimmune etiologies were felt to be low in the differential. Furthermore, given unremarkable imaging, potential cholestatic causes, including biliary obstruction, were ruled out.

Diclofenac-associated hepatoxicity bears a favourable prognosis if the offending drug is promptly removed; resolution occurs within 4–6 weeks of liver injury.[35] In this case, diclofenac was discontinued on admission and repeat laboratory testing three weeks later showed that enzyme levels and synthetic liver function had returned to baseline. Nevertheless, there have been instances of chronic liver injury (abnormal liver tests for more than 3 months) requiring corticosteroid therapy for complete recovery.[36] As most cases of diclofenac-associated liver injury are asymptomatic, routine monitoring may be required for early detection and timely management. Indeed, the United States Food and Drug Administration label on topical diclofenac recommends that transaminases be monitored within 4–8 weeks after initiating treatment, albeit there are no current monitoring recommendations after dose changes.[13]

4. Conclusion

Herein we report a case of topical diclofenac induced hepatotoxicity as manifested by moderate derangements in liver enzymes and complete resolution following drug withdrawal. Routine monitoring of LFTs may be indicated in patients requiring higher dosages for timely recognition and treatment of hepatic injury.

Patient consent

Informed consent was obtained.

Disclaimers

The abstract has been presented at the Society of Hospital Medicine Maryland Chapter annual scientific abstract competition on November 29th 2022 in Columbia, Maryland, and has been selected for presentation at the Annual Society of Hospital Medicine conference (Converge) on March 30th 2023 in Austin, Texas.

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Conflict of interest

All authors declare no conflict of interest.

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