Case Report

Angiotensin-Converting Enzyme Inhibitor Associated Hepatotoxicity

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INTRODUCTION

Hepatotoxicity is an infrequently reported adverse effect of angiotensin-converting enzyme (ACE) inhibitor therapy. We report a patient who reacted to two different ACE inhibitors with biochemical and clinical evidence of hepatitis, and review the literature on this infrequent but increasingly reported event.

CASE

A 64 year-old female was admitted to hospital with a chief complaint of nausea and vomiting, abdominal pain, diarrhea, and general malaise of six days duration with increased shortness of breath. The history of her present illness included a previous hospital admission with similar complaints and elevated liver function tests after taking lisinopril for three weeks. At that time, her lisinopril was discontinued, her liver enzymes normalized and her symptoms improved. Prior to that admission, she had reported a subjective intolerance to the captopril she had been taking for three months to treat her congestive heart failure (CHF), which led to her therapy being changed to lisinopril. At the time of discharge, it was unclear whether lisinopril had been causative and because of the severity of her CHF, captopril was restarted.

Her past medical history included hypertension for 14 years, a silent myocardial infarction (MI) four years ago, and a second MI complicated with CHF four months ago. She had had an appendectomy, a hysterectomy, and hepatitis at age four. She was a non-smoker and a non-drinker. Review of systems was remarkable only for her dyspnea. On examination, the patient appeared quite ill. The patient's blood pressure was 160/100 mmHg, heart rate 100 beats per minute, respiratory rate 24 per minute, and she was afebrile. Chest examination revealed diffuse crackles, normal S_1 and S_2 with an S_3 and an elevated jugular venous pressure. Examination of the abdomen revealed some slight tenderness in her left lower quadrant. There was no peripheral edema present. The remainder of the physical exam was unremarkable. Her reported drug allergies and intolerances were numerous and included penicillin, lithium, naproxen, nifedipine, prazosin, indapamide, and hydralazine. At the time of admission, the patient had been taking captopril, digoxin, furosemide, spironolactone, and enteric coated ASA.

Serum chemistries were remarkable for elevated liver enzymes including, aspartate aminotransferase (AST) 3250 U/L [0-35 U/L], total bilirubin 37 μmol/L [2-18 μmol/L], lactate dehydrogenase (LDH) 6980 U/L [50-150 U/L], and alanine aminotransferase (ALT) 1329 U/L [<35 U/L]. Her alkaline phosphatase, 60 U/L, was within the normal range [50-120 U/L]. Serum electrolytes were normal except for a potassium of 5.6 μmol/L [3.5-5.0 μmol/L]. White blood cell count was elevated at 21.4 x 109/L [(4-11) x 10^9/L]. Her BUN was 12.1 μmol/L [3.0-6.5 μmol/L] and serum creatinine 143 μmol/L [50-110 μmol/L]. A chest X-ray showed evidence of failure with florid pulmonary edema, while an abdominal ultrasound suggested an enlarged liver.

The patient was diagnosed with an exacerbation of CHF with a suspected hepatotoxic reaction to captopril. The captopril was discontinued immediately following admission, and her elevated liver function values declined, and within approximately two weeks were

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approaching the normal range (Table I). Her nausea, abdominal pain and diarrhea also resolved within the same time frame. Although ischemic "hepatitis" due to severe CHF could not be completely ruled out in this patient, the timing of her recovery and the reoccurence of her symptoms upon rechallenge with captopril strongly supported the diagnosis of ACE inhibitor associated hepatotoxicity. During the remainder of her hospital stay, her CHF was stabilized and she was discharged home on digoxin, furosemide, spironolactone, hydralazine, isosorbide dinitrate, and enteric coated ASA. She was instructed not to take any ACE inhibitors in the future.

DISCUSSION

ACE inhibitors are commonly prescribed for CHF and hypertension. With the increased use of these drugs, more of the less common, serious, adverse effects are being recognized. At present, there have been 36 cases of ACE inhibitor-associated hepatotoxicity reported in the literature in 34 patients.[1-5] In addition, a few unpublished cases have been reported to various manufacturers of ACE inhibitors.[3] Of those reported in the literature, there were 28 cases associated with captopril,[1,2,5] six associated with enalapril[2,4] and two associated with lisinopril.[3,6] Only two episodes of cross-reactivity between ACE inhibitors are reported and both of these involve a cross reaction between captopril and enalapril.[7,8]

Table 1: Liver Function Tests

Hospital Day	AST (U/L)	ALT (U/L)	Total Bilirubin (μmol/L)	LDH (U/L)	Alkaline Phosphatase (U/L)
1	3250	n/m	37	6980	60
2	1804	1329	37	2060	68
3	721	1011	44	1410	65
4	362	680	38	n/m	71
5	188	475	32	740	68
6	106	340	26	758	60
7	73	230	21	754	64
8	57	163	25	687	68
9	48	138	23	n/m	70
12	44	69	14	453	74
15	48	n/m	14	394	71
19	67	56	16	461	76
22	49	49	14	259	65
26	46	52	10	285	57
28	49	n/m	14	294	62

n/m = not measured

The pattern of presentation of ACE inhibitor-induced hepatotoxicity appears to be somewhat variable. The duration of ACE inhibitor therapy is of little use in predicting whether a patient will develop a hepatotoxic reaction to ACE inhibitors, as wide ranges in time of onset have been reported. In a review of 19 cases of ACE inhibitor associated hepatotoxicity, Hagley et al reports a mean duration of therapy of 14 weeks, and a median time of one month with a range from five days to 12 months. This excludes one patient who developed hepatotoxicity six weeks following a dose increase of captopril from 25mg to 50mg after having taken it for two years.[2] Rahmat et al reviewed 14 cases of captopril associated hepatotoxicity. They found the range of the interval between the initiation of captopril treatment and the onset of jaundice to be one week to ten months, with the majority between one and eight weeks.[1] Our patient initially had taken captopril for almost three months with subjective complaints of nausea, vomiting, abdominal pain, and general malaise. This intolerance to captopril led to a change to lisinopril, which she took for three weeks before her first hospital admission. She was then rechallenged on captopril for six days before again presenting to hospital.

The symptoms of hepatotoxicity demonstrated by our patient consisted primarily of nausea, vomiting, abdominal pain and general malaise. Although her bilirubin was elevated, she did not show clinical signs of jaundice, like the majority of the patients described in the literature. Among those reviewed by Rahmat and Hagley, jaundice tended to be the most common clinical feature.[1,2] All 14 patients reviewed by Rahmat experienced clinical jaundice,[1] while 11 of 19 patients in Hagley's group demonstrated this symptom.[2] Relatively rapid withdrawal of the ACE inhibitor may have accounted for our patient's lack of clinical jaundice, as jaundice has been shown to develop in asymptomatic patients with elevated liver enzymes who continue to receive ACE inhibitors.[2] Other commonly reported symptoms include fatigue, nausea, vomiting, rash, pruritus, fever, abdominal pain, and confusion.[2]

In accordance with the clinical findings, cholestasis appears to be the most common pattern of hepatic injury associated with ACE inhibitors. Rahmat et al devised a classification system using AST and alkaline phosphatase laboratory findings to categorize hepatotoxic patterns of injury into either cholestatic (hepatocanalicular type), pure hepatocellular or mixed cholestatic and hepatocellular. They found that the majority of patients experienced cholestatic injury secondary to captopril. Only one of 14 patients demonstrated pure hepatocellular injury.[1]

The findings of Hagley et al agree with this distribution.[2] Biopsies evaluated in each of these reviews also support this conclusion.[1,2] Despite these findings, our patient, when classified by this method, demonstrated a purely hepatocellular injury. Other recent reports describe lisinopril induced hepatotoxic injury without cholestasis,[3] and mixed cholestatic and hepatocellular injury in response to enalapril therapy.[4]

In most cases, the hepatotoxic effects induced by ACE inhibitors appear to resolve following cessation of the ACE inhibitor therapy.[1,2] Even with prolonged exposure and significant liver failure, a gradual improvement in liver function may occur with cessation of therapy.[2] Continued use of ACE inhibitors, once hepatotoxicity has occurred, may lead to fulminant liver failure and death.[6,7] Two cases of death secondary to the hepatotoxic effects of captopril have been reported.[5,9] Those who survive will recover with minimal sequelae of liver damage, but it may take some time, ranging from two weeks to nine months.[2] Our patient required approximately one month to fully recover, although her clinical course was complicated by CHF. Rechallenges have been attempted and resulted in worsened liver function tests.[10]

Although the mechanism of ACE inhibitor-associated hepatotoxicity is not fully understood, several authors have postulated theories. Initially it was suggested that the sulfhydryl group was involved in captopril-induced hepatotoxicity.[7] Since that time, there have been reports of cross-reactivity between enalapril, and captopril,[7,8] and now lisinopril and captopril, suggesting a common mechanism of injury, yet neither enalapril nor lisinopril contain sulfhydryl groups.[7]

Hagley et al[2] propose that hepatotoxicity is due to intrinsic properties of ACE inhibitors as opposed to structural properties. These authors suggest inhibition of kininase II by ACE inhibitors and the consequent continued activation of bradykinin may cause susceptible patients to produce selective prostaglandins that favour bile stasis. This may manifest clinically as a mild to moderate elevation of alkaline phosphatase and cholestasis. In addition, the authors hypothesize that continued exposure to ACE inhibitors while experiencing cholestasis may result in elevated hepatic leukotriene concentrations and ultimately produce more severe hepatic injury.

Hilburn et al[3] postulated that the terminal proline ring present on captopril, enalapril and lisinopril may somehow mediate the hepatotoxic reaction. The tolerance to delapril, which does not contain a proline ring, while experiencing hepatotoxicity to both captopril and enalapril, would support this theory.[3] However, other cases, where enalapril was tolerated but lisinopril was not,[6] and vice versa,[4] may complicate this hypothesis.

Finally, several authors advocate a hypersensitivity mediated hepatotoxic reaction to ACE inhibitors.[1,2,6,8,11] Low incidence, a typically short interval between drug administration and symptoms and abnormal laboratory values especially on rechallenge, presence of fever, myalgias, rash and eosinophilia in several cases support such hypothesis.[2]

In summary, pharmacists should be aware that ACE inhibitors may cause serious hepatotoxic reactions. As symptoms generally resolve following cessation of therapy, early recognition and discontinuation of ACE inhibitor therapy is essential. It appears that this is a class effect, and such a reaction to one ACE inhibitor would suggest that all ACE inhibitors be avoided.

REFERENCES

1. Rahmat J, Gelfand RL, Gelfand MC, et al. Captopril-associated cholestatic jaundice. *Ann Intern Med* 1985; 102:56-8.
2. Hagley MT, Hulisz DT, Burns CM. Hepatotoxicity associated with angiotensin-converting enzyme inhibitors. *Ann Pharmacother* 1993; 27:228-31.
3. Hilburn RB, Bookstaver D, Whitlock WL. Comment: angiotensin-converting enzyme inhibitor hepatotoxicity: further insights. *Ann Pharmacother* 1993; 27:1142-3.
4. Valle R, Carrascosa M, Cillero L, et al. Enalapril-induced hepatotoxicity. *Ann Pharmacother* 1993; 27:1405.
5. Pedersen JH, Clementsen PS, Hoyer S, et al. Captopril-induced toxic hepatitis. *Ugeskr-Laeger* 1992; 154:2911-2.
6. Larry D, Babany G, Bernuau J, et al. Fulminant hepatitis after lisinopril administration. *Gastroenterology* 1990; 99:1832-3.
7. Hagley MT, Benak RL, Hulisz DT. Suspected cross-reactivity of enalapril- and captopril-induced hepatotoxicity. *Ann Pharmacother* 1992; 26:780-1.
8. Shionoiri H, Nomura S, Oda H, et al. Hepatitis associated with captopril and enalapril but not with delapril in a patient with congestive heart failure receiving chronic hemodialysis. *Curr Ther Res* 1987; 42:1171-6.
9. Bellary SV, Isaacs PET, Scott AWM. Captopril and the liver (letter). *Lancet* 1989; 2:514.
10. Zimran A, Abraham AS, Hersko C. Reversible cholestatic jaundice and hyperamylasaemia associated with captopril treatment. *Br Med J* 1983; 287:1676
11. Rosellini SR, Costa PL, Gaudio M, et al. Hepatic injury related to enalapril (letter). *Gastroenterology* 1989; 97:810.