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Unexpected outcome (positive or negative) including adverse drug reactions

Probable hepatotoxicity associated with the use of metformin in type 2 diabetes

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Summary

This is a case report of a 44-year-old obese female who developed subclinical hepatic injury 4 weeks after starting metformin for type 2 diabetes. She had a rise in her alanine aminotransferase which peaked at 5 months (738 U/l) and rapidly declined within days of discontinuing her metformin. No other positive evidence of alternative causes for the hepatic injury was found. The likelihood of metformin-induced injury was 7 on the Naranjo scale of adverse drug reactions. A brief review of the 11 previously reported cases in the English medical literature is also made.

BACKGROUND

Metformin-associated hepatic injury is rare; 11 case reports of hepatic damage associated with metformin have been reported in the English literature. This case represents the 15th and youngest reported case of probable hepatotoxicity associated with metformin in the treatment of type 2 diabetes. It highlights the difficulty in detecting such cases and serves to underline the need to be aware of this rare but possible side effect of metformin.

CASE PRESENTATION

A 44-year-old obese Sudanese female presented to her family physician with new-onset diabetes and was prescribed metformin 500 mg (two times daily). On routine follow-up, it was noted that her alanine aminotransferase (ALT) began to rise 1 month after starting the metformin and reached a maximum of 738 U/l at 5 months. Prior to her peak ALT, she had been referred for a gastroenterology opinion, but this was inconclusive and the possibility of non-alcoholic steatohepatitis (NASH) was raised because of fatty infiltration of the liver on abdominal ultrasound. Throughout, she did not have any clinical signs or symptoms of hepatic injury.

Her medical history included stable palindromic rheumatism and steroid-induced osteoporosis. Her medication, excluding the metformin included prednisolone 10 mg (once daily), tramadol 100 mg (once daily as required), calcium 500 mg (once daily), hydroxychloroquine 400 mg (two times daily) and aspirin 81 mg (once daily). She had no other medical history of note, denied any non-prescription medication use and did not consume alcohol.

INVESTIGATIONS

ALT (table 1)

Other results

Her alkaline phosphatase (ALP) was normal throughout. A small rise in the γ-glutamyl transferase (GGT) peaking at 42 IU/l at 5-month postmetformin occurred. During this period, she did not have a clinical flare up of her arthritis. Her erythrocyte sedimentation rate (ESR) was 39 and 48 at the beginning of the fourth month postmetformin. During this time, she had a negative viral hepatitis serology (A, B and C), and antinuclear, antimitochondrial and antismooth muscle antibodies were all negative. An ultrasound of the abdomen was negative for evidence of biliary obstruction but showed evidence of diffuse fatty infiltration.

DIFFERENTIAL DIAGNOSIS

- Metformin-induced drug hepatitis
- NASH
- Autoimmune hepatitis.

TREATMENT

The metformin was stopped by the patient's family physician.

OUTCOME AND FOLLOW-UP

Following 5-day postcessation of metformin, the ALT showed a significant reduction to 273 U/l and the GGT had normalised to 27 IU/l. At 1-month postcessation, the ALT had normalised to 16 U/l and remained normal at 2 months. The patient was started on glimepiride 1 mg once daily after stopping the metformin. A rechallenge test was

Table 1 Results of ALT investigation

Time poststarting metformin (weeks)	ALT (U/l)
2	31
4	60
12	262
20	738
20+5 Days postcessation	273
20+8 Days postcessation	170
20+1 Month postcessation	16

ALT, alanine aminotransferase.

Table 2 Summary of previous case reports of metformin-induced hepatic damage (ordered by age)

Study	Case details	Clinical presentation (N, nausea; V, vomiting)	Duration between start of metformin and symptoms	Investigative evidence of hepatic injury and peak values for liver function tests (IU/l)	Normalisation of biochemical markers postcessation of metformin	Likely mechanism of hepatic injury
Swislocki *et al*[18]	75 Years, male, White	Felt well	8 Weeks	AST 322 ALT 413 ALP 684	4 Weeks	Hepatocellular (rechallenge period only 4 weeks but initial problem occurred at 8 weeks)
Kutoh *et al*[10]	73 Years, female, Japanese	N and V, abdominal pain, jaundice	3 Weeks	AST 689 ALT 772 ALP 635	7 Weeks	Cholestatic
Nammour *et al*[14]	68 Years, male	Jaundice, pruritus (cholestatic jaundice)	4 Weeks	ALT 109 ALP 383 GGT 809 TBil 268	8 Weeks persistently raised ALP (350)	Cholestatic
Deutsch *et al*[15]	67 Years, female	Jaundice, fatigue, weakness	6 Weeks	ALT 905 AST 1152 ALP 121 GGT 248 TBil 82 μmol/l	12 Weeks	Hepatocellular
Desilets *et al*[9]	64 Years, male, White	Jaundice, fatigue	2 Weeks	ALT 289 ALP 994 TBil 362 μmol/l	12 Weeks	Cholestatic
Shailaja *et al*[12]	63 Years, female	Jaundice, pruritus, fatigue	4 Weeks	AST 66 ALT 87 ALP 572 GGT 216 Liver biopsy: neutrophilic infiltration in liver, marked intracellular and intracanalicular bile stasis	16 Weeks	Cholestatic
Cone *et al*[17]	61 Years, male	Jaundice, N, fatigue and unintended weight loss	2 Weeks	AST 623 ALT 571 ALP 143 GGT 325	8 Weeks	Hepatocellular
Scott *et al*[13]	55 Years, male, White	Jaundice	'Few weeks'	TBil 269 ALT/AST 'high' Liver biopsy: hepatitis secondary to intrahepatic hepatocellular necroinflammatory injury	16 Weeks	Cholestatic
Parikh *et al*[8]	54 Years, male, White	Jaundice, fatigue, pale stools	2 Weeks after dose increase 1.5–2 g daily	ALT (×4 ULN) ALP (×5 ULN)	6 Weeks	Cholestatic
Aksay *et al*[16]	52 Years, male	2 Weeks, N and V	2 Weeks	ALT 1469 IU/l TBil 44 μmol/l	10 Days	Hepatocellular
Babich *et al*[11]	52 Years, female, White	2 Weeks fatigue, fourth week jaundice	4 Weeks	AST 583 ALT 651 ALP 500 Liver biopsy: severe hepatitis: pericentral necrosis, parenchymal inflammation with lymphocytes and plasma cells, and lymphocytic vasculitis	2 Weeks	Hepatocellular

ALT, alanine transaminase; AST, aspartate transaminase; GGT, γ-glutamyl transferase; TBil, total bilirubin; ULN, upper limit of normal.

discussed with the patient, but she declined. She has been subsequently followed-up for a period of 2 years during which her ALT has remained within normal limits.

DISCUSSION

The patient developed biochemical evidence of hepatocellular injury without any related clinical symptoms throughout the course of her follow-up. The likelihood that this was an autoimmune hepatitis is low as the patient did not report any musculoskeletal symptoms and her ESR during this period was lower compared with her palindromic rheumatism flare ups. Furthermore, her ALT has remained normal despite further flare ups of her palindromic rheumatism in the subsequent follow-up period. Altogether, this makes an autoimmune hepatitis unlikely.

The presence of fatty-liver infiltration on ultrasound led to the consideration of NASH as a possible cause. However, the relatively rapid rate of change of the ALT in the upward and downward phases cannot be explained by the slower natural history of NASH. Ironically, the

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possibility of NASH led the gastroenterologist to discount metformin as a possible cause.

A drug interaction analysis using Lexi-Interact online software between metformin, hydroxychloroquine, prednisolone and calcium only identified a single possible interaction between metformin and the other medication being taken at the time. The identified effect was a diminished hypoglycaemic effect of metformin because of the interaction of prednisolone. There was no interaction identified which increased the hepatotoxic effect of metformin.

The bilirubin was not measured and ideally would have been quite useful to measure but a negative abdominal ultrasound, normal ALP and absence of clinical symptoms throughout this episode make a cholestatic cause unlikely. The later rise in GGT coinciding with the peak rise of ALT was probably due to intrahepatic cholestasis secondary to hepatocellular damage.

On the basis of the previous reports in the literature, the average time between commencing metformin and the onset of clinical symptoms ranges from 2 to 8 weeks. This was mirrored in this case with an increase in ALT at 4 weeks though peak ALT occurred at 5 months. The recovery of the ALT was within the range of reported cases at 1 month.

Given the lack of evidence for a cause for the rise of ALT and the rapidity of recovery of ALT with cessation of metformin therapy, the conclusion was made that this was a probable adverse drug reaction to metformin. In terms of the Naranjo scale, which is used to score the likelihood of an adverse drug reaction, a score of 7 was obtained implying a probable adverse drug reaction to metformin.

Metformin, a biguanide, is a commonly used treatment in type 2 diabetes. It is generally considered a safe drug but is rarely associated (0.06 cases per 1000 patient years) with lactic acidosis[1] especially in dehydrated patients or in the presence of multiple morbidities. The isolated hepatic effect of metformin is variably reported by drug information resources. The Summary of Product Characteristics for metformin, a mandatory European Drug Information document, mentions this rare side effect and classes it as either isolated[2] or very rare.[3] However, Lexi-Drugs Online[4] and Epocrates,[5] two widely used drug formularies by physicians in USA and in many parts of the Eastern Mediterranean region, do not list this as a possible adverse reaction and only mention that hepatic dysfunction is considered a relative contraindication as it increases the likelihood of lactic acidosis. Micromedex, a more detailed drug database mainly used by pharmacists in the latter region, mentions this side effect but underestimates the frequency as it only cites three cases.[6] This shows the patchy or partial awareness of this metformin-induced side effect in the drug reference databases.

A search of the literature shows 14 case reports (table 2), 11 in the English literature and 3 in the non-English literature, of hepatic injury where metformin has been implicated. The first published case report was made in 1991 in Turkish.[7] Case report authors underestimate the number of reported cases on this subject.[8–10] This is probably due to the lack of a consistent vocabulary in the titling of such case reports with a variety of key terms being used when referring to the hepatic injury: 'hepatitis',[7 11–14] 'hepatotoxicity',[8 11 15–17] 'psuedohepatotoxicity',[18] 'cholestatic jaundice'.

Learning points

- Metformin-induced hepatotoxicity is a rare but possible adverse drug reaction that physicians should be aware of given its common usage.
- Hepatotoxic adverse effects associated with metformin usually occur after 4–8 weeks of therapy.
- Physicians should be aware that differences exist between the major drug information resources used in the world.
- The Sherlock Holmes' dictim "When you eliminate all other possibilities, what remains, no matter how improbable, is the answer" is a useful strategy when dealing with adverse drug reactions which are rare.

Competing interests None.

Patient consent Obtained.

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