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CASE REPORT

Noncholestatic acute hepatocellular injury following candesartan administration

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Arterial hypertension is a highly manageable disorder due to a variety of drugs available for its treatment. Since the late 1990s, angiotensin II receptor blockers have been widely prescribed, achieving appropriate control in patients' blood pressure. Few cases of serious adverse effects have been reported to date. Here, we present a case of acute hepatocellular injury secondary to candesartan administration. Further studies should be performed in patients who present with this adverse effect, in order to prevent more serious outcomes.

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Background and aims

Angiotensin (AT) II receptor blockers (ARBs) have been widely used in the past two decades as a safe and efficient option for the management of hypertension, targeting the **AT 1 receptor**, alone or in combination with other agents. **Candesartan** is one of the ARBs for which few adverse reactions have been reported since its approval in the United States in 1998, despite millions of annual prescriptions [1]. These have been mostly reports of headache, dizziness, fatigue, cough, gastrointestinal dyspepsia and fetal toxicity [2], all of which are expected outcomes of its therapeutic actions on blood pressure. In regard to candesartan's effects on liver function, there have been a few reports of serum aminotransferase elevations of less than 1%, and these were no higher in controlled trials than for placebo therapy [2–4]. We present a case of an acute hepatocellular injury due to Candesartan and review the few similar cases reported, including those published in Spanish.

Materials and methods

Patient data were recorded in the patient's medical history file during his treatment, and patient consent for the publication of his case was obtained. A PubMed search including the terms 'hepatitis', 'hepatotoxicity', 'liver toxicity' and 'candesartan' was performed, and produced 13 results, only four if which were relevant to the case, the other nine consisting of studies focusing on the use of ARBs in the treatment of non-alcoholic streatohepatitis/non-alcoholic fatty liver disease (NASH/NAFLD), fibrosis and other articles unrelated to hepatotoxicity caused by candesartan.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [5], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [6].

Case report and results

A 28-year-old male was initially assessed for hypertension after he presented for a medical consultation following a referral for elevated blood pressure readings on a household electronic sphygmomanometer, found incidentally. No other symptoms were reported, and the physical examination was normal except for a blood pressure reading of 168/96 mmHg.

The patient's medical history revealed no relevant family history of disease, an alcohol consumption of around 50 g of alcohol per day, a balanced diet and moderate exercise 3–4 times per week, consisting of boxing and jogging. All vaccination schemes were complete and up to date; there was no history of previous disease, surgical interventions or blood transfusions, and no use of medication or dietary supplements.

Candesartan was prescribed by the treating cardiologist, starting with a dose of 8 mg day^{-1} once daily (day 0). As a general measure, routine laboratory tests were ordered and performed 1 week after initiating treatment (day 8), consisting of complete blood count, blood chemistry analysis, a thyroid panel, thrombin time, activated partial thromboplastin time and urinalysis; the results of these were within normal ranges, with the exception of a lactate dehydrogenase level of 253 IU l^{-1} (reference range 125–220 IU l^{-1}), an aspartate aminotransferase (AST) level of 197 IU l^{-1} (reference range 13–38 IU l^{-1}) and an alanine aminotransferase (ALT) level of 578 IU l^{-1} (reference range 6–58 IU l^{-1}). There were no changes in other hepatic function markers, as total bilirubin was 1.0 mg dl^{-1}, with a direct bilirubin level of 0.4 mg dl^{-1}, an indirect bilirubin level of 0.6 mg dl^{-1} and an alkaline phosphatase level of 60 IU l^{-1} (reference range 26–140 IU l^{-1}). The patient's physical examination was unremarkable on this occasion as well, and his alcohol consumption habits had not changed. He underwent a hepatitis viral panel [testing for the surface antigen of the hepatitis B virus (HBsAg), anti-hepatitis B core antigen immunoglobulin M (Anti-HBc IgM), anti-hepatitis A virus immunoglobulin M (Anti-HAV IgM) and antihepatitis C virus antibodies (Anti-HCV)], which came back negative for viral infection. Cytomegalovirus, Epstein–Barr virus, and antinuclear, anti-mitochondrial and anti-smooth muscle antibodies were negative. The result of studies on iron and copper metabolism were normal. An ultrasound showed grade 1 steatohepatitis with no other abnormalities, and no liver biopsy was taken. It is important to note that although the patient was advised to lower his alcohol consumption, there was no change in intake throughout the investigation.

The patient's blood pressure was lowered but failed to reach the target levels, so the dose of candesartan was increased to 16 mg once daily (day 9). The hepatic function tests were repeated a week later, and showed that the AST level had risen to 316 UI l^{-1} and the ALT level to 885 UI l^{-1}, with no cholestatic pattern (day 16). Medication was discontinued on the day after the results were received, and the patient was placed on a new regimen of **amlodipine** 5 mg twice daily (day 17). Two weeks after the previous hepatic function tests were performed (day 29), another hepatic function panel was carried out, which showed an important reduction in the AST level to 120 UI l^{-1}, and the ALT level to 380 UI l^{-1}. The last hepatic function tests were taken 17 days later (day 46), and showed normalization of both AST and ALT levels. A curve of both aminotransferase level progression can be seen in Figure 1.

A score of causality assessment was performed with the variables for our patient, using the Roussel Uclaf Causality Assessment Method (RUCAM), giving a score of 9, indicating a highly probable adverse reaction, as shown in Table 1 [7].

Analysis of literature and discussion

Candesartan is generally a very safe and effective blood pressure-lowering medication [4]. To date, the mechanism by which candesartan may produce hepatotoxicity remains unknown. Although some rare instances of clinically

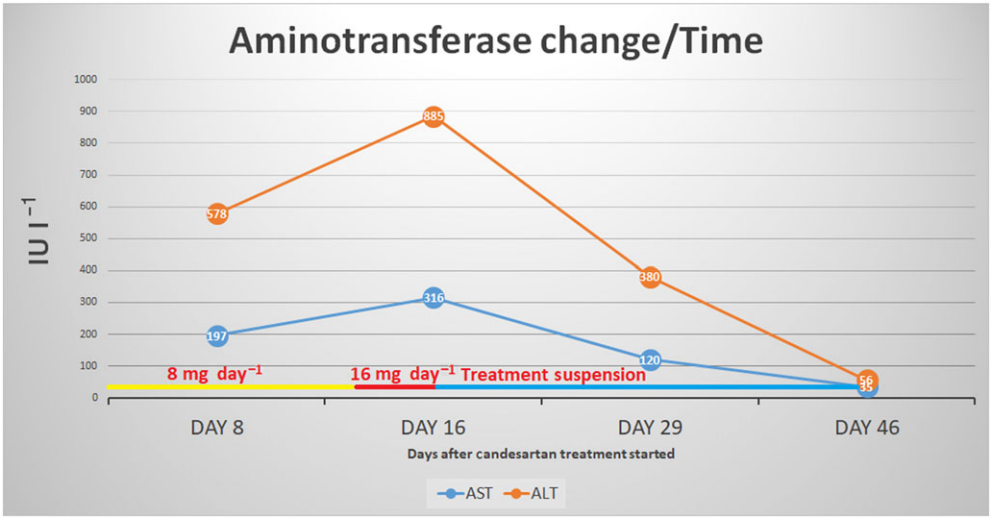

Figure 1

Aminotransferase levels *vs.* time. Candesartan was started on day 0 at 8 mg day^{-1}. Laboratory tests were carried out on day 8. The dose was increased to 16 mg day^{-1} on day 9. A correlation with candesartan was strongly suspected following a rise in aminotransferase levels, secondary to the dose being increased, where other possible causes were excluded. The numers represent international units/ liter as noted on the Y axis

Table 1

Roussel Uclaf Causality Assessment Method (RUCAM) score for the patient

Type of liver injury	Hepatocellular
Time of onset of the event	First exposure
Time from intake to reaction onset	5–90 days (+2)
Time from withdrawal until reaction onset	Not applicable (0)
Alcohol risk factor	Present (+1)
Age risk factor	<55 years (0)
Course of the reaction	>50% improvement in 8 days (+3)
Concomitant therapy	None (0)
Exclusion of nondrug-related causes	Ruled out (+2)
Previous information on hepatotoxicity	Reaction published but unlabelled (+1)
Response to readministration	Not available
Total score: 9 (highly probable adverse reaction)	

noticeable liver injury have been reported, these are extremely scarce. We found a case report by Basile *et al*. [8] (also referenced in the LiverTox [2]) Jiménez-Sáenz *et al*. [9] and Vallejo *et al*. [10] provided a score of causality assessment, (e.g. RUCAM), but did evaluate for possible known causes for the hepatotoxicity and the fact that all patients improved after changing from candesartan to other hypertensive medications.

Taking into account the four reports [8–10, 12], excluding our own: three patients were female and one male, with an age range of 41–82 years. The candesartan dose used in three of the case reports was 16 mg day^{-1}, but was not mentioned in the fourth report. All of the reported patients presented with jaundice. The diagnosis was second confirmed in these cases within the first month, except for one patient who presented 5–6 months after candesartan intake (who was, coincidentally, the patient with highest aminotransferase levels). Enzyme levels varied from 111–1600 UI l^{-1} for AST and 244–2700 UI l^{-1} for ALT, and total bilirubin varied from 8.28 mg dl^{-1} to 46.8 mg dl^{-1}. Recuperation times between the suspension of candesartan treatment and total normalization varied from 3 weeks to 12 weeks, with only two patients having increases in bilirubin levels after liver enzyme levels had started to decrease; these

patients received corticosteroids as an empirical measure for around 6–7 weeks. It is important to highlight that out of a total of four patients, three were from the same town in Spain, and one was from Italy. Our patient has 25% Spanish ancestry, raising the question of whether this could be ethnically related, as mentioned previously by another author [9]. As our case shows, some patients might have subclinical hepatic adverse reactions, and some of these might go unnoticed.

As a class, ARBs in clinical use include eight structurally similar molecules, but with different pharmacokinetics. All of these agents have been associated with a minimal rate of serum enzyme elevations during chronic therapy, usually mild to moderate and self-limiting, and they rarely require dose modification or discontinuation. These vary between drugs and types of clinical expression, and are usually hepatocellular in nature [11].

Conclusions

Candesartan was found to cause subclinical acute hepatotoxicity in our patient. This reaction should be suspected when abnormalities are found and should be assessed further in the clinical setting. We believe that blood chemistry should be tested as a general follow-up in the patient's progress, as should be done after starting a new medication, to ensure that there are no negative outcomes that could lead to adverse outcomes. This could help to identify more asymptomatic cases, and to understand the underlying mechanism behind them, as well as identifying patients who present with liver injury or other abnormalities that could go unnoticed.

Competing Interests

There are no competing interests to declare.

Contributors

All authors were involved in the case, as well as the development and approval of the manuscript.

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