

Increased Plasma Lactate Level Associated to the Use of Atorvastatin: A Study Comparing Cases and Controls

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Abstract

This study aimed to assess the risk of hyperlactatemia (LA) in patients who received atorvastatin (ATV) treatment. An observational and retrospective study using a case-crossover study design. The participants who received atorvastatin (10 - 80 mg) were included in the sample. The main variable in the study was the total number of treatment days for all the medications administered to each patient (PD). All PDs with lactate > 4 mmol/L were cases, while all PDs with lactate ≤ 4 mmol/L were controls. The odds of ATV exposure were calculated for both cases and controls, and the odds ratio (OR) between cases and controls was also calculated. 640 participants, aged 87 years (±6), body mass index of 31.3 (± 2.9) kg/m², and 47% were female. The mean plasma lactate concentrations were 5.0±0.7 mmol/L for the cases and 2.9 ± 0.5 mmol/L for the controls. Total PDs = 5220, PDs with lactate ≥ 4 mmol/L = 319; PDs with lactate < 4 mmol/L = 4901. OR = 2.0 (95% CI: 1.52-2.63; Z4.97; P<0.0001); 73 out of 632 cases were exposed to ATV compared to 246 out of 4269 controls. The likelihood of LA seems to be moderate (2 ≤ OR < 3, as per Cohen's standards).

Keywords: Atorvastatin, Lactate, Case-control, Pharmacoepidemiology

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Introduction

Lactic acid (LA) is generated during regular physiological functions, mainly broken down by the liver and kidneys into carbon dioxide (CO₂) and water, and is frequently observed in illnesses. When the clinical course worsens, the severity increases. Significantly, extremely high levels of lactic acid can cause serious hemodynamic effects and result in fatality. Thus, Serum lactate levels can serve as an indicator of potential danger and a target for treatment [1-3].

Lactate levels within the normal range are below two mmol/L, while hyperlactatemia (hLA) is characterized by levels between 2 mmol/L and 4 mmol/L, and levels above

4 mmol/L are considered severe. Elevated LA levels are linked to a higher risk of mortality regardless of organ failure and shock [1].

On the other hand, there are two types of lactic acidosis. Type-A lactic acidosis is caused by reduced blood flow and low oxygen levels; while Type-B lactic acidosis is characterized by the absence of tissue oxygen deprivation or reduced blood flow. Although type-B lactic acidosis is less frequent than type-A, both types share the underlying issue of mitochondria being unable to metabolize the amount of pyruvate they receive [1].

Drug-induced (DI) lactic acidosis is a type-B lactic acidosis example. Indeed, some drugs can lead to lactic acidosis, such as alcohols, acetaminophen, highly active

antiretroviral therapy, beta-adrenergic agonists, biguanides (metformin), cocaine, cyanogens, halothane, propofol, isoniazid, salicylates, valproic acid, sulfasalazine [4].

Nevertheless, there have been limited clinical trials on drug-induced LA and/or lactic acidosis, with a majority being either retrospective or prospective studies with small participant pools.

Therefore, the use of statin medication can lead to a decrease in Coenzyme Q10 (CoQ10), which in turn can affect mitochondrial oxidative phosphorylation [2]. LA and/or lactic acidosis may occur due to the combination of other medications, leading to DI-hLA and/or DI-lactic acidosis. Indeed, atorvastatin (ATV), which is an HMG-CoA reductase inhibitor, has been shown to reduce CoQ10 levels in the bloodstream. Suggestions have been made that myopathy caused by HMG-CoA reductase inhibitors may be linked to CoQ10 deficiency in tissue mitochondria, and ATV therapy could lead to the development of hLA and/or lactic acidosis as a complication [3]. However, in some patients, this can occur without a clear reason, and therefore, drugs may be a factor in its development.

Because there is no evidence connecting CoQ10 deficiency with a rise in plasma lactate over 4 mmol/L and, in some instances, an increase by the enzyme of 5, lactic acidosis may not occur. The goal was to assess the risk of hLA in patients who received ATV treatment.

Materials and Methods

An observational and retrospective study was carried out using a case-crossover study design, where individuals act as both cases and controls by incorporating a period before the outcome event. The duration in which the outcome occurs is referred to as the case period, while the period before the case period acts as a control [5].

Furthermore, a design that relied on person-day measurements for cases and controls was employed, as opposed to individual-based measurements. Person-day (PD) is a calculation of the combined time in days that all participants dedicate to a study, taking into account the days spent on analysis by individuals [6]. A participant can contribute days to the research as a comparison if they do not have the health condition being studied, and can also do so if they do have the condition being studied [7]. The participants in the study were all patients who were hospitalized in the Internal Medicine and Geriatric departments of a teaching hospital, in Zaragoza (Spain), between 2022 and 2023. As the study was retrospective and non-experimental, with pooled data obtained from secondary sources, and carried out in a Spanish public hospital, review by an ethical committee was not necessary. However, this research adhered to the ethical

guidelines outlined in the 1975 Declaration of Helsinki, updated in 2013.

All patients who received ATV (10 - 80 mg) were included in the sample. Patients who were currently or previously receiving medications or had medical conditions that affected their plasma lactate levels (such as albuterol, salbutamol, epinephrine, linezolid, metformin, nucleotide reverse transcriptase inhibitors, propofol, nitroprusside, barbiturates, valproic acid, salicylates; AIDS, alcoholism, cancer, cirrhosis, kidney failure, respiratory failure) were not included in the study. The main variable in the study was the total number of treatment days for all the medications administered to each patient in the sample. All PDs with LA > 4 mmol/L were included as cases, while all PDs with LA ≤ 4 mmol/L were included as controls. The odds of ATV exposure were calculated for both cases and controls, and the odds ratio (OR) between cases and controls was also calculated.

Information was gathered from the hospital's lab and supported by electronic prescription recording systems. The Chi-square test was utilized to determine the statistical significance of variances among 28 drugs, with a Bonferroni correction applied to adjust for multiple comparisons ($n = 28$; $P < 0.05/28 = 0.0017$).

Results and Discussion

The study involved 640 participants, aged an average of 87 years (± 6), with a body mass index of 31.3 (± 2.9) kg/m², height measuring 159 (± 12) cm, weighing 81 (± 18) kg, and 47% were female. They were on five or more medications, getting between 10 and 80 mg of ATV, and admitted to the internal medicine division of a small hospital with fewer than 200 beds, spending an average of 7.5 days. The mean LA concentrations were 5.0 $\pm$ 0.7 mmol/L for the cases and 2.9 $\pm$ 0.5 mmol/L for the controls.

Number of drugs = 28; Total PDs = 5220, PDs with lactate ≥ 4 mmol/L = 319; PDs with lactate < 4 mmol/L = 4901. OR = 2.0 (95% CI: 1.52-2.63; Z4.97; $P < 0.0001$): 73 out of 632 cases were exposed to ATV compared to 246 out of 4269 controls.

Based on the OR results, the likelihood of hLA seems to be moderate ($2 \leq \text{OR} < 3$, as per Cohen's standards). Nonetheless, since ATV is utilized for the pharmacological prevention of different diseases, it is often combined with other medications that can also heighten the likelihood of hLA, leading to an increased risk of lactic acidosis in some instances.

The myopathy caused by statin drugs, which can lead to high CPK levels and be painful or tender, is well documented and rare. However, a more common side effect experienced by individuals taking these drugs is a sense of decreased energy levels [8]. Due to statins

inhibiting mevalonate synthesis, ubiquinone levels decrease, impacting mitochondrial energy production and potentially causing energy deficiency [9]. Therefore, individuals taking statins may benefit from supplementing with ubiquinone (Co-Q10) to counteract this effect and improve energy levels as suggested by a study [10]. Additionally, the increase in lactate-pyruvate ratio reflects a decrease in mitochondrial oxidation [2]. Statins function by blocking HMG-CoA reductase, which leads to a decrease not only in cholesterol production but also in the synthesis of other nonsterols like coQ10, resulting in reduced coQ10 levels. CoQ10 plays a vital role as a carrier in the mitochondrial respiratory chain and is involved in oxidative phosphorylation. As a result, there is a lower level of mitochondrial complex I activity due to insufficient substrate (acetyl-CoA and α -ketoglutarate tricarboxylic acid cycle effect) and diminished electron carrier transport (coQ10 effect) [10]. In this regard, case reports and clinical studies have shown that statins may lead to hLA and/or lactic acidosis or an increased blood lactate/pyruvate ratio or respiratory exchange ratio [2, 3]. Comparable outcomes have also been shown in research on animals [11]. Nevertheless, some research did not detect a significant increase in lactate levels when using statins [12].

In our research, using real-world data, we found a positive association between ATV usage and hLA (> 4 mmol/L). The study is novel in the sense that it focuses on a specific medication and its potential impact on LA levels, which could have important implications for the use of atorvastatin in certain patient populations. Also, the study used a within-subject design, where participants served as their controls. This allowed for a more robust evaluation of the direct effects of ATV use, without the confounding influence of inter-individual variability.

Finally, it should be noted that this research was done retrospectively using medical records to evaluate outcomes, potentially introducing bias. It was carried out in one hospital and focused only on patients in internal medicine and geriatric wards, reducing the generalizability of the findings. Additionally, the research is based on information gathered from secondary sources and is limited to proposing potential hypotheses.

Conclusion

In short, the odds ratio for high plasma lactate levels above 4 mmol/L is OR=2 when atorvastatin, administered in amounts ranging from 10 to 80 milligrams, is used for various reasons. However, it is recommended to supervise its utilization when used alongside other drugs with comparable toxic effects.

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Ethics statement: As the study was retrospective and non-experimental, with pooled data obtained from secondary sources, and carried out in a Spanish public hospital, review by an ethical committee was not necessary. However, this research adhered to the ethical guidelines outlined in the 1975 Declaration of Helsinki, updated in 2013.

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