Case Study

# High Levels of Blood Lactate Associated with the Use of Low Dose Aspirin: A Case-Control Study

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## Abstract

We evaluate the risk of severe hyperlactatemia (LA) >4 in patients on chronic treatment with low doses of aspirin (ASP) and estimate the magnitude of the association. For this, a case-crossover study design, where patients who have experienced the outcome (cases) are a part of their controls by containing a period before the onset of the outcome. Additionally, a design based on person-day measurements, rather than individuals, was used for cases and controls. When comparing the group of cases (exposed to ASP/not exposed), we found: 127/578 vs. group controls (ASP exposed/unexposed): 547/3,968, and an OR=1.6 (95% CI:1.29) was obtained (-1.97; z= 4.31; p<0.0001). The risk of lacticaemia greater than 4 mmol/L with the use of low-dose aspirin (100 mg) in its main indication (secondary prophylaxis of vascular ischemic event) appears to be weak (OR=1.6). However, monitoring is recommended when used together with other drugs with the same toxicity profile. Lactate monitoring must be incorporated into an interventional and therapeutic plan so that the patient benefits from these measurements.

**Keywords:** Aspirin, Lactate, Case-control study, Vascular ischemic event

## Introduction

Lactic acid is produced as a result of normal physiological processes. However, it also is commonly found, especially in elevation, in pathological states. This elevation can lead to significant changes in blood flow and circulation and can, therefore, be a risk marker and a therapeutic objective. The larger the level and the more protracted it takes for raised serum lactate to normalize, the higher the chance of death [1-3].

Typical lactate levels are below 2 mmol/L, whereas hyperlactatemia (LA) is when lactate levels range from 2 mmol/L to 4 mmol/L, and severe as levels above 4 mmol/L, which may lead, in the latter, to lactic acidosis with pH equal to or lower than 7.35 and PaC02 less than or equal to 42 mmHg [4].

Healthcare providers need to recognize that high levels of lactate in the blood can happen even when tissue is well supplied with oxygen. However, lactic acidosis typically develops when there is insufficient tissue perfusion, disruptions in carbohydrate metabolism, and the administration of specific drugs. (as drug-induced) [4].

There are two types of lactic acidosis: type A caused by hypoperfusion and hypoxia, and type B unrelated to tissue hypoxia or hypoperfusion. Nonetheless, they both face the basic issue of mitochondria's incapacity to metabolize the quantity of pyruvate provided to them.

Drug-induced lactic acidosis is an example of type-B lactic acidosis [4]. Thus, medications such as, for example, alcohols, acetaminophen, highly active antiretroviral therapy, beta-adrenergic agonists, biguanides (metformin), cocaine, cyanogens, halothane, propofol, isoniazid, salicylates, valproic acid, sulfasalazine, can cause it.

Research on drug-induced hyperlactatemia is limited, mostly consisting of small-scale retrospective or prospective studies. In 2011, Jung and his team carried out a prospective analysis across multiple centers [5].

On the other hand, we know that treatment with aspirin [6-8], through a decrease in coenzyme Q10 (CoQ10), can cause an impairment of mitochondrial oxidative phosphorylation, with

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hyperlactatemia and possible lactic acidosis. In fact, aspirin has been documented to reduce serum CoQ10 concentrations and lactic acidosis may develop as a complication of aspirin treatment [9]. Furthermore, lacticaemia (LA) can occur without an apparent predetermined cause, in a subgroup of patients, and in these cases, its induction by drugs must be considered.

Therefore, the objective was to evaluate the risk of severe LA >4 and, in some cases, the appearance of lactic acidosis (LA >5) in patients on chronic treatment with low doses of aspirin (ASP), in this case, due to its cumulative effect.

## Materials and Methods

We conducted a case-crossover study design, where individuals who are considered cases also serve as their controls by including a period before the occurrence of the outcome. The time frame involving the result is known as the case period, whereas the period preceding the case period serves as a control [10].

Additionally, a design based on person-day measurements, rather than individuals, was used for cases and controls. Person-day is an estimation of the total time at risk in days that all participants contributed to a study, based on the days individuals spend on analysis [11]. A participant can provide days to the research as a control if they do not have the health condition being studied, and can also do so if they do have the condition being studied [12].

The objective of this case-control study was to estimate the magnitude of the association between exposure to low-dose aspirin and LA > 4 mmol/L. The sample consisted of all patients admitted, during 2022 and 2023, to the Internal Medicine service of a basic general hospital with less than 200 beds. Those patients on previous or current treatment with medications and/or with diseases that altered plasma lactate values (e.g., albuterol, statins, salbutamol, epinephrine, linezolid, metformin, nucleotide reverse transcriptase inhibitors, propofol, nitroprusside, barbiturates, acid valproic; AIDS, alcoholism, cancer, cirrhosis, kidney failure, respiratory failure) were excluded.

The main variable was the total number of person-days of treatment (PD) for all medications received by each patient during the study period. Cases consisted of patient PDs with LA levels >4 mmol/L, while controls included patient PDs with LA levels ≤4 mmol/L. The odds of being exposed to ASP versus not exposed were compared in both cases and controls, and the odds ratio (OR) was calculated between the two groups, cases versus controls.

Data were obtained from the hospital laboratory and assisted electronic prescribing recording systems.

The Chi-square test was utilized to determine the statistical significance of variances, with the Bonferroni adjustment taken into account due to the 28 drugs tested ($n = 28$; $p < 0.05/28 = 0.0017$).

## Results and Discussion

537 individuals were included in the study, with an average age of 87(± 6) years, body mass index of 31.3 (± 2.9) kg/m$^2$, height of 159 (± 12) cm, weight of 81(±18) kg, and 47% female. They were taking multiple medications (≥ 5), receiving 100 mg of ASP, and hospitalized in the internal medicine department of a small hospital with under 200 beds, staying an average of 7.5 days. The average LA levels were 4.9 ± 1.0 mmol/L mg/dl for the cases and 2.1 ± 0.3 mmol/L for the controls.

The total number of PD was 5,220. For the cases (LA>4mmol/L) and controls (lactate≤4mmol/L), they were 705 and 4,515, respectively. When comparing the group of cases (exposed to ASP/not exposed), we found: 127/578 vs. group controls (ASP exposed/unexposed): 547/3,968, and an OR=1.59 (95% CI:1.29) was obtained (-1.97;z= 4.31;p<0.0001)

According to the OR obtained, the associated risk of LA appears to be weak (OR<2, according to Cohen's criteria). However, given that in the pharmacological prophylaxis of vascular ischemic attack, it is used in conjunction with other drugs that, in turn, can also increase the risk of LA, this could be elevated and in certain cases even present lactic acidosis.

Lactic acidosis in a patient does not always result in acidemia. The emergence of lactic acidosis is influenced by the level of hyperlactatemia, the body's ability to buffer, and the presence of other factors like tachypnea and alkalosis associated with conditions such as liver disease and sepsis. As a result, elevated lactate levels in the bloodstream or lactic acidosis can be associated with acidic, normal pH, or alkaline conditions [13]. Cohen and Woods categorized lactic acidosis into two groups: type A and type B [14]. Type B2 is triggered by various types of medications and poisons, such as biguanides, alcohols, iron, isoniazid, zidovudine, and salicylates [15].

Aspirin, a widely used non-prescription drug, is appreciated for its ability to reduce inflammation, relieve pain, and lower fever. Nevertheless, it has the potential to be extremely poisonous or deadly when taken intentionally, accidentally, or in excess for therapeutic purposes. Aspirin prevents mitochondria from effectively processing pyruvate, resulting in increased lactate levels and potential lactic acidosis [16].

Treatment generally includes withdrawal of the offending medication and delay or lack of recognition is associated with very poor outcomes.

Finally, this type of study, based on data extracted from secondary databases, although it reflects usual clinical practice, can only be used to raise hypotheses.

## Conclusion

The risk of lacticaemia greater than 4 mmol/L with the use of low-dose aspirin (100 mg) in its main indication (secondary prophylaxis of vascular ischemic event) appears to be weak (OR=1.6). However, monitoring is recommended when used together with other drugs with the same toxicity profile. Lactate monitoring must be incorporated into an interventional and therapeutic plan so that the patient benefits from these measurements.

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