Review

Bench-to-bedside review: Severe lactic acidosis in HIV patients treated with nucleoside analogue reverse transcriptase inhibitors

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Abstract

Nucleoside reverse transcriptase inhibitors (NRTIs) are effective antiretroviral therapy for the treatment of HIV-infected patients. NRTIs can induce mitochondrial impairment that leads to a number of adverse events, including symptomatic lactic acidosis. In the present review, we describe the underlying mechanism of NRTI-induced toxicity and the main clinical features of this infrequent, but severe, emerging complication. We also summarise experimental data and clinical observations that support the use of L-carnitine supplementation to reverse NRTI-induced mitochondrial impairment.

Keywords antiretroviral drug, critically ill patients, HIV, lactic acidosis, mitochondria

Nucleoside analogue reverse transcriptase inhibitors (NRTIs) are effective antiretroviral therapies for the treatment of HIV-infected patients. Treatment with NRTIs has been associated with mitochondrial toxicity [1] responsible for adverse events including hepatic steatosis [2], myopathy [3], neuropathy [4], myelotoxicity [5] and overproduction of lactate [1].

Symptomatic lactic acidosis following the use of NRTIs was first described by Jolliet and Widmann [6] and by Chatta and colleagues [7] in HIV-infected patients treated with azidothymidine. Several reports since then have established that other NRTIs can induce lactic acidosis [8–30]. This severe adverse event is infrequent but its occurrence may be underestimated [31]. Progression of lactic acidosis can lead to irreversible multiple organ failure despite drug withdrawal [8].

In the present review, based on Medline research and using personal data, we describe the pathophysiology and the clinical spectrum of lactic acidosis in an attempt to define a population with a poor prognosis. Based on clinical data and experimental evidence, we discuss the use of L-carnitine as a specific treatment for life-threatening NRTI-induced lactic acidosis.

Mitochondrial functions and NRTI toxicity

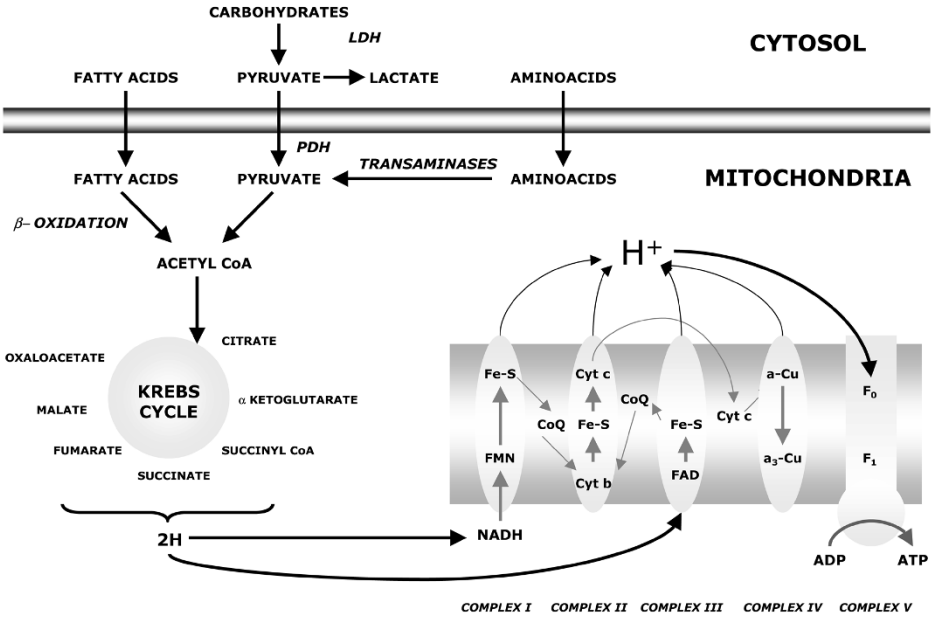
Mitochondrial respiratory chain

The main function of mitochondria is to produce energy through electron-chain transport and oxidative phosphorylation (summarised in Fig. 1). The core of the pathway is a complex of five subunits (subunits I–V) located on the inner mitochondrial membrane. Electrons pass the chain from various substrates, providing energy to the proton pump that creates an electrochemical gradient between mitochondria and their environment. Different substrates can enter the electron-chain transport at complex I (the reduced form of nicotinamide adenine dinucleotide [NADH]–coenzyme Q oxidoreductase) or complex II (succinate–coenzyme Q oxidoreductase), which provide electrons to complex III (coenzyme QH_2–cytochrome oxidoreductase). Complex III then reduces cytochrome *c*, which passes electrons to complex IV (cytochrome *c* oxidase). Complex V (ATP synthase) produces ATP.

To feed this chain, degradative metabolic pathways transform substrates into energetic compounds. The oxidative decarboxylation of pyruvate leads to the production of acetyl-coenzyme A. Fatty acids enter the mitochondrial metabolism after β-oxidation, which allows the production of two acetyl-

NADH = reduced form of nicotinamide adenine dinucleotide; NRTI = nucleosidic reverse transcriptase inhibitor.

Figure 1



Mitochondrial electron chain transport and oxydative phosphorylation. Most of the energy produced by metabolic pathways is contained in the reduced form of nicotinamide adenine dinucleotide (NADH) and in the reduced form of flavine adenine dinucleotide ($FADH_2$), and is transformed in ATP by mitochondria. Reduced mitochondrial coenzymes give their two electrons to carriers that carry them to molecular oxygen, the final electron acceptor, using oxydo-reduction reactions. A protonic gradient allows hydrogen to cross the inner membrane and produce ATP. a-Cu, coenzyme a-copper; a_3-Cu, coenzyme 13-copper; CoA, coenzyme A; CoQ, coenzyme Q; Cyt, cytochrome; F_0, F_0 family ATP synthase; F_1, F_1 family ATP synthase; Fe-S, iron-suphur cluster; FMN, flavine-adenine mononucleotide; H, hydrogen; LDH, lactate dehydrogenase; PDH, pyruvate dehydrogenase.

coenzyme A molecules and one acyl-coenzyme A molecule shorter than the initial substrate. Acetyl-coenzyme A then enters the citric acid cycle or Krebs cycle to release carbon dioxide, hydrogen, NADH, the reduced form of flavine adenine dinucleotide ($FADH_2$), GTP and coenzyme A.

Mechanisms of NRTI-induced lactate elevation

The toxicity of NRTI is related to alterations of the mitochondrial breathing pathway at different levels. The mechanisms of toxicity related to the use of NRTI are summarised in Table 1.

Longstanding use of NRTI induces damage of βDNA and γDNA polymerases. The dysfunction of γDNA polymerase leads to mitochondrial accumulation of abnormal nucleoside acids that alter termination and internalisation of mitochondrial DNA [32]. A recent article confirms that mitochondrial DNA levels are significantly decreased in patients with symptomatic, nucleoside-related hyperlactataemia, and confirms that reduction of mitochondrial DNA precedes symptomatic hyperlactataemia and resolves on the discontinuation of therapy [33]. Nevertheless, another report states that, despite the mitochondrial DNA depletion, the oxidative capacity of the mitochondrial respiratory chain is preserved in lymphocytes derived from treated asymptomatic HIV-infected patients. This does not exclude the possibility of decreased mitochondrial respiratory-chain function in other tissues [34].

As mitochondrial DNA encodes 13 out of 80 enzymes of the breathing pathway, this dysregulation leads to the decrease in ATP synthesis and metabolism. In addition, NRTIs also decrease electron transfer by impairing the NAD^+/NADH cycle [35].

NRTIs thus impair the β-oxidation cycle and disrupt oxidative phosphorylation [1]. These pathways physiologically allow fatty acids and pyruvate to enter as energetic substrates in the mitochondrion. When NRTI toxicity occurs, long-chain fatty acids (characterised by a carbon scaffold above 12 residues) do not contribute to ATP production and accumulate into the cytosol of myocytes and hepatocytes. An increase in glycolysis then leads to the overproduction of lactic acid, which imbalances the lactate:pyruvate ratio [36]. The hepatic failure sometimes observed in this context compromises clearance of lactate and contributes to the development of what is then classified as type II lactic acidosis (i.e. related to the deregulation of cell metabolism and not directly linked to tissue hypoxaemia).

Apoptosis, the programmed cell death phenomenon driven by specific signalling pathways (reviewed in [37]) in response to stress conditions, also contributes to NRTI toxicity. This physiologic event is tightly regulated by the balance between proapoptotic and antiapoptotic signals. The imbalance in

Table 1

Cellular effects of nucleosidic reverse transcriptase inhibitors (NRTIs) and carnitine

	Toxicity of NRTIs	References	Effect of carnitine	References
Metabolism	Impairment of β-oxidation cycle	[1]	Long-chain fatty acids carrier	[55]
	Accumulation of long-chain fatty acids into the cytosol	[34]	Protection of cytochrome *c* oxidase from octanoic acid-induced damage	[61]
	Decrease in ATP concentration	[32]	Cofactor of the electron chain from complex I–V	[60]
	Decreased electron-chain transport	[32]		
	γDNA polymerase damage	[33]		
	NAD^+/NADH impairment			
Apoptosis	Increased apoptosis	[36–38]	Decreased global apoptosis	[44–46]
	Overexpression of the receptor Fas	[38]	Decreased ceramide generation	[46,49–52]
			Decreased mitochondrial apoptosis	[49]
			Link with Bcl2?	[50]

NAD^+, nicotinamide adenine dinucleotide; NADH, reduced form of nicotinamide adenine dinucleotide

favour of proapoptotic signals can lead to activation of caspases, the cysteine proteases that cleave target proteins to determine apoptosis. Several studies suggest that NRTIs play a proapoptotic role. In B-lymphoid cell types [38,39] and peripheral blood mononuclear cells [40], azidothymidine can trigger apoptosis and inhibition of the cell cycle [39] associated with overexpression of the death domain receptor Fas [40], although it is established that mitochondrial apoptosis can be responsible for an increased lactate production [41].

Clinical features of NRTI-induced lactic acidosis in HIV-infected adults

Although the incidence of symptomatic lactic acidosis in adult HIV-infected patients treated with NRTIs may have been previously underestimated, recent data suggest that the occurrence of NRTI-induced lactic acidosis is increasing [31]. The estimated incidence varies between 1.3/1000 in 1995 [9] and 14.8/1000 recently [28], but this discrepancy may be related to differences in case definition [31]. Descriptions of clinical features and laboratory findings are sparse and the literature does not precisely define the clinical spectrum of this disorder.

To identify the clinical features of NRTI-induced lactic acidosis in HIV-infected adults, we recently reviewed charts from published observations and personal cases [42]. Twenty patients were survivors and 19 patients did not survive the disorder. The occurrence of symptomatic lactic acidosis or hepatic failure attributed to the use of NRTIs in adult HIV-infected patients defines severe mitochondrial cytopathy. Although this disorder often occurs in overweight females, no risk factor has been clearly identified. Most patients are diagnosed with AIDS at the time of the occurrence of the adverse event. Cases have been attributed to the use of all NRTIs currently used in human therapy, although they seem to occur more frequently when stavudine and lamivudine are combined. The average delay between the introduction of NRTI and the diagnosis of mitochondrial cytopathy is 8 months . The time from admission to death was 5 days (range 1–17 days) in the nonsurvivor population.

Clinical manifestations are often nonspecific (summarized in Table 2. Asthaenia is encountered in 70% of cases. Anorexia (40%) and weight loss (20%) are also commonly reported. The body temperature is normal in 50% of the cases, but it can range between 35.3 and 39°C for the remaining patients. Abdominal signs are reported in most patients: nausea and vomiting are frequent (87.5%), as is abdominal pain (82%), often localised in the right upper quadrant. Examination finds hepatomegaly (75%), confirmed by ultrasound tomography findings consistent with hepatic steatosis. Muscular weakness is reported in 20% of the cases. Tachypnoea is very common (83% of the cases) and mostly related to severe acidosis.

Lactic acidosis is indeed a constant biological feature of mitochondrial cytopathy. The first recorded arterial blood lactate concentration ranges between 2.9 and 43 mmol/l, and life-threatening acidosis occurs in 42% of the cases. Enzyme liver assays show marked cytolysis (79%) and anicteric cholestasis (73%). The prothrombin time is significantly decreased in 45% of the patients. Other common laboratory test abnormalities include elevated pancreatic enzymes (33%) and increased creatine phosphokinase or lacticodehydrogenase concentrations. The liver is constantly involved, and pathology examination usually reveals steatosis ($n=11$) that can be classified as macrovacuolar, microvacuolar or mixed. Electronic microscopy of the liver, when available [8,12], shows ballonised mitochondria with loss of cristae. Inflammation and necrosis of the pancreas gland are also

Table 2

Common findings in 39 cases of nucleosidic reverse transcriptase inhibitor-induced lactic acidosis

Clinical feature	Percent of cases
Asthaenia	70
Muscular weakness	20
Anorexia	40
Loss of weight	20
Fever or hypothermia	50
Nausea and vomiting	87.5
Abdominal pain	82
Hepatomegaly	75
Tachypnea	83
Laboratory findings	
Hyperlactataemia and metabolic acidosis	100
Hepatic cytolysis	79
Hepatic cholestasis	73
Low prothrombin rate	45
Elevated lacticodehydrogenase	100
Macrovacuolar or microvacuolar steatosis	100

described. Lung pathology mostly indicates nonspecific inflammatory oedema. Light microscopy never shows any involvement of skeletal muscles in this setting.

The outcome of NRTI-induced lactic acidosis is often unfavourable. Uncontrolled shock and/or hepatic failure usually leads to death within 8 days following hospital admission. Supportive care including haemodialysis, alkalinisation, vasoactive drugs and mechanical ventilation is inefficient. In some cases, patients have been treated with prostaglandin [13] and with thiamine [15] without any improvement.

In an attempt to identify prognostic factors, we compared available data and the clinical course from hospital charts of survivors and of nonsurvivors [43]. Clinical features did not differ between the two populations. Conversely, arterial blood pH and bicarbonates almost reached statistical significance, probably because of the limited number of available observations. In fact, the first registered blood lactate was significantly different between survivors and nonsurvivors. The mean values of the initial blood lactate level in survivors and in nonsurvivors were 7.3 ± 3.8 and 18.6 ± 8.8 mmol/l, respectively ($P < 0.01$). We used the LOWESS smoothing function and the locally weighted least-squares method to identify a blood lactates threshold that is likely to predict poor outcome. A value of 9 mmol/l was associated with a positive predictive value of 82%, with a negative predictive value of 94.5%, and with high sensitivity and specificity.

The initial blood lactate level can thus predict the course in symptomatic lactic acidosis related to the use of NRTIs. Blood lactate below 9 mmol/l at diagnosis is associated with a less severe disorder, whereas a value above this threshold is predictive of a fatal outcome.

L-carnitine as a possible treatment for NRTI-induced severe lactic acidosis in HIV-infected patients

Rationale for the use of L-carnitine in NRTI-induced lactic acidosis

Carnitine is derived from γ-hydroxy-β-butyric acid. Although a regular diet is the primary supply of carnitine, endogenous synthesis is possible from sulphated amino acids (reviewed in [44]). Carnitine levels are decreased in HIV-infected patients through several mechanisms, including malabsorption, increased excretion, overconsumption of energy in fatty acids metabolism and the use of drugs, including NRTIs [44,45].

Carnitine is a pivotal cofactor for mitochondrial aerobic metabolism [46]. It carries long-chain fatty acids through the inner mitochondrial membrane to allow their use in the β-oxidation circle. It also interacts downstream at different steps as a cofactor between complex I–complex V of the electron chain [47]. Carnitine directly stimulates phase IV of the mitochondrial breathing cycle, and prevents the detrimental effect of octanoic acid on the cytochrome *c* oxidase [48].

An emerging concept suggests that carnitine could also modulate apoptosis. Carnitine decreases the number of apoptotic cells and lowers caspase 3-like activity in Jurkat T cells after stimulation of the death domain receptor Fas [49], in the serum-starved P19 teratoma cell line [50] and in cardiomyocytes exposed to doxorubicin [51]. In the latter model, L-carnitine seems to lower the doxorubicin-induced sphyngomyelinase activity and decreases the concentration of ceramides, messengers involved in programmed cell death. Fibroblasts deficient for carnitine palmitoyl transferase 1, the enzyme that converts carnitine into palmitoylcarnitine, are resistant to apoptosis induced by staurosporine [52], a drug that triggers the mitochondrial apoptotic pathway by opening mitochondria transition pores. In addition, a clear association between carnitine palmitoyl transferase 1 and the antiapoptotic mitochondrial protein Bcl2 has been found using several techniques including a yeast two-hybrid system [53]. These data suggest that L-carnitine modulates apoptosis at the mitochondrial level.

L-carnitine reverses the mitochondrial toxicity of NRTIs *in vitro*. Incubation of cell lineages with NRTIs reproduces features encountered in human NRTI-related cytopathy (i.e. modification of the ultrastructure of the mitochondria and accumulation of lipid droplets in the cytoplasm) [54]. In human myotube cultures, the addition of carnitine in the medium improves these changes whether or not azidothymidine is withdrawn [55]. A clinical study confirmed the anti-

apoptotic activity of carnitine in CD4-positive lymphocytes from peripheral blood of HIV-infected patients [56]. Samples analysed after treatment by daily infusions of L-carnitine show a decreased number of apoptotic cells that correlates with a drop in ceramide concentration.

Hypertriglyceridaemia is a disorder commonly related to the use of NRTIs [57]. The underlying mechanism involves mitochondrial impairment and would preferentially target hepatocytes. In a preliminary study, L-carnitine dramatically reversed antiretroviral therapy-related hypertriglyceridaemia in HIV-infected adults [58]. Reversal of lactic acidosis related to NRTIs after treatment including L-carnitine has also been reported in patients with blood lactate above 10 mmol/l at the beginning of the treatment [43,59].

L-carnitine as a potential treatment for life-threatening NRTI-induced lactic acidosis

Carnitine is an important compound for the mitochondria bioenergetic system that may modulate apoptosis. It has also been observed that carnitine could reverse the mitochondrial toxicity of NRTIs *in vitro* and *in vivo* [44,55,58,59].

In an attempt to define whether L-carnitine could be an effective treatment for patients with life-threatening NRTI-related lactic acidosis, we prospectively investigated the effects of L-carnitine in six critically ill, HIV-infected patients [43]. These patients had arterial blood lactate above 10 mmol/l and severe organ dysfunction, possibly requiring dialysis. L-carnitine was used as a specific treatment, with a dosing regimen of 50 or 100 mg/kg per day if continuous dialysis was required. Six patients received the treatment according to the protocol. With a mean Simplified Acute Physiology Score II score of 81, with blood lactate levels ranging from 13 to 20.1 mmol/l and with pH values between 7.3 and 6.7, these patients had a predicted intrahospital death probability of 91% [60]. When available, carnitine dosages revealed a decrease in the free cartinine:total serum carnitine ratio and an increase in urine excretion, features commonly encountered in this setting. Three patients out of six survived. Their arterial blood lactate level returned to baseline within 15 days and no increase in blood lactate was noted during the followup. These preliminary results suggest that L-carnitine may be useful for the treatment of life-threatening lactic acidosis related to the use of NRTIs.

Conclusion

Following the widespread use of NRTIs for the treatment of HIV-infected patients, increasing evidence has demonstrated that these drugs can induce mitochondrial dysfunction and lactic acidosis. Experimental data show that NRTIs alter mitochondrial breathing at different steps [1]. Increased lactacidaemia induced by NRTIs is explained by a shift toward anaerobic metabolism with inverted lactate:pyruvate ratio [36], by increased apoptosis leading to lactate overproduction, and by decreased lactate clearance secondary to hepatic dysfunction [28]. The pathophysiology of NRTI-induced acidosis might be even more complex, and genetic risk factors could also play a role.

Despite increased physician awareness of NRTI-related lactate overproduction, clinical features are so aspecific that lactic acidosis can rapidly progress to life-threatening conditions before NRTIs are withdrawn. In NRTI-related lactic acidosis, the blood lactate concentration, a potential marker of mitochondrial impairment, seems to have a highly significant prognostic value. Whereas some workers consider mitochondrial cytopathy severe if blood lactate levels are above 5 mmol/l [26], we have found that arterial blood lactate at the time of diagnosis can predict outcome and that patients with lactate levels above 9 mmol/l are likely to develop life-threatening NRTI-induced lactic acidosis and die [43].

Very few HIV-infected patients with severe lactic acidosis have survived with the use of specific therapies [22,25]. Considering the rationale for the use of L-carnitine to treat NRTI-induced severe lactic acidosis and related organ failures, we conducted a small open trial of L-carnitine in critically ill patients and reported survival of three out of six patients with initial lactate levels above 9 mmol/l [43]. Several drugs have been proposed for the treatment of symptomatic lactic acidosis related to NRTIs because of their antiapoptotic and metabolic effects. Nevertheless, these promising data are very preliminary. Added to other studies, this preliminary result suggests that L-carnitine is a potential treatment for NRTI-induced mitochondrial dysfunction with severe lactic acidosis, although additional data should be provided to determine its efficiency.

Competing interests

None declared.

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