Toxic Effects of Sodium Fluoroacetate Metabolic Poisoning in Cellular Models

Bryan McCranor, US Army Medical Research Institute of Chemical Defense
Rebecca Lewandowski, US Army Medical Research Institute of Chemical Defense
Talearia Young, US Army Medical Research Institute of Chemical Defense
Nazira Alli, US Army Medical Research Institute of Chemical Defense
Marilynda Abilez, US Army Medical Research Institute of Chemical Defense
Katherine Sherman, US Army Medical Research Institute of Chemical Defense
Jennifer Devorak, US Army Medical Research Institute of Chemical Defense
Benjamin Wong, US Army Medical Research Institute of Chemical Defense

Sodium fluoroacetate (Compound 1080) is a colorless, odorless, tasteless, water-soluble metabolic poison, traditionally used as a pesticide against nuisance mammals. In the body, 1080 is synthesized to fluorocitrate, which inhibits the citric acid cycle and reduces the rate of cellular metabolism. Compound 1080, with a human LD50 of 2-10 mg/kg, has a latent period of 0.5 to 6 hours before clinical symptoms are observed [1, 2], which include nausea, vomiting, abdominal pains, salivation, irrational fear, weakness, tachypnea, cyanosis, and sweating [3-5]. No known antidote exists for 1080, and current treatment protocols consist of only general supportive measures [6]. Compound 1080 is a potential weapon of mass destruction. In 2004 Rep. Peter DeFazio (D-Ore.) asked the Department of Homeland Security to ban its production because of terrorism fears [7], and he introduced a bill in 2017 to achieve those same goals [8]. In March 2015, eco-terrorists in New Zealand threatened to poison infant formula and other dairy products with 1080 because of their Department of Conservation's use of the chemical for pest control [9, 10]. The overall goal of our research is to utilize human cardiomyocyte, kidney epithelial, and liver epithelial *in vitro* models to predict which potential therapeutics may be beneficial against 1080 poisoning. We studied the effects of both sodium fluoroacetate and fluorocitrate on *in vitro* models and observed that fluorocitrate significantly impacts cell counts in both the liver cells and cardiomyocytes. Increased oxidative stress was observed in the liver model, and decreased cell viability was seen in cardiomyocytes at concentrations of 100 µM fluorocitrate and above. Fluorocitrate also negatively impacted mitochondrial respiratory capacity in multiple models. We assessed potential therapeutic compounds in our *in vitro* models and saw encouraging results with the antioxidants n-acetyl-l-cysteine and reduced l-glutathione, as well as with d,l-isocitric acid. This work lays the foundation for further investigations into novel therapeutic targets and the development of medical countermeasures for 1080 poisoning.

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