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The Potential Use of 2-Aminothiazoline-4-carboxylic Acid (ATCA) as a Forensic Marker for Cyanide Exposure in Medicolegal Death Investigation: A Review

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TABLE OF CONTENTS

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ABSTRACT: Cyanide (CN) is one of the most toxic of all substances and can be found in various natural and anthropogenic sources. Sensitive and effective methods for the confirmation of CN exposure are crucial in medical, military, and forensic settings. Due to its high volatility and reactivity, direct detection of CN from postmortem samples could raise inconclusive interpretation issues that may hinder accurate determination of the cause of death. The detection of the alternative CN metabolites as markers to test CN exposure may offer a solution to reduce the potential for false-negative and false-positive results. 2-Aminothiazoline-4-carboxylic acid (ATCA) is a minor metabolite of CN and has been proposed to be a potential alternative forensic marker for the confirmation of CN exposure. According to the current state of knowledge, ATCA has not yet been associated with other metabolic pathways except for CN detoxification. Moreover, ATCA is stable under various conditions over time. This article reviews analytical methods developed for the analysis of ATCA as well as studies related to potential use of ATCA as a marker for the diagnosis of CN exposure. The need for research related to the use of ATCA as a reliable forensic marker for CN exposure in medicolegal death investigations is also discussed.

KEYWORDS: 2-Aminothiazoline-4-carboxylic acid, biomarkers, cyanide exposure, cyanide poisoning, death investigation, forensic markers, forensic science.

INTRODUCTION

Infamous for its use as a chemical warfare agent during World War I and World War II [16,57], cyanide (CN) can also be found in numerous natural and anthropogenic sources. The most common natural source of CN exposure is the consumption of plants that contain cyanogenic glycosides, which are rapidly converted to CN once consumed. Cyanogenic glycosides can be found in the seeds of various fruits, such as apples, cherries, plums, apricots, peaches, and bitter almonds, as well as in the roots of certain plants, including cassava, sorghum, and bamboo [68].

Cyanide in anthropogenic sources is more pervasive than one might expect. Approximately 300,000 tons of CN is produced yearly in the United States to meet the needs of various industries [21]. For instance, in photography, electroplating, and plastic and metal processing industries, both aqueous and solid forms of CN salts are frequently used [21,28,74]. Legal industrial applications along with illegal uses of CN (homicide and terrorist acts [17,32]) pose risks for public safety. According to the American Association of Poison Control Centers, there were 198 CN exposure cases reported in the United States in 2016, approximately a 6% increase over the number of cases reported in 2014 [22,49].

Marker for Confirming the Exposure of Cyanide

With the acute toxicity of CN, reliable, fast, and sensitive analytical methods are needed for the confirmation of its exposure in medical, military, and forensic settings. Confirmation of exposure by direct analysis of CN in biological samples is suggested to be challenging due to its high volatility and reactivity [10,39,48]. While direct analysis of CN may be most appropriate immediately following exposure, the analysis of its metabolites is considered to be more feasible after a significant amount of time has passed. Upon entering the biological system, CN is readily metabolized into thiocyanate (SCN^-), 2-aminothiazoline-4-carboxylic acid (ATCA) and its tautomer 2-iminothiazoline-4-carboxylic acid (ITCA), protein adducts, a-ketoglutarate cyanohydrin (a-KgCN), and cyanocobalamin [6,25,61,66]. SCN^- is the major metabolite of CN. Advantages of targeting SCN^- include its nonvolatility and much longer half-life than CN [36,66]. However, the detection of SCN^- is nonspecific for CN exposure, because it is present endogenously at high concentrations and is involved in metabolic pathways other than CN [36,66,72]. Therefore, some research has explored ATCA as a potential marker. Multiple sensitive methods have been developed to extract and analyze ATCA from various biological matrices [7,11,13,20,27,36–38,40,41,53,54,59,61,70,77], and reviews concerning the analysis of CN and other metabolites have been published [4,26,36,43,61,64,69]. In this article, we shall both review the analytical methods developed for the determination of ATCA from biological samples and also evaluate the potential use of ATCA as a forensic marker in death investigations. The need for research related to the use of ATCA as a reliable forensic marker for CN exposure in medicolegal death investigations will also be discussed.

ABOUT THE AUTHORS

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Sun Yi Li received B.S. degrees in chemistry and forensic chemistry from Towson University (Towson, MD), and is currently enrolled in the Ph.D. program in forensic science at Sam Houston State University (Huntsville, TX).

Ms. Li has interned in the toxicology department of the Office of Chief Medical Examiner – Maryland Department of Health (Baltimore, MD) and in the trace evidence analysis department at Harris County Institute of Forensic Science (Houston, TX). She has experience in toxicology and trace analysis research during her graduate study. Ms. Li received the Institute for Forensic Research – Training and Innovation Scholarship in 2018 from the College of Criminal Justice at Sam Houston State University.

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Ilona Petrikovics received an M.S. degree in general chemistry and a Ph.D. degree in organic chemistry from L. Kossuth University of Arts and Sciences (Debrecen, Hungary) as well as a Ph.D. in medicinal biology from L. Kossuth University Medical School (Debrecen, Hungary). She is currently a professor in the Department of Chemistry at Sam Houston State University.

Dr. Petrikovics has two decades of background in cyanide and other chemical warfare agent antagonism studies in the United States, working on various aspects of many projects: organic synthesis, structure elucidation, chemical analysis of toxins/drugs and metabolites in biological systems, formulation of antidotes (nanoencapsulation technology, e.g., liposomes, polymeric nanodelivery systems, cyclodextrin and PEG formulations); immobilization and nanotechnology applications for detection, decontamination, and antagonism of chemical warfare agents, toxicity studies (in vitro and in vivo animal models – rats, mice, guinea pigs). Dr. Petrikovics has strong knowledge and experiences in drug stability and pharmacokinetic studies for various types of drugs and agents, especially with the sulfur donor type cyanide antidote dimethyltrisulfide (DMTS). Dr. Petrikovics also has two patent applications on the primarily investigated sulfur donor type cyanide antidote DMTS, and its poly80 formulation (Petrikovics I, Kovacs K: Formulations of dimethyl trisulfide for use as a cyanide antidote; US Patent 9,456,996; issued October 4, 2016. Rockwood GA, Petrikovics I, Baskin SI: Dimethyl trisulfide as a cyanide antidote; US Patent 9,375,407; issued June 28, 2016).

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