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Biomarkers in patients admitted to the emergency department after exposure to acrylonitrile in a major railway incident involving bulk chemical material

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ABSTRACT

Background: A railway incident with victims of exposure to the cyanogenic substance acrylonitrile (ACN).
Aims: We retrospectively (i)built an inventory of the clinical characteristics of individuals admitted to surrounding emergency departments (ED's) and (ii)studied the correlation between *N*-2-cyanoethylvaline (CEV), a biomarker used in a population study for evaluating exposure to ACN, with lactate and thiocyanate (SCN), biomarkers determined during emergency care.
Results: 438 patients from 11 ED's were included and presented with known symptoms of ACN poisoning but also with concern about the risks.

A comparison of CEV with lactate or SCN was possible in 108 and 73 patients respectively.

CEV was very high in a critically ill patient with a high lactate. There was no correlation with CEV in the patients with normal or slightly elevated lactate concentrations. A correlation of CEV with SCN was only observed in smokers.
Limitations: First there is a lack of data in some clinical files concerning the time and duration of exposure and the smoking-status.

A *second* limitation is that blood samples for biomarkers were not taken systematically in all patients, which may have induced bias.

A *third* limitation is that blood sampling was possibly done outside the correct time window related to the delayed toxicity of ACN.

Finally the number of severely-intoxicated patients was low and ACN exposure may not have taken place e.g. in individuals consulting with psychological symptoms. These aspects may have contributed to the below detection limits' analyses of biomarkers.

Abbreviations: ACN, acrylonitrile; CEV, *N*-2-cyanoethylvaline; CN, cyanide; ED, emergency department; HCN, hydrogen cyanide; LOQ, limit of quantification; SCN, thiocyanate.

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Conclusions: CEV was markedly elevated in a severely-intoxicated patient with high lactate, a sensitive marker for CN intoxication. We found no correlation of CEV with normal or slightly elevated lactate concentrations but clinicians should consider the possibility of subsequent rises due to the delay in ACN toxicity. CEV correlated with SCN in smokers, which may be explained by ACN in tobacco smoke and deserves further exploration.
Further studies are necessary to evaluate the correlation between biomarkers in acute chemical exposures to ACN and these should be carried out prospectively using a preplanned template.

1. Introduction

A railway incident with a fire and a spill of ACN on May 4th 2013 in Wetteren (Belgium) (De Smedt et al., 2014; Van Nieuwenhuyse et al., 2014) resulted in a large number of persons seeking medical aid in the ED's of the surrounding hospitals. Health risks included the presence of explosive substances in some wagons, fire in a wagon containing ACN (resulting in potentially high HCN concentrations in the air) and possible dermal and inhalational exposure to ACN with delayed toxicity, because it is metabolized *in vivo* to CN (Agency for Toxic Substances and Disease Registry (ATSDR), 1990; Institute for Health and Consumer Protection, European Chemicals Bureau, 2004; World Health Organization (WHO), International Agency for Research on Cancer (IARC), 1999; World Health Organization (WHO), 1983). ACN toxicity was rather unexpectedly observed at a supposedly safe distance from the incident and appeared to be due to contamination of the sewer system with ACN during fire fighting (De Smedt et al., 2014). In some houses, the domestic waste-water system appears to have been poorly isolated from the sewer system, and ACN vapors apparently accumulated in the property. In addition many individuals had concerns about the possibly carcinogenic effect of exposure to ACN (Agency for Toxic Substances and Disease Registry (ATSDR), 1990; Institute for Health and Consumer Protection, European Chemicals Bureau, 2004; World Health Organization (WHO), International Agency for Research on Cancer (IARC), 1999; World Health Organization (WHO), 1983).

CEV, lactate, SCN and CN are biomarkers for the assessment of ACN exposure and toxicity but have considerable differences in characteristics, as summarized in Table 1. CEV is the adduct formed by reaction of ACN with the N-terminal valine in human globin and can be considered as a marker for ACN exposure. Lactate is formed due to anaerobic metabolism following inhibition of the electronic transport chain by CN and SCN is the detoxification metabolite of CN formed by mitochondrial rhodanese. The biomarker CN directly measures the presence of both exogenous and endogenously formed CN.

In investigations after the railway incident, exposure to ACN was initially identified using CEV, because of its long decay half life while SCN, lactate and in some cases CN were determined during the medical care of patients. The aim of this study is to retrospectively (i)inventarise the clinical data and (ii)to analyse whether concentrations of the biomarker CEV correlated with those of lactate and SCN.

2. Methods

2.1. Data collection

The files of all patients presenting at all 10 ED's of the surrounding hospitals and one first care department of a hospital in the near vicinity of the incident were analysed retrospectively by one of the authors (SC). The study period was from May 4, the day of the disaster, until May 11, 2013 (De Smedt et al., 2014; Onderzoeksorgaan voor Ongevallen en Incidenten op het Spoor, 2014; Simons et al., 2016; Van Nieuwenhuyse et al., 2014).

A patient was included in the study whenever the file either mentioned symptoms or clinical findings possibly related to ACN or CN exposure or when concern of supposed exposure was the reason for consulting. For each episode a standardized list was used for collecting demographic data, medical history, clinical findings and, when available, results for lactate, SCN and CN. When laboratory data were available for more than one time point in an episode the value on admission was used. Details of the sampling time of lactate are given in Web Appendix Fig. S1a. The smoking status was derived from the CEV population study (De Smedt et al., 2014; Van Nieuwenhuyse et al., 2014).

Serum samples for SCN were taken by emergency physicians, general practitioners, and occupational health physicians between May 6th and 15th, following a directive by the authorities. Details of the sampling time are given in Web Appendix Fig. S1b.

2.2. Laboratory analyses

CEV was analysed in blood samples obtained 14–55 days after the incident as part of a study on population exposure. A detailed description of the procedure has been published elsewhere. (De Smedt et al., 2014; Törnqvist et al., 1986; Van Nieuwenhuyse et al., 2014). CEV concentration at the time of the earlier SCN and lactate measurement was estimated by assuming that the concentration is given by the measured CEV concentration divided by the factor 1-t*0.008 where "*t*" is the number of days elapsed between admission and sampling for CEV; the constant 0.008 is the reciprocal value of the life span of the erythrocytes (i.e. approximately 126 days). This formula assumes zero order kinetics for the degradation of the erythrocytes (Bader and Wrbitzky, 2006; De Smedt et al., 2014; Van Nieuwenhuyse et al., 2014).

Lactate was measured either via capillary puncture or in a blood sample using routine clinical chemistry analysers. An upper reference cut-off value of 1.7 mmol/L was used. In patients with more than one admission only the blood lactate during the first contact was used.

SCN results were obtained from the clinical admission files of the patients and also by screening the data base of the laboratory of Ghent University Hospital; this laboratory received serum samples from the other hospitals involved for analysis, using a method as previously described (Lundquist et al., 1995). In 2 patients with a SCN concentration on more than one ED admission the highest value was used. A slightly different value was found in 2 patients in the clinical as compared with the laboratory file; the clinical file was used in preference because it was related to the admission.

Cyanide was determined using a slight modification of the method described in Lambert et al. (1995). (Table 1).

2.3. Analysis of data and statistics

Demographic data, patient characteristics and clinical outcome variables are reported as mean and standard deviation (SD) for