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# Thiocyanate Blood Levels in Chlorobenzylidenemalononitrile (CS) Riot Control Gas Patients; the Egyptian Experience

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## Abstract

This study aims to clarify the systemic toxic effects of chlorobenzylidenemalononitrile (CS) and to confirm or reject the possibility of cyanide intoxication on the exposed patients. The study was conducted in PCC Ain Shams University, on exposed rioters during the November 2011 demonstrations to CS gas in Cairo. Control groups included light and moderate to heavy smokers as well as non-smokers. Plasma thiocyanate, the metabolite of cyanide was assayed in all groups. Plasma thiocyanate of victims of CS exposed gas showed no significant differences from light smoker volunteers and was not significantly different when followed up after 2 weeks. Clinical and laboratory workup did not detect any of the evidence pertaining to cyanide poisoning. No fatality was recorded in the studied series. It is concluded that transient exposure of street rioters to CS gas (2.8 minutes average) in open air, hence with limited CS gas concentration would not produce cyanide toxicity.

## Keywords

Chlorobenzylidenemalononitrile; CS; Riot control agents; Egypt; Thiocyanate; Cyanide poisoning

## Introduction

Riot control agents referred to "tear gas" are chemical compounds that temporarily make people unable to function by causing irritation to the eyes, mouth, throat, lungs, and skin. The most common known compounds are chloroacetophenone (CN) and chlorobenzylidenemalononitrile (CS). Other examples include chloropicrin (PS), which is also used as a fumigant; bromobenzylcyanide (CA); dibenzoxazepine (CR); and combinations of various agents.

When CS is metabolized, cyanide can be detected in human tissue [1]. According to the United States Army Center for Health Promotion and Preventive Medicine, CS emits "very toxic fumes" when heated to decomposition, and at specified concentrations CS gas is an immediate danger to life and health. They also state that those exposed to CS gas should seek medical attention immediately [2]. Exposure almost instantly results in irritation, burning, and swelling of the conjunctivae of the eye, accompanied by excessive tearing and uncontrollable closure of the eyelid. In some cases, the subject experiences an aversion to light. As the agent enters the respiratory tract, it causes irritation and burning in the nose and mouth as well as excessive nasal discharge and salivation. It causes pain and discomfort in the throat and chest, resulting in sometimes violent coughing spasms and difficulty breathing. The respiratory effects are the most pronounced and most capable of causing individuals to flee from the exposure. Advantages to measuring thiocyanate are that appreciable concentrations may be found immediately after exposure, and that it is considered to be more stable than cyanide [3].

Over almost a week the riot control agent CS has been used to disperse the demonstrations in the nearby areas surrounding Tahrir square in Cairo on November 2011. Groups of exposed demonstrators presented to the poison control center with a history of exposure to tear gas and holding the CS-labeled tear gas canisters. CS-exposed patients presented with breathlessness, cough, throat constriction and extreme fatigue with generalized weakness, some of which were actually transported on stretchers of ambulance.

Rumors circulated among media and social interaction internet pages, claiming that CS gas possess a potential for cyanide intoxication, and abortifacient effect of tear gas on pregnant women even in remote areas. It was even mistaken for VX type nerve agents. The rumors were triggered by the death of two persons in the vicinity of tear gas exposure.

This study aims to clarify the systemic effects of chlorobenzylidenemalononitrile (CS) and to confirm or reject the possibility of cyanide intoxication on the exposed patients.

## Patients and Methods

Only the patients exposed to chlorobenzylidenemalononitrile CS gas within 2 hours of exposure, providing the CS-labeled canisters have been included in the study. Other patients exposed to lachrymatory agents without strong evidence of CS gas were excluded from the study. Patients with previous history of airway disease especially bronchial asthma were as well ruled out from the study. Duration of exposure was noted for each case until patient escaped to an area 100 meters from site of heavy exposure

CS gas exposed patients were followed up after 2 weeks. Observations included blood thiocyanate assay, clinical examination of skin, eyes and respiratory tracts with study of arterial blood gas, plasma pseudo cholinesterase, transaminases blood urea and chest x ray.

Control patients included three groups of patients each 18 in number; the first group is a non-smoker group of patients, the second is the mild smokers, and the third group included the moderate to heavy smokers.

The test is performed on plasma of the following groups

Group I (n=18): Normal negative nonsmoker control group, non-exposed to any cyanide containing chemical or lachrymatory.

Group II (n=18): Light smokers (fewer than 10 cigarettes per day) [4,5].

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Group III (n=18): Moderate to heavy smokers (more than 10 cigarettes per day).

Group IV (n=18): Patients exposed to lachrymatory CS gas in the nearby area of Tahrir square. Patients were selected after providing the evidence of CS labeled lachrymatory canister. Other victims in different areas, different times who failed to provide the evidence of exposure particularly to CS gas were excluded from the study.

Group V (n=14): Patients of group IV, 2 weeks after exposure to CS gas. This group served as control for the same individuals tested in group IV.

Number of patients on each group is 18 (except the group V which comprised 14 patients), from which blood samples are taken 2 hours after the last exposure to smoking or CS gas.

### Thiocyanate spectrophotometric plasma assay

The procedure depends on the method described by Moffat et al. [6]. To 0.5 ml sample, a 4.5 ml of 5% solution of trichloroacetic acid is added, allowed to stand for 15 min, mixed and centrifuged. Two ml of supernatant liquid and 2 ml of working standard thiocyanate solution (0.05 µmol/ml) and 2 ml of $H_2O$ (blank) were transferred to 3 separate tubes. While excluding light, 4 ml of the acidic ferric nitrate sol (80 gm of ferric nitrate nonahydrate in 250 ml of 2 M nitric acid dissolved with sufficient $H_2O$ to produce 500 ml) were added to each tube, mixed and the absorbance of the sample and standard sol recorded at 460 nm using the blank solution as reference.

Concentration in the sample is calculated by comparison with a standard thiocyanate solution 0.05µmol /ml run during the test.

Thiocyanate calibration curve was constructed daily before testing using different (0.05, 0.25, 0.5, 1.0 µmol/ml) standard thiocyanate concentrations in water with good linearity ($r^2$=0.9492 - $r^2$=0.9996). Spiked thiocyanate in plasma showed good recovery ranging between 88.8 and 108%. Inter-day precision of the test was good with RSD ranging between 3.6 and 12.5%.

Results of different groups are statistically tested using student t test and analysis of Variance (One way ANOVA) F test.

## Results

All patients were forced to flee the area of heavy exposure after a period ranging between one to 5 minutes with a mean of 2.8 minutes to reach an area 100 meters distant from heavy exposure site. Time delay between exposure and reaching the casualty department ranged between 20 minutes and 50 minutes (Table 1).

All patients (n=18) suffered severe conjunctival congestion, blepharospasm, profuse tearing. All patients experienced shortness of breath on exposure, severe coughing and throat and chest constriction. Six out of 18 patients had vomited before reaching the center. All experienced nausea. Three patients experienced severe weakness and were not able to move, and transferred to the hospital by ambulance; all other patients hurried by their own communications. Burning feeling was experienced in the face especially periorbital, and perinasal areas.

All patients exhibited flushing of face and or skin erythema on exposed areas. All patients suffered severe conjunctival congestion, tearing and nasal discharge. Ten patients had swollen eyelids. Hoarse voice denoting laryngitis was evident in almost all of the patients. Chest examination revealed severe wheezes and coarse crepitations in 16 out of 18 patients; in one patient stridor was equally evident. None of the patients exhibited cyanosis. All patients had normal blood pressure. Six patients had mild tachycardia less than 110 beats/minute.

**Table 1:** Clinical and laboratory abnormalities of CS gas exposed victims (n = 18).

| Clinical / laboratory abnormality | n | % |
|---|---|---|
| Average time of Exposure (min) | 2.8 | |
| Time delay between exposure and reaching Poison Control Center | 20 - 50 | |
| Conjunctival congestion | 18 | 100% |
| Tearing of eyes and blepharospasm | 18 | 100% |
| Face and skin erythema | 18 | 100% |
| Nasal and throat burning | 18 | 100% |
| Stridor | 18 | 100% |
| Hoarse voice | 18 | 100% |
| Chest wheezes and crepitations | 16 | 88.8% |
| Cyanosis, hypoxemia or respiratory failure | 0 | 0 |
| Tachycardia | 6 | 33.3% |
| Biochemical laboratory abnormalities | 0 | 0 |
| History of muscle weakness (Before reaching PCC) | 3 | 16.6% |
| History of brief loss of consciousness (Before reaching PCC) | 1 | 5.5% |
| Treatment extending more than 6 hours | 1 | 5.5% |
| Residual clinical/ laboratory abnormality after 2 weeks | 0 | 0 |

In all patients, arterial blood gas, plasma pseudo cholinesterase, liver transaminases, blood urea and serum electrolytes were all within normal limits. These results were not significantly different after 2 weeks (Table 2). Chest X ray was within normal limits except for increased bronchovascular markings in 3 patients. Their follow up was equally within normal limits

All patients were treated with oxygen, salbutamol and dexamethasone inhalation and dexamethasone systemic injections. Treatment continued until patients were able to wean from nebulizer therapy. Other treatment included steroid based eye drops, rinsing the skin with water. All patients, except one, were discharged after 3 to 4 hours with residual skin burning and mild conjunctival congestion. The last patient needed continued aerosol bronchodilator and steroid therapy for 12 hours and was discharged one day after admission. He was diagnosed as reactive airway disease that was not evident on follow up of patients 2 weeks after the CS exposure.

### Thiocyanate results

Using one way ANOVA and student t tests, CS gas exposed patients did not reveal any statistically significant difference with light smokers (p=0.282) or with CS gas followed up patients after 2 weeks (p=0.466). However, moderate to heavy smokers had a significantly higher thiocyanate level than CS gas exposed patients (p=0.004) and light smokers (p=0.0001). Nonsmokers had significantly lesser thiocyanate blood levels than light smokers (p<0.0001) and CS gas exposed patients (p<0.0003)(F test value=14.6881) (Tables 3 and 4).

**Table 2:** Laboratory values of CS exposed patients, the day of exposure (Group IV) compared with the values, 2 weeks after exposure (Group V).

| | | Mean | SD | t | P |
|---|---|---|---|---|---|
| **PaO2 (mmHg)** | Group IV | 85.7 | 10.0 | t= 0.686 | P= 0.50 |
| | Group V | 83.4 | 8.61 | | |
| **PaCO2 (mmHg)** | Group IV | 36.5 | 3.38 | t= 0.442 | P= 0.66 |
| | Group V | 37.0 | 2.88 | | |
| **pH** | Group IV | 7.37 | 0.042 | t= 0.313 | P= 0.76 |
| | Group V | 7.36 | 0.024 | | |
| **ALT (IU/L)** | Group IV | 27.4 | 9.22 | t= 0.32 | P= 0.75 |
| | Group V | 28.4 | 7.64 | | |
| **AST (IU/L)** | Group IV | 29.7 | 6.83 | t= 0.05 | P=0.96 |
| | Group V | 29.9 | 7.9 | | |
| **Urea (mg/dl)** | Group IV | 28.9 | 6.28 | t= 0.05 | P=0.96 |
| | Group V | 28.8 | 3.89 | | |
| **Pseudo ChE (IU/L)** | Group IV | 7059 | 1312 | t= 0.641 | P= 0.53 |
| | Group V | 7337 | 1085 | | |

Pseudo ChE: Plasma pseudocholinesterase – ALT: Alanine aminotransferase – AST: Aspartate aminotransferase

**Table 3:** Analysis of Variance of Thiocyanate plasma levels in patients of different groups submitted to the study.

| | Nonsmokers control group n = 18 | Light Smoker's patients n =18 | Moderate to Heavy Smokers n =18 | CS gas exposed patients n =18 | CS gas exposed patients after 2 weeks n=14 |
|---|---|---|---|---|---|
| **Mean (µmol /L)** | 31.551 | 54.509 | 81.296 | 58.502 | 59.196 |
| **Range (µmol /L)** | 18.5 – 46.3 | 26.1 – 82.3 | 50.46-144.1 | 19.97-113.2 | 37.07-92.7 |
| **SD** | 12.78 | 13.46 | 23.87 | 25.86 | 17.76 |
| F test value = 14.6881 | | **p < 0.0001** | | | |

**Table 4:** Student t test of Thiocyanate plasma levels in patients of different groups.

| | Group I Non Smokers | Group II Light Smokers | Group III Moderate to Heavy Smokers | Group IV CS-exposed patients | Group V Patients 2 weeks after CS-exposure |
|---|---|---|---|---|---|
| **Group I** | | HS | HS | HS | HS |
| **Group II** | t= 5.25<br>P < 0.00001 | | HS | NS | NS |
| **Group III** | t= 7.79<br>P < 0.00001 | t= 4.14<br>P =0.0001 | | HS | HS |
| **Group IV** | t= 4.0<br>P < 0.0003 | t= 0.58<br>P = 0.282 | t= 2.74<br>P = 0.004 | | NS |
| **Group V** | t= 5.48<br>P <0.0001 | t= 0.84<br>P = 0.201 | t= 2.89<br>P = 0.0035 | t= 0.08<br>P = 0.466 | |

HS: Highly significant difference; NS: Non significant difference

## Discussion

Results of plasma thiocyanate revealed no significant differences between the CS-exposed patients and light smokers. Heavy smokers, indeed, had significantly higher plasma thiocyanate levels pertained to their smoking habit compared to CS gas exposed group and all other groups. Naturally occurring thiocyanate background levels are different for each person, making it difficult to quantify low-level cyanide exposure without establishing baseline levels for an individual prior to exposure. The group V served as control basal level of plasma thiocyanate for the individuals in group IV. No significant difference was evident between CS exposed patients of group IV and themselves (Group V) after 2 weeks of exposure. All groups had significantly higher thiocyanate blood levels than non-smokers. In fact, CS exposed patients were either non-smokers, light or moderate to heavy smokers explaining the non-significant difference with light smokers.

These results exclude the possibility of systemic cyanide absorption whether by inhalation or by skin exposure as alleged by some authors. Heinrich assumed that besides the direct toxic effect of high concentrations of CS on the lung, the formation of hydrogen cyanide (HCN) from malononitrile, a metabolite of CS, and its toxic effect, especially on the most sensitive brain cells, cannot be ignored when possible lethal effects of CS exposure are discussed [7]. No significant change was noted among the CS exposed patients in plasma thiocyanate level, 2 weeks after acute exposure (p=0.466). Actually, signs and symptoms of CS exposure were reduced and disappeared in less than 2 hours after admission except for one patient who probably suffered increased airway hyper-reactivity. This clinical entity has been described as exaggerated physiological abnormality [8,9].

CS (o-chlorobenzylidenemalononitrile) is hydrolyzed to 2-chlorobenzaldehyde and malononitrile. Malononitrile contains two cyanide moieties, and it is thought that at least one of these is liberated and attaches to sulfur via the enzyme rhodanese to form thiocyanate, which is excreted in the urine [10]. Although thiocyanate was described in urine of exposed animals and man after inhalation

exposure yet the model described by Heinrich includes the firing of CS gas canisters in relatively closed spaces in a building for a prolonged time to force the inhabitants to leave known as the Waco Texas accident. This model that posed intense CS exposure dose with high CS gas concentration for a relatively long duration resulted in the death of seventy persons. This exposure was 8000 mg.min/$m^2$ in some rooms which is actually close to the lowest lethal values on experimented monkey's 11,246 - 62,400 mg.min/$m^3$ . Exposure is equivalent to gas concentration (mg.$m^3$) in the air multiplied by time (in minutes) c x t [7]. These exposure values are far higher than the injurious CS concentration to 50% of humans calculated to be 10 – 20 mg.min/$m^3$ below which trained troops would flee the area [2,3,7]. The human tolerable exposure to CS was calculated to be 135 mg/min.$m^3$ a concentration at which humans are forced to leave the place secondary to considerable burning and chest and throat constriction [7].

In the Egyptian experience a physician has reportedly died from tear gas used against demonstrators when police shot the gas in a field hospital located in Mohamed Mahmoud Street. The physician fainted and entered a coma after policemen obstructed the exit of the hospital [11] according to the local newspaper Al-Masry Al-Youm [12]. The prolonged exposure due to delay of the escape and the relatively high concentration of gas in a relatively closed place in the field hospital might have caused the exposure concentration to reach the lethal dose.

The cause of death in CS fatal accidents has been attributed to cyanide poisoning reaching 0.5mg/L in the Waco accident, or pulmonary edema with intra-alveolar hemorrhages, atelectasis and subsequent respiratory failure [10,13] secondary to the injurious effects of CS on the lung and airways. This was demonstrated in the Heinrich experiments on dogs and monkeys [7]. In the Egyptian accident, one or both mechanisms might be the cause of the fatality reported to be due to suffocation. Unfortunately, no blood samples were retrieved from this victim to compare plasma thiocyanate with that of the patients included in this study who fled CS exposure of the open air street after an average of 2.8 minutes.

In a patient who ingested a CS pellet, blood cyanide level was 0.01mg/L a level corresponding to cigarette smoker ruling out the real toxic hazard of cyanide toxicity from CS gas usual exposure [10]. In a British report, if complete absorption of all the CS during a 1-minute exposure at 10 mg/$m^3$, and if both cyanides on the molecule were liberated— and evidence suggests that only one is liberated—the total amount of cyanide received would be equivalent to that received from two puffs of a cigarette [14]. A cigarette would produce cyanide level of 0.013 mg/L far below the dangerous level of cyanide of 0.2 mg/L [7]. Death secondary to toxic pulmonary edema in experimental animals exposed to CS gas was described by Sidell on 1997. Pathology revealed congestion of the alveolar capillaries and intrapulmonary veins, with areas of alveolar hemorrhages and hemorrhagic atelectasis. Pulmonary edema, with the absence of inflammatory cell infiltration was attributed to direct injury to the pulmonary capillary endothelium and pulmonary damage [10]. 2-chlorobenzaldehyde has been shown to be released from the thermal dispersion of CS canisters in addition its isomer 4-chlorobenzylidenemalononitrile and other degradation products [15]. According to material safety data sheet [16] 2-chlorobenzaldehyde has been described as a severely irritant to respiratory tract producing burns on the skin and respiratory tract. At least one or more degradation components of CS in high concentrations could be responsible for the direct toxic, non-cardiogenic pulmonary edema that explains suffocation of the locked-in doctor in the field hospital. The Himsworth report [17] on British law enforcement use of CS determined that exposure to the agent could result in death with concentration several hundred times greater than the exposure dosage that produces intolerable symptoms.

## Conclusion

Transient CS gas exposure in open air does not produce any significant cyanide toxicity. Thiocyanate blood levels were not significantly different from the group of light smokers or from the same group when tested 2 weeks after exposure. Like light smokers, the CS exposed group of patients had significantly higher thiocyanate levels compared to nonsmokers and significantly lower levels when compared with moderate to heavy smokers. The usual few minutes' exposure of CS gas in an open area, as applied for riot control, does not produce cyanide toxicity as evidenced by results of plasma thiocyanate of this study on human exposure. Unless the CS exposure is in a closed area and for long duration, the CS gas would not produce any real hazard from cyanide toxicity or toxic pulmonary edema.

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