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Clinical Presentation and Prognostic Factors in Sodium Monofluoroacetate Intoxication

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ABSTRACT

Background: The diagnosis of sodium monofluoroacetate intoxication in humans is usually based on a history of ingestion and clinical findings. Although several previous reports have described the clinical course and outcome of patients who ingested this drug, prognostic indicators of short-term survival are not available. Methods: A retrospective study of 38 consecutive cases of sodium monofluoroacetate poisoning at the National Cheng Kung University Hospital, 1988–1993, to analyze the clinical findings and to predict mortality. Results: Seven of 38 patients (18%) died. The most common symptom was nausea or vomiting (74%). The most frequent ECG finding was nonspecific ST-T and T wave abnormalities (72%). Hypocalcemia (42%) and hypokalemia (65%) were the common electrolyte abnormalities. The clinical and laboratory characteristics were compared for the survival and mortality groups. Significant differences in hypotension, respiratory rate, pulse rate, creatinine, potassium, elevated alanine aminotransferase, pH, PCO_2, APACHE II score, and subjective respiratory distress were noted. Discriminant analysis identified hypotension, increased serum creatinine, and decreased pH as the most important predictors of mortality, with sensitivity of 86% and specificity of 96%. Conclusions: Hypotension and the early onset of metabolic acidosis and increased serum creatinine are associated with poor short-term survival. These prognostic variables can be useful in the care of patients with suspected sodium monofluoroacetate intoxication. It is suggested that all such patients should be observed intensively for at least 48 h.

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INTRODUCTION

Sodium monofluoroacetate (SMFA) is a potent rodenticide originally produced during World War II. It is now prohibited because of its high toxicity but some illegal products still can be found in southern Taiwan. The fluoroacetate metabolite, fluorocitric acid, blocks cellular metabolism by inhibiting the Krebs cycle. The estimated lethal dose ranges from 2 to 10 mg/kg, with a mean of 5 mg/kg in man. Clinical signs of SMFA poisoning can be characterized by a latent period of about 30 min to 2.5 h after the administration of the compound, but may be delayed for 20 hours.[1-4] The diagnosis of SMFA intoxication in humans is usually based on a history of ingestion and clinical findings. Although several previous reports have described the clinical course and outcome of patients who ingested this drug,[4-7] prognostic indicators of short-term survival are not available. In this study, the clinical course and variables in patients with SMFA intoxication were retrospectively summarized and analyzed in an attempt to predict mortality by the clinical and laboratory parameters.

METHODS

The charts of patients with SMFA ingestion presenting to the National Cheng Kung University Hospital from August 1988 to September 1993 were reviewed. The diagnosis of SMFA was based on a verifiable history, identification of an empty poison bottle, and compatible clinical picture. Victims dead on arrival and those with coingestions were excluded. Unless specifically contraindicated, all patients ingesting SMFA underwent gastric lavage and the administration of activated charcoal. The emergency department (ED) records were reviewed for prehospital interval, initial vital signs, Glasgow coma scale (GCS), systolic blood pressure, body temperature, pulse and respiratory rates. Additional data included days of hospital stay, symptoms, and electrocardiograph abnormalities. Laboratory variables on arrival and/or during admission included arterial blood gas, blood urea nitrogen (BUN), creatinine, alanine aminotransferase, sodium, potassium, calcium, phosphate, white blood cell count, hematocrit, and platelets. The APACHE II scores following the initial clinical and laboratory data were tabulated.[8]

Statistical Analyses

All statistical analyses were performed using SAS version 6.03. For univariate analysis, continuous variables for survival and mortality patients were compared through the use of Student's *t*-test or two-sample Wilcoxon test as appropriate. Categorical data were compared by using chi-square or Fisher's exact test. P value less than 0.01 was considered to be statistically significant. All prognostic variables identified by univariate analysis were further selected by stepwise linear discriminant analysis. The selected factors were used to construct a predictive index using Fisher's linear discriminant function.

RESULTS

Thirty eight patients were included in our study group. All had ingested SMFA with suicidal attempt. Seven of the 38 patients died (mortality rate 18.4%). The general characteristics of these seven patients (mortality group) were compared with those of the 31 patients in the survival group. No differences in age and gender were found (Table 1). The mean prehospital intervals for the fatalities was longer than for the survivors (mean $\pm$ SE, 10.9 $\pm$ 5.7 vs 3.4 $\pm$ 0.6 h), but revealed no statistical significance. The most frequent symptom was nausea and/or vomiting. Other common signs and symptoms included diarrhea, agitation, respiratory distress, and abdominal pain (Table 2). Two persons had seizures. Twenty-five patients received 12-lead electocardiography and ECG monitoring. The most frequent electrocardiographic (ECG) finding was nonspecific ST-T and T wave abnormalities (18/25). Other frequent ECG abnormalities included prolonged QTc interval (7/25), premature ventricular beat (6/25), ventricular tachycardia (5/25), and atrial fibrillation with rapid ventricular response (4/25). Univariate comparisons of clinical variables on arrival at the ED and during the hospitalization course in survival and mortality group are presented in Tables 1 and 3. Hypocalcemia and hypokalemia were common and were more likely to occur in the fatalities than in the survivors (57 vs 36% and 100 vs 58%, respectively). Significant differences in the prevalence of systolic BP $<$ 90 mm Hg upon arrival at ED were observed. Initial respiratory and pulse rates, creatinine, potassium, total bilirubin, alanine aminotransferase,

Table 1

Status on ED Arrival for Survival and Mortality Groups

	Survival (n = 31)	Dead (n = 7)	p
Age	40.8 ± 18.6	47.3 ± 19.6	NS
Gender (male/female)	15/16	5/2	NS
Prehospital interval (h)	3.4 ± 3.2	10.9 ± 12.9	NS
SBP < 90 mm Hg (%)	5/26 (16.1 %)	7/7 (100%)	< 0.01
Temperature (°C)	36.4 ± 0.54	36.1 ± 0.54	NS
Pulse rate (bpm)	92.3 ± 12.3	109.7 ± 14.4	0.01
Respiratory rate (b/min)	20.9 ± 2.7	26.1 ± 5.6	0.01
Glasgow coma scale	14.5 ± 1.6	13.9 ± 1.9	NS
Hematological Data			
WBC ($10^3/\mu L$)	9.6 ± 6.8	13.5 ± 7.1	NS
Platelet count ($10^3/\mu L$)	234.7 ± 71.2	171.6 ± 100.4	NS
Hematocrit %	41.5 ± 5.5	43.7 ± 5.3	NS
Biochemical Data			
Urea nitrogen, mg/dL	16.9 ± 10.7	24.7 ± 11.7	NS
Creatinine, mg/dL	1.2 ± 0.9	2.8 ± 1.6	< 0.01
Sodium, mmol/L	142.0 ± 4.5	141.4 ± 4.8	NS
Potassium, mmol/L	3.4 ± 0.5	3.0 ± 0.3	< 0.01
Chloride, mmol/L	105.6 ± 4.2	108.9 ± 9.6	NS
Total calcium, mg/dL	8.5 ± 1.7	8.3 ± 1.2	NS
Total bilirubin, mg/dL	0.8 ± 0.4	2.6 ± 1.8	NS
ALT ↑ (%)	16%	83%	< 0.01
Glucose, mg/dL	160.6 ± 68.7	195.7 ± 156.7	NS
Arterial blood gases			
pH	7.4 ± 0.1	7.3 ± 0.1	< 0.01
PO_2 mm Hg	92.1 ± 20.9	100.9 ± 28.2	NS
PCO_2 mm Hg	35.5 ± 5.1	26.0 ± 4.5	< 0.01

Data expressed as means ± SD; NS: not significant. ALT ↑: Alanine aminotransferase, increased 2x than the normal value.

Table 2

Clinical Symptoms and Signs (%) in Patients with SMFA Intoxication during Admission

	Total (n = 38)	Survival (n = 31)	Dead (n = 7)	p
Nausea, vomiting	73.7	74.2	71.4	NS
Diarrhea	28.9	25.8	42.9	NS
Agitation	28.9	22.6	57.1	NS
Abdominal pain	26.3	22.9	42.9	NS
Respiratory distress	21.1	6.5	85.7	< 0.01
Seizure	5.3	0	28.6	< 0.01

Table 3

Hospitalization Course of Surviving and Dead Patients with SMFA Intoxication

	Total (n = 38)	Survival (n = 31)	Dead (n = 7)	p
Hospital stay, (days)	6.2 ± 6.7	7.3 ± 6.9	1.4 ± 0.5	< 0.01
Hypocalcemia (%)	42.1	36	57	NS
Hypokalemia (%)	65.8	58.1	100	< 0.01
Metabolic acidosis (%)	21.1	3.5	100	< 0.01
ALT ↑ (%)	21.1	16	83	< 0.01
Hyperbilirubinemia (%)	10.5	0	57.1	< 0.01
Serum creatinine ↑ (%)	26.3	12.9	85.7	< 0.01
Leukocytosis (%)	34.2	29.1	57.1	< 0.01
Shock (%)	34.2	19.4	100	< 0.01
APACHE II score	5.9 ± 5.7	3.8 ± 3.6	13.7 ± 4.9	< 0.01

pH, and PCO_2 were also noted to be significantly different in the fatal cases. All deaths occurred within 72 h after exposure so hospital stay was significantly longer in survival patients. The APACHE II was revealed as significantly higher in the nonsurvivors (13.7 ± 4.9 vs 3.8 ± 3.6, $p < 0.05$). The course of two fatalities was complicated by acute renal failure.

The prognostic variables observed upon ED arrival which predicted mortality as identified by univariate analysis, with p value less than 0.01, included systolic < 90 mm Hg, tachypnea and tachycardia, elevated creatinine, lower pH, and lower PCO_2. A stepwise discriminant procedure applied to these variables, except systolic < 90 mm Hg which is a binary response, resulted in two significant prognostic indicators: creatinine and pH. Fisher's linear discriminant function (LDF) using initial creatinine level (μmol/L) and pH is LDF = 0.023 x creatinine (μmol/L) − 58 x pH.

Since all patients with an initial systolic blood pressure ≥ 90 mm Hg survived, only those patients with systolic blood pressure < 90 mm Hg were discriminated by using LDF. After combining LDF with initial blood pressure, through conditional discriminant analysis, the following predictive rules apply:

- Systolic blood pressure ≥ 90 mm Hg predicts survival;
- Systolic blood pressure < 90 mm Hg and LDF ≥ − 416 predicts fatality; while LDF < − 416 predicts survival.

This conditional analysis indicated a sensitivity of 0.867 and a specificity of 0.967 to predict mortality due to SMFA intoxication.

DISCUSSION

The diagnosis of SMFA poisoning is usually made by history, clinical signs, and chemical analysis. Methods reported for the analysis of SMFA in biological materials include gas chromatography of the methyl and higher esters, gas chromatography-mass spectrometry of the ethyl ester, thin layer chromatography, and defluorination with sodium biphenyl.[2,9-10] All these methods involve time-consuming esterification and extraction procedures which result in lack of reproducibility and limit their clinical utility.

After a lethal dose of SMFA was ingested, death occurred within 72 h with almost all deaths soon after the ingestion. The time requirements for laboratory assay of SMFA also limit its predictive value. The aim of this study was to clinically differentiate patients with serious disease and a high probability of death.

The clinical manifestations of SMFA poisoning are extraordinarily variable. Nausea, vomiting, and abdominal pain initially occur, followed by anxiety,

agitation, muscle spasm, stupor, seizure, and coma.[1-2,4-7] In our cases, nausea, vomiting, and abdominal pain were the most common manifestations. Extreme anxiety, verbosity, irritability, and hyperactivity were noted. Subjective complaints of respiratory distress were more prevalent in the fatalities.

Trabes *et al.* reported a direct influence of SMFA on the brain with the unique disturbances in the cellular metabolism of glucose.[11] Generalized tonic-clonic seizures treatment with phenytoin and/or diazepam were recorded in two fatal cases. Coma is a late sign, and there was no difference in the initial coma score (GCS) recorded at the emergency room for the survival and mortality groups. Most of the patients were conscious when they arrived at ED but abrupt deterioration occurred in the fatalities.

Reversible acute renal failure, either oliguric or nonolioguric, has been reported in SMFA intoxication.[6] In our series acute oliguric renal failure occurred in two nonsurvivors.

Sinus tachycardia and hypotension are the common cardiovascular signs and the cardiac rhythm may deteriorate into ventricular tachycardia/ fibrillation or sudden cardiac arrest.[5] Ventricular tachycardia is a poor prognostic sign, and precedes 6 of 7 deaths. Sudden asystole was also noted in one of the fatalities. Other electrocardiographic abnormalities included prolonged QTc interval, ventricular premature beats, nonspecific T wave abnormalities and ST-T changes, atrial fibrillation with rapid ventricular response, and sinus tachycardia. The most findings were nonspecific ST-T change and T wave abnormalities, considered due to the cardiotoxic effect of SMFA and electrolyte abnormalities. Hypocalcemia and hypokalemia were the most common electrolyte abnormalities. Potassium or calcium chloride or cardiac glycoside has been reported to enhance the cardiovascular manifestations of toxicity.[10] However, Taitelman *et al.* reported two cases treated with calcium chloride in whom the markedly prolonged QT interval was restored to normal.[12] Calcium and potassium were routinely supplied to correct electrolyte abnormalities in our patients. Ethanol treatment of 16 patients may have aggravated the hypokalemia.

The management of SMFA intoxication includes symptomatic and supportive care. There is no known established antidote for fluoroacetate intoxication. IV glyceryl monoacetate (monoacetin) and ethanol have been advocated to prevent or reverse the toxic effects of fluoroacetate in animal studies.[11] The efficacy of these treatments in humans is unknown. Sodium fluoroacetate ingestion accompanied by ethanol ingestion was reported in a 29-year-old woman resulting in only mild toxicity.[11] In our series, one young woman ingested 240 mg SMFA, a usually lethal dose, mixed with 30% ethanol, Sn-Rung wine. Vomiting, hyperactivity, long QTc in ECG record, hypocalcemia, and hypokalemia were noted but she soon recovered and was discharged in stable condition. In another even a 39-year-old man ingested 45 mL 50% ethanol, Gau-Liang wine, with about 480 mg SMFA. This resulted in nausea, vomiting, convulsion, hyperactivity, respiratory distress, hypocalcemia, hypokalemia, ventricular tachycardia, and death at 24 h after ingestion. Although the immediate administration of ethanol after exposure may be helpful, larger delayed doses may not be beneficial. Five of the seven fatal cases received ethanol therapy more than one hour after SMFA ingestion, it obviously did not improve survival.

This study indicates that a systolic blood pressure < 90 mm Hg or presentation with metabolic acidosis or increased serum creatinine are associated with poor short-term survival after SMFA poisoning. It is suggested that all patients be observed intensively for at least 48 h. The risk of immediate death is less likely if there are no risk factors evident on presentation.

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