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Original Article

Therapeutic Response to Folinic Acid in Methanol Poisoning Epidemic in Shiraz

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Abstract

Background: Methanol poisoning may result to death and permanent complications, sporadic cases of methanol poisoning are fairly rare and the largest experience are generally gained from managing methanol intoxication epidemics. The main metabolite of methanol is acid formic that is the prime metabolite responsible for toxic effects of methanol and since folate dependent systems are responsible for the oxidation of formic acid to CO_2 and water. It is believed that administration of folic acid enhances the metabolism of formate. Though therapeutic effects of folic or folinic acid has never been fully tested in clinical trails in human. Our objective was to evaluate therapeutic effect of folinic acid in methanol poisoned persons.

Methods: In recent methanol poisoning epidemic due to "bootleg" Liquor consumption in Shiraz at 2004, Sixty-two patients have hospitalized. Folinic acid was administered to 19 patients and therapeutic effect of folinic acid was studied.

Results: There was no significant difference between two groups of patients and number of decreased visual acuity, renal function, hospital stays and needs to bicarbonate therapy and hemodialysis. The only effect was decreasing acidosis in folate treated patients.

Conclusion: Regardless of prior animal studies and case reports, with attention to our study limitation we didn't found significant protective effect of folinic acid infusion among methanol poisoning patients. The only effect was decreasing acidosis in folate received patients. Further studies in optimal situation is needed for definite judgment.
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Keywords ● Leucovorin ● methanol ● poisoning

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Introduction

The ingestion of high dose of methanol caused metabolic acidosis, respiratory difficulty, optic nerve damage and central nervous system disturbances. Near total causes of methanol poisoning are due to ingestion. It may result from methanol ingestion for suicidal attempt, accidental use by children and sometimes due to cheaper price than ethanol for fortify of illicit spirits. Many epidemics associated with these circumstances are reported from around the world.[1-8]

In spite of improved treatment, morbidity and mortality in methanol poisoning remains high, mainly because of an often

difficult, and therefore delayed, diagnosis.[9]

Although methanol itself is not highly toxic, it is metabolized by alcohol dehydrogenase to formaldehyde and subsequently produces its toxic metabolite formic acid that causes most organ damages.

Inhibiting the formation of toxic metabolites by alcohol dehydrogenase and/or urgent dialytic removal of these alcohols and their metabolites are the cornerstones of therapy. Supportive measures include gastric lavage in the first hour post ingestion. Bicarbonate infusion may improve metabolic acidosis, but buffer therapy has not been shown to improve outcome. Hypocalcemia and hypoglycemia should be corrected. Thiamine (50 to 100 mg), folate (up to 50 mg), and pyridoxine (100 mg) are usually administered.[10] Also the competitive substrate ethanol is commonly administered in an attempt to inhibit methanol metabolism. Beside ethanol use, Fomepizole (4-methylpyrazole) is an inhibitor of alcohol dehydrogenase and can be used in ethanol poisoning; also The FDA has approved it for ethylene glycol and methanol poisoning. The protocol consists of a 15 mg/kg IV loading dose followed by a 10 mg/kg IV bolus q12h. After 48 h, the bolus dose should be increased to 15 mg/kg q12h to account for enhanced fomepizole metabolism.

After experimental studies on monkeys, Noker and Tephly hypothesized that folate compounds could decrease formate accumulation after methanol by stimulating formate oxidation or utilization and suggested a possible use for folates in the treatment of certain case reports of human methanol poisoning[11] and till now many reports exist about effect of folic acid on many other animals,[12-15] but there is no strong clinical evidence in humans.

In this study we determined the methanol level and described usage of folinic acid for therapeutic purpose in patients with methanol poisoning in large outbreak in Shiraz. This is also the largest scale outbreak in which folinic acid has been used as an antidote.

Material and Methods

Patients and procedures

The outbreak of methanol poisoning described in this paper occurred in Shiraz, central city of Fars province in south of Iran. Sixty-two patients with a median age of 53 years were admitted from late June 2004 until early July 2004 (20 days), in 3 main hospital of Shiraz with impression of methanol poisoning. The cause of poisoning was consumption of illegal fortified alcoholic beverages. All people who used illegal alcoholic beverage in time period of study and around epidemic time were announced with public information sources(local radio and television programs, newspapers) for referring to 3 major hospital of city (Namazee,Shahid Faghihi and Shahid Beheshti hospitals) and physical examination and blood acidosis were determined for every body. According to serum PH and ophthalmic complaints, patients received the treatment.

This is probably a minimum figure, as more patients could be expected to be poisoned and didn't come to hospital and somebody had died without the diagnosis of methanol poisoning. Among admitted patients history of alcohol consumption, serum methanol level and acidosis were used for diagnosis. Serum electrolytes, urea nitrogen, and creatinine and arterial blood gases were measured at base line and subsequently at regular intervals. Also patients had close monitoring of vital signs and physical examination for detection of any progression in disease course. Determinations of best corrected visual acuity, funduscopic examinations, complete blood counts, liver-function tests, electrocardiographic studies, and urinalyses were performed at the time of enrollment. The patients were visited by ophthalmologist daily during the study and also one month after discharge.

Treatment

For the patient presented with ophthalmologic abnormalities or significant acidosis, the acidosis was corrected with intravenous sodium bicarbonate. Further generation of toxic metabolite was blocked by the administration of intravenous ethanol infusion.

Hemodialysis also used for correcting severe metabolic abnormalities and to enhance methanol and formate elimination. For the methanol poisoned patient without evidence of clinical toxicity, the first priority was to inhibit methanol metabolism with intravenous ethanol.

The above treatment protocol and supportive cares were according to standard protocol (American Academy of Clinical Toxicology) without use of Fomepizol due to unavailability of this drug.[16] Acidosis at presenting time was one of the major factors in triage of patients and key factor in starting therapy, but definite diagnosis of methanol intoxication requires the confirmed increase in serum methanol level by gas chromatography.[17] We also used four dose of folinic acid as 1mg/kg/body weight, up to a total dose of 50mg, each vial of Folinic acid was diluted in 5% dextrose in water and administered over 30–60 minutes and administered intravenously, every 6 hours for 19 patient as soon as possible, other patients (43 cases) didn't received folinic acid. Informed consent was obtained from the patients who

were awake or from relatives if the patients who were unconscious. Selection of patients for folinic acid prescription was influenced by some factors such as limited number of drug and availability of drug at the terminal days of epidemiy, so only restricted number of patients received drug and true randomized control trial could not be planned.This drug is also recommended by mentioned academy for treatment. This procedure was approved by the ward Ethics Committee.

Laboratory Methods

Plasma samples obtained for the reference laboratory were frozen immediately then methanol concentration in serum was determined by the use of gas chromatography method. A Shimadzu-14A model temperature-programmed head scape gas chromatograph (GC) equipped with a CBP-10 capillary column (25 m length) and a flame ionization detector (FID) was used to analyze the samples. Acetonitrile was used as internal standard and the column temperature was started at 40 ^{o}C (it was held for 5 min.) with subsequent heating at 5 ^{o}C/min. to 180 ^{o}C where it was held for 10 min. the injector and detector temperature were 230 ^{o}C and 240 ^{o}C subsequently. Helium also was injected in column with volume of 1 ml and flow rate of 30 ml/min. the same analysis was done on sample derived from illicit liquor.

Statistical analyses

Mean values were compared with use of Student's unpaired t-test and nominal variables with use of Fisher's exact test. Correlations were determined with the Pearson correlation coefficient. All analysis was done by SPSS 13 software.

Results

There were 62 patients in this study that all of them were men. The mean (±SD) age of the admitted patients was 31± 12.7 years. Mean age of folinic acid received patients were 30.83 ± 12.6 years and untreated ones were 30.93 ± 11.5 years. All of the patients were drunk fortified liquor. Initial serum methanol and ethanol level were determined in patients that were 27.70±31.07 mg/dl and 23.52±28.12 mg/dl respectively. There was no significant difference between serum levels of methanol and severity of symptoms and condition between folinic acid treated and untreated patients (p-value=0.63) (table 1).

From 62 admitted patients, 57 patients discharged with good condition without any complication that 40 of these didn't received folinic acid.

Five patients at time of discharge had visual abnormalities, manifested as symptoms such as significant blurred vision or other abnormal findings such as hyperemia of retina on examination. From these five patients, 2 were treated by folinic acid and 3 were not. There was not significant difference between treated and untreated patients (P =0.16).

Comparing the 2 groups during hospital course, 5 patients who were treated with folinic acid and 4 patient from untreated group developed raising of renal function indices (BUN and Creatinine), and there was no significant difference between two groups (P> 0.05). All of patients had normal kidney function test (creatinine < 0.5 mg/dl) at time of discharge (table 2).

Effects of folinic acid on PH of two groups were compared with statistical analysis and effect of other variables such as hypotension,

Table 1: Description two groups according to presenting conditions.

	Treated with folinic acid	Untreated with folinic acid
Number of patients	19	43
Mean of serum bicarbonate level (±SD) †	8.29±5.1	9.16±5.8
Mean APACHEE II Score(±SD)	20.83±7.5	19.52±8.8
Mean blood urea nitrogen(±SD)‡	30.93±11.5	30.83±12.6

† milimol /liter
‡miligram/dl

Table 2: Comparison between two groups according to ophthalmic complication, renal failure, bicarbonate infusion and hospital stay.

	Treated with folinic acid	Untreated with folinic acid	P-value
Number of patients with Ophthalmic complications (%)	1(5.55)	4(4.54)	>0.05
Number of patients with Renal Failure (%)†	4(22.22)	5(5.68)	>0.05
Amount bicarbonate infusion‡(mean±SD)	165.15±64.95	163.35±72.31	>0.05
Hospital Stay(hours) (mean±SD)	37.33±21.17	49.90±24.12	>0.05

†Creatinine >1.5 mg/dl
‡miliequivalent

or renal failure was excluded by regression tests. We found higher PH levels at the end of treatment (mean 7.04 ±0.22) in folinic acid untreated group than folate treated group (mean 7.18 ±0.16) but this effect didn't had any influence on the need for acidosis management methods such as hemodialysis or bicarbonate infusion rates (figure 1).

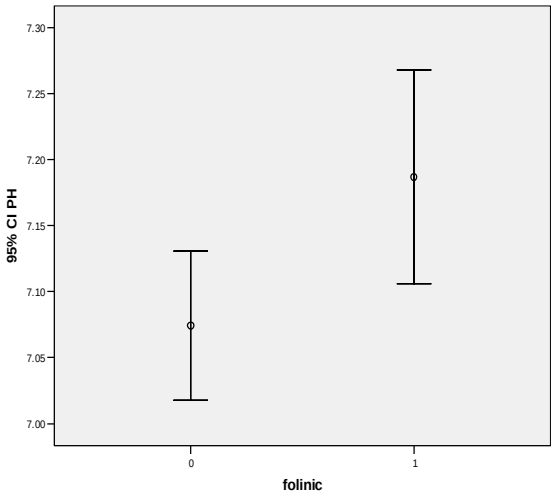

Figure 1: effect of folinic acid on acidosis.
0=untreated patients with folinic acid
1=treated patients with folinic acid

Folinic acid received patients had a mean hospital stay of 37.33±21.17 hours and untreated group had 49.90±24.12 hours .This difference was not statistically significant between two groups.

Discussion

Methanol poisoning is fairly common in our country. We didn't found actually any therapeutic effect of folinic acid on ophthalmic complication of methanol poisoning. Also this drug couldn't reduced rate of acute renal failure in the poisoned persons. The effect of drug for reduction of acidosis was significant and we observed beneficial effect of drug for raising PH. This outbreak according to the number of patients was a rare event in recent years in world. Also according to number of patients who treated with folinic acid, this survey is unique till now. No dermatologic reaction such as pruritis, rash, urinary or respiratory symptoms as wheezing occurred with use of folinic acid.

Due to unpredictable nature of outbreak and unavailability of drug in all hospitals at beginning of catastrophe, complete and perfect study design for ideal clinical trial could not be possible so we had some restrictions in trial. The potentially valuable use of folinic acid to enhance the metabolism of formic acid has often been overlooked. While there are no human clinical trials that confirm the benefit of using a folic acid derivative for this purpose, the animal studies may show some clues for using in treatment of methanol poisoning.[13,14] One of the most important studies about this effect is the survey of Johlin FC and et al regarding comparison between human, rat and monkey's liver content of tetrahydrofolate. In human liver, tetrahydro folate levels were only 50% of those observed for rat liver and similar to those found in monkey liver. Total folate was also lower (60% decreased) in human liver than that found in rat or monkey liver. Interestingly, mouse liver contains much higher hepatic tetrahydrofolate and total folate than rat or monkey liver. This is consistent with higher formate oxidation rates in this species,[18] so higher rate of methanol induced ophthalmic complication in human and monkey than mouse and rat is due to lower level of tetrahydrofolate and folic acid in former group.

Our study was one of limited human clinical trials that showed the effect of folinic acid on methanol poisoning. We had some limitations in our survey such as study design(due to unpredicted nature of epidemic), laboratory facility, availability of drugs such as fomepizol and folinic acid. So true randomized clinical trial couldn't be planned and definite conclusion about the results need further studies. The used dose of folonic acid didn't improved ophthalmic effects of methanol. Perhaps a higher dose of drug may have a better clinical response and therapeutic effect on human but our study showed the therapeutic effect of drug for treatment of acidosis in methanol poisoned persons. Other studies with higher doses and monitoring of serum folinate level is needed for obtaining useful conclusion.

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