Acute Renal Injury Following Methanol Poisoning: Analysis of a Case Series

David Verhelst,[1] Pierre Moulin,[2] Vincent Haufroid,[3] Xavier Wittebole,[4] Michel Jadoul,[1] and Philippe Hantson[4]

Departments of [1]Nephrology, [2]Pathology, [3]Industrial Toxicology and Occupational Medicine, and [4]Intensive Care, Cliniques St-Luc, Université catholique de Louvain, Brussels, Belgium

The objective of this paper is to document the prevalence of indicators of acute renal injury in a series of methanol-poisoned patients treated in an intensive care unit and to discuss the possible mechanisms. This is a retrospective analysis of the medical records of 25 consecutive patients admitted to the intensive care unit after severe intentional methanol poisoning. Acute renal impairment was defined as a serum creatinine concentration higher than 177 μmol/L and/or a urinary output on admission and for the first 24 h below 0.5 ml/kg/h. Clinical pathological signs of acute renal injury were found in 15 patients. In comparison with the 10 other patients taken as control group, the patients who developed renal injury had a lower blood pH value on admission, a higher serum osmolality, and a higher peak formate concentration. Two factors contributing to renal injury could be identified: hemolysis and myoglobinuria. The role of osmotic changes ("osmotic nephrosis") or of a direct cytotoxic effect of formic acid remains speculative. Analysis of proteinuria suggests that proximal tubular cells may be preferentially affected. Results of histopathological evaluation of the kidney on a limited sample size ($n = 5$) were inconclusive but suggestive of possible hydropic changes in the proximal tubule secondary to methanol toxicity. Acute renal injury may be associated with other signs of severity in methanol poisoning, but it is almost always reversible in survivors. Indicators of acute renal injury were identified. The pathophysiology of this acute renal injury is multifactorial and far more complex than shock-related tubular necrosis.

Keywords Acute Renal Injury, Formic Acid, Hemoglobinuria, Methanol Poisoning, Myoglobinuria, Osmotic Nephrosis

Severe methanol intoxication is rare but frequently lethal. Methanol is rapidly absorbed throughout the gastrointestinal tract and is converted in the liver into formaldehyde and then formic acid by the action of alcohol dehydrogenase and acetaldehyde dehydrogenase. Methanol toxicity is mediated by its main metabolite, formic acid, which is responsible for metabolic acidosis, brain, and optical nerve lesions. There is a clear correlation between formate, but not methanol, concentrations and these complications (Liu et al. 1998). Other complications may also occur such as acute pancreatic injury (Hantson and Mahieu 2000). Poor prognosis criteria include coma and seizure at presentation and severe metabolic acidosis (Liu et al. 1998; Mahieu, Hassoun, and Lauwerys 1989).

The kidney is usually not considered as a target organ in methanol poisoning. Acute renal failure has been described in a few case reports. It was related to terminal complications of methanol intoxication, but reversible episodes have been also documented (Closs and Solberg 1970; Erlanson et al. 1965; Fink 1943; Grufferman, Morris, and Alvarez 1985; Hoy, Scandling, and Carbonneau 1983; Rabinovitch 1922).

The aim of this retrospective study was to determine the prevalence of acute renal injury and to elucidate the factors associated with acute renal injury in a cohort of patients admitted to an intensive care unit with methanol poisoning.

METHODS

Patients

We retrospectively reviewed the medical records of the methanol-poisoned patients treated in the intensive care unit (ICU) between 1987 and 2001. The cases were identified by the discharge diagnosis obtained from the ICU patients' database. Inclusion criteria were a history of deliberate methanol ingestion, with a blood methanol concentration greater than 6.2 mmol/L, or a high-anion-gap metabolic acidosis. Exclusion criteria were a history of preexisting renal impairment and the coingestion of other toxic substances. On the whole, data were available for 25 patients. The data were abstracted and analyzed independently by two intensive care physicians.

The clinical variables analyzed were age, gender, onset delay of acute renal injury (hours from ingestion), associated complications, and outcome. The biological variables studied were minimal arterial blood pH, peak serum creatinine level (μmol/L),

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Address correspondence to Philippe Hantson, MD, PhD, Department of Intensive Care, Cliniques Universitaires St-Luc, Avenue Hippocrate, 10, 1200 Brussels, Belgium. E-mail: hantson@rean.ucl.ac.be

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peak blood methanol level (mmol/L), peak blood formate level (mmol/L), peak serum creatinine phosphate kinase (IU/L), serum osmolality measured on admission (mOsm/kg H_2O), peak lactate dehydrogenase level (IU/L), haptoglobin, urine analyses including sediment, and measurement of myoglobinuria and hemoglobinuria. In five patients with acute renal failure, levels of low-molecular-weight proteins were measured (β_2-microglobulin, *N*-acetyl-β-D-glucosaminidase [NAG] and retinol-binding protein [RBP]).

The end point of the analysis was the prevalence of acute renal injury. Acute renal injury was defined as a serum creatinine concentration higher than 177 μmol/L and/or a urinary output at admission and for the first 24 h below 0.5 ml/kg/h. Patients were divided into two groups: those meeting one of these criteria (group I) and those not (group II).

Renal Biopsy

Out of the 25 patients, 6 died, and an autopsy including kidney histology was obtained for three. On the other hand, two patients with brain death were organ donors and renal biopsy was available for both. Brain death is defined as the irreversible loss of both cortical and brainstem activities. In case of methanol poisoning, brain death is usually due to brain edema with refractory high intracranial pressure in relationship with the severity of the metabolic acidosis. Brain death is not associated with specific indicators of acute renal injury.

All renal biopsies were examined by light microscopy, after processing by standard histological techniques. Material was not appropriate for electron microscopic study.

Statistics

The comparisons between groups were performed using the unpaired Student's *t* test (two-tailed). MedCalc software (Gent, Belgium) was used for calculations.

RESULTS

Case Series

The characteristics of the two groups are presented in Table 1. In both groups, patients were treated by intravenous ethanol administration except for two in the group with renal impairment who received only fomepizole as antidotal therapy. One patient also received fomepizole after ethanol discontinuation. All patients were given folinic acid and sodium bicarbonate supplementation. Hemodialysis was performed to eliminate methanol in all cases except in one case in the group with renal impairment.

Fifteen patients (group I) developed signs of renal impairment within 48 h after methanol poisoning. Results are given in Tables 2 and 3. In 12 of them, red-brown or very dark urine was observed during the first hospital day. Eleven patients with acute renal injury showed evidence of hemolysis, as shown by an increase in serum lactate dehydrogenase and bilirubin, together with a drop of haptoglobin level, whereas these parameters remained normal in the control group. Eight patients with renal dysfunction presented significant myoglobinuria (data not recorded in four patients) without significant increase in creatinine phosphate kinase (CPK). These data were not available in group II. Both hemolysis and myoglobinuria were detected in seven patients with renal impairment.

In five cases in group I, measurements of low-weight-molecular proteins in urine were available and showed extremely high urinary concentrations.

Statistical analysis (Table 1) showed that the patients with acute renal injury had a significantly lower minimal arterial blood pH (6.97 $\pm$ 0.2 versus 7.3 $\pm$ 0.19, $p = .001$). Although the maximal blood methanol concentration was higher in the patients with acute renal injury, this difference was not statistically significant. The maximal blood formate level was statistically higher in group I (16.7 $\pm$ 10.8 mmol/L versus 8 $\pm$ 4.6 mmol/L, $p = .05$) however. Serum osmolality at admission was also

TABLE 1
Comparison between the groups with and without renal impairment

	Acute renal dysfunction (group I) $n = 15$	Control (group II) $n = 10$	Statistical analysis
Gender (M/F)	11/4	4/6	
Age (years)	42.6	33.2	*NS*
Peak serum creatinine (μmol/L)	243.6 $\pm$ 200.7	73.1 $\pm$ 23.1	$p = .001$
Peak CPK (IU/L)	9520 $\pm$ 26147	159 $\pm$ 153	$p = .001$
Peak blood methanol (mmol/L)	85.5 $\pm$ 87.5	43.3 $\pm$ 45.5	*NS*
Peak blood formate (mmol/L)	16.7 $\pm$ 10.8	8 $\pm$ 4.6	$p = .05$
Minimal arterial pH	6.97 $\pm$ 0.20	7.30 $\pm$ 0.16	$p = .001$
Admission serum osmolality (mOsm/kg H_2O)	417 $\pm$ 102	325 $\pm$ 25	$p = .03$

Note. Values are expressed as mean $\pm$ standard deviation. The comparisons between groups were performed using two-tailed Student's *t* test.

TABLE 2
Characteristics of the methanol poisoned patients who developed signs of renal injury

Patient (gender, age)	Minimum arterial blood pH	Maximum blood methanol levels (mmol/L)	Maximum blood formate levels (mmol/L)	Maximum serum creatinine level (μmol/L) (Nl: 70.7–115) and delay from ingestion	Onset delay of acute renal injury (hours from ingestion)	Associated complications (other than visual)	Outcome
1 (M, 34)	6.84	18.7	11.1	397.8 (day 4)	15	↗ Pancreas enzymes	Recovery
2 (M, 72)	6.80	46.8	46.7	349.2 (day 6)	22	↗ Pancreas enzymes, hypoxia, refractory hypotension	Death
3 (M, 27)	6.95	23.1	14	145.9 (day 2) Initial oliguria	48	None	Recovery
4 (M, 36)	7.17	50	NA	92.8 (day 2) Initial oliguria	48	None	Recovery
5 (M, 32)	6.70	58.7	13.3	103.4 (day 2) Initial oliguria	24	↗ Pancreas enzymes	Death
6 (M, 49)	6.75	9.3	15.1	318.2 (day 3)	20	↗ Pancreas enzymes, vasoplegia, shock	Death
7 (F,18)	7.19	16.3	20	92.8 (day 1) Initial oliguria	NA	Pancreatitis	Recovery
8 (F, 58)	6.85	53	17.8	181.2 (day 3)	72	↗ Pancreas enzymes	Recovery
9 (M, 27)	7.10	321.5	20.2	183.9 (day 2)	24	Pancreatitis	Recovery, peritoneal dialysis for 4 days
10 (M, 30)	6.76	68.7	19.1	159.1 (day 2)	48	↗ Pancreas enzymes	Recovery
11 (F, 68)	7.26	107.7	NA	247.5 (day 4)	72	↗ Pancreas enzymes, vasoplegia	Recovery
12 (M, 47)	7.23	224.7	3.1	884 (day 10)	12	↗ Pancreas enzymes	Recovery, iterative hemodialysis for 30 days
13 (F, 54)	7.22	153.2	6.7	225.4 (day 3)	12	Pancreatitis, hypoxia, shock	Death
14 (M, 46)	6.79	99.9	22.6	150.3 (day 1) Initial oliguria	20	Seizure, hypothermia, vasoplegia, shock, hypoxia	Death, kidney donation
15 (M, 41)	7.00	30.3	7.2	122 (day 1) Initial oliguria	18	Cardiac arrest, hypoxia	Death, kidney donation

NA, not available; acute renal injury as defined in methods.

TABLE 3
Factors associated with renal dysfunction

Patient (gender, age)	Admission measured serum osmolality (mOsm/Kg H_2O)	Urinalysis	Additional data	Maximum serum CK level (IU/L) (Nl < 170)	Hemolysis (LDH↗, bilirubin↗, haptoglobin↙)	Myoglobinuria (ng/ml) (Nl < 10)
1 (M, 34)	322	Acetonuria ++, proteinuria 0.3 g/L, hyaline casts		1353	−	ND
2 (M, 72)	351	Normal		70	+	<10
3 (M, 27)	340	Proteinuria +, hyaline and granular casts	RBP 17200 μg/g creatinine (<300)	2200	+	>3000
4 (M, 36)	374	Proteinuria ++, acetonuria ++, RBC 15–20/F, hyaline casts + + +		130	+	35
5 (M, 32)	377	Proteinuria 0.57 g/L, RBC 15–20/F, hemoglobinuria +, hyaline and granular casts +	RBP 220000 μg/L (<250), β_2-microglobulin 170000 μg/L (<250), NAG 53 IU/L (<10)	337	+	4950
6 (M, 49)	361	Proteinuria +, granular casts ++, hemoglobinuria ++		102600	+	147980
7 (F, 18)	394	Proteinuria +, granular casts +, hemoglobinuria + + +	β_2-microglobulin 29570 μg/L (<250)	279	+	5037
8 (F, 58)	381	RBC 6–8/F, proteinuria +	RBP 174240 μg/g creatinine (<300), β_2-microglobulin 23790 μg/g creatinine (<300)	800	+	<10
9 (M, 27)	730	RBC 15–20/F, granular casts, proteinuria 2.1 g/L	RBP 17169 μg/g creatinine (<300), β_2-microglobulin 39811 μg/g creatinine (<300), NAG 39.6 IU/g creatinine (<10)	17080	+	>25000
10 (M, 30)	438	RBC 4–6/F, hyaline and granular casts +		7090	−	+
11 (F, 68)	435	RBC 150/F		421	+	ND
12 (M, 47)	530	Proteinuria 0.3 g/L, 200–300 hematuria, granular casts		399	+	10752
13 (F, 54)	381	Proteinuria 0.3 g/L		3298	+	>20000
14 (M, 46)	476	Proteinuria + + +, glucosuria + + +, WBC 30–40/F		175	−	ND
15 (M, 41)	364	Hyaline casts		6578	−	ND

RBC, red blood cells; WBC, white blood cells; /F: high-power field; RBP, retinol binding protein; NAG, *N*-acetyl-β-D-glucosaminidase; ND, not determined.

significantly higher in patients with renal impairment (417 ± 102 mOsm/kg H_2O versus 325 ± 25 mOsm/kg H_2O, $p = .03$).

Among associated complications (other than visual), we found biochemical or radiological signs of acute pancreatitis in 11 cases, cardiovascular collapse in 6 cases, and hypoxia in 4 cases. These complications were restricted to group I.

Outcome

There were no fatalities in the group II. Out of the 15 patients with renal impairment, 6 died. The primary cause of death was brain edema in five cases and acute necrotising pancreatitis in one case. Nine patients made a complete renal recovery, but one of them (patient 12) required hemodialysis for several weeks. Two patients (patients 1, 7) had a complete visual recovery, whereas the remaining seven had permanent visual defects, with a marked decrease in visual acuity associated to signs of optic neuropathy at visual evoked potentials examination.

Due to our previous favorable experience, kidney donation for organ transplantation was discussed for two patients in "brain death" status (patients 14, 15). The kidneys were harvested and successfully transplanted. Kidney graft biopsies were performed at the time of transplantation.

Histological Analysis

Material was available from five patients. Among the three patients who underwent an autopsy, two (patients 2, 13) had histological evidence of hydropic changes in proximal tubular cells (Figure 1). For the third patient, the kidney samples displayed autolytic changes due to time interval between death and autopsy, preventing hydropic tubular changes to be unequivocally diagnosed. Kidney graft biopsies performed before transplantation revealed minor tubulointerstitial lesions as usually seen in grafts and ascribable to ischemia-reperfusion sequence. No evidence for hydropic changes was seen. No glomerular or vascular lesions were observed.

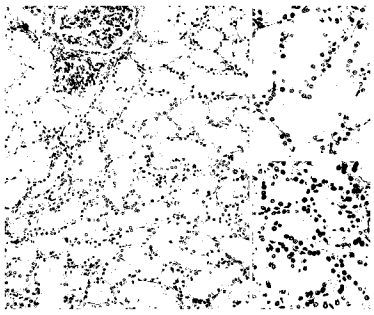

FIGURE 1

A, Kidney cortex (150×), patient SE. Glomeruli with normal appearance, swollen epithelial cells in the proximal tubules in almost all the nephrons at a variable degree of intensity, well-preserved distal tubules, no interstitial fibrosis or inflammation. *B*, Proximal tubule with clarified but still finely granular cytoplasm (320×). Note that hydropic change is seen in all the cells. *C*, Proximal tubule from a control human kidney remove for tumour (320×). The apical brush border is not well preserved. Epithelial cells are smaller and their cytoplasm appears densely stained in comparison with *B*.

DISCUSSION

The prevalence of acute renal injury as defined earlier seemed very high (60%) in this series of 25 consecutive methanol-poisoned patients. We agree that the definition of acute renal impairment was somewhat arbitrary. Creatinine clearance is another possible marker of renal injury not included in our criteria. However, hemodialysis was performed in all the patients (except one) soon after admission, precluding a correct interpretation of creatinine clearance. Given that only patients categorized as having acute renal injury had more severe systemic toxicities (outside of visual effects), our results also showed that our definition was helpful to categorize the patients who have a good prognosis or who will develop serious complications including death. Acute renal injury may be therefore considered as another marker of severity in methanol poisoning. Visual complications were important in this subgroup of patients as it was previously documented (Hantson et al. 1999).

The kidney is usually not considered as a primary target organ in methanol poisoning. Acute renal failure has previously been considered as a terminal complication of methanol poisoning, but reversible episodes of acute renal injury have been documented (Closs and Solberg 1970; Erlanson et al. 1965; Fink 1943; Grufferman, Morris, and Alvarez 1985; Hoy, Scandling, and Carbonneau 1983; Rabinovitch 1922). Their pathophysiology is uncertain but old pathological descriptions are consistent with proximal tubular necrosis without glomerular lesions (Erlanson et al. 1965; Fink 1943; Rabinovitch 1922). Our data indicate that methanol poisoning may lead, at least in part, to hydropic changes in proximal tubular epithelial cells, without significant lesions of the glomeruli. This pattern may progress towards further renal injury but may also resolve.

Several mechanisms could probably explain the renal injury in our study (Figure 2):

- As severe hypotension requiring vasopressive drug administration was noted in 6/15 cases, acute renal injury due to reduced kidney perfusion may be an important pathway.
- Myoglobinuric and hemoglobinuric renal failure may likely be another mechanism observed in our patients. As illustrated in Table 3, myoglobinuria was detected in 7/11 cases with renal injury in which it was measured. This feature was not present in patients without kidney dysfunction. Eleven patients with renal impairment presented signs of hemolysis versus none in the control group. The pathophysiology of hemoglobinuric

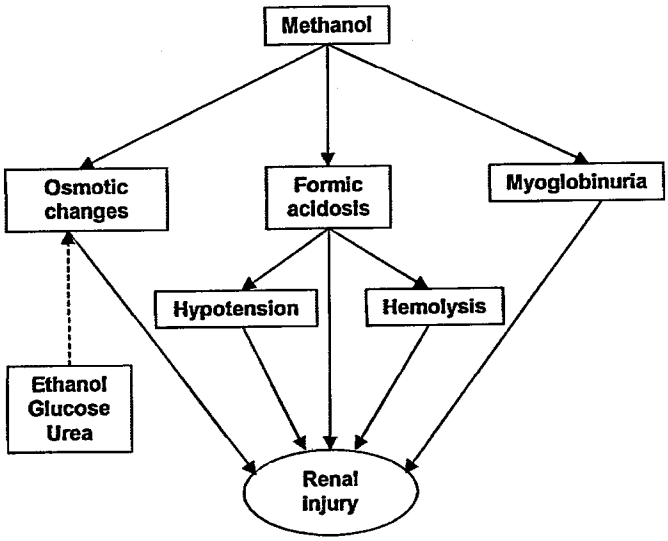

FIGURE 2
Possible mechanisms of methanol-related acute renal injury.

and myoglobinuric acute renal failure has been studied extensively in animal models (Zager 1996). The main pathophysiologic mechanisms are renal vasoconstriction, intraluminal casts formation, and direct hemeprotein-induced cytotoxicity. An important factor favoring precipitation of myoglobin and hemoglobin is a low pH of tubular urine (Zager 1996). In our series, CPK peak concentration was not very high, a fact making the development of acute renal injury intriguing. However, in our patients, we speculated that the low pH of tubular urine enhanced myoglobin and hemoglobin toxicities. Although methanol has not been frequently considered as a cause of rhabdomyolysis and renal failure, our clinical data and laboratory findings are in agreement with previous observations suggesting that hemoglobinuria and myoglobinuria could be involved simultaneously (Closs and Solberg 1970). Elevation of CPK levels has been described in a previous report of epidemic methanol poisoning (Swartz et al. 1981). Rhabdomyolysis syndrome may be caused by numerous factors. In case of acute poisoning, this complication is mainly observed in comatose patients and is related to pressure necrosis. In this series, 12 patients had altered consciousness but none presented evidence of muscle compression. Two other patients were conscious on admission but extremely agitated. We did not record seizures episodes. On the other hand, various drugs and toxic substances have been reported to have a direct toxic effect on the muscle. Although ethanol may contribute to muscle injury in a variety of ways, no direct toxic effect of methanol on skeletal muscle has been clearly identified (Sung and Rubin 1972). There is also no literature indicating that methanol has direct hemolytic properties. Obviously, as treatment of methanol poisoning includes ethanol administration, the combination of both alcohols might also be responsible for some hemolytic manifestations. Hemolysis with anemia (Zieve syndrome) has been mainly described following chronic ethanol abuse, but is almost never observed following ethanol "binge" (Benedetti et al. 1986). Hemolysis of human red blood cells by high ethanol concentration has been experimentally observed (Tyulina et al. 2000). This hemolysis is related to colloid-osmotic process. It has also been suggested that formic acid might induce hemolysis via a direct cytotoxic action on the red blood cells (Moore et al. 1994; Sigurdsson, Bjornsson, and Gudmundsson 1983; Westphal et al. 2001). However, experimental data showed that hemolysis in this case is probably not due to a direct cytotoxic effect but is related to the degree of metabolic acidosis, in agreement with other models of acid-induced hemolysis (Verstraete et al. 1989).

- Most of the methanol poisoned patients exhibit severe metabolic acidosis as a consequence of both formic acid accumulation and, to less extent, lactic acid production. We observed a significant correlation between formate levels and development of acute renal injury. Formic acid is an inhibitor of mitochondrial cytochrome oxidase (Liesivuori and Savolainen 1991). The inhibition increases with decreasing pH, suggesting that the active inhibitor is the undissociated acid. This results in tissue hypoxia and cellular injury. The influx of calcium into cells is one of the possible mechanisms of toxicity (Liesivuori and Savolainen 1991). Moreover, the absorption of sodium chloride in the proximal tubule is markedly stimulated by formate (Knauf et al. 2001; Wang, Giebisch, and Aronson 1992). In a model of rat proximal tubule microperfused in situ, infusion of formate leads to a rise in proximal tubular cells volume (Aronson and Giebisch 1997; Wang, Giebisch, and Aronson 1992). In our case series, vacuolar distension of proximal cells was associated with high concentrations of low-molecular-weight proteins in urine, potentially explained by a direct formate toxicity on proximal tubular cells.
- Finally, the possible role of osmotic changes on renal tubular cells should also be taken into account. In our series, patients who developed acute renal injury had higher measured serum osmolality on admission, whereas blood methanol concentration did not significantly differ from that observed in the control group. Moreover, histological data showed vacuolar distension of proximal tubular cells. The effect of osmotic changes on the kidney has mainly been described after administration of radiocontrast products, mannitol, hydroxyethyl starch, and intravenous

immunoglobulin therapy (Ahsan et al. 1994; Cittanova et al. 1996; Visweswaran, Massin, and Dubose 1997). Osmotic injury to the renal tubule may account for reversible low-grade proteinuria, as the proximal nephron is responsible for the reabsorption of low-molecular-weight proteins that are normally filtered by the glomerulus. Interestingly, when reporting on their experience with kidney donation after fatal methanol poisoning, Friedlaender et al. (1996). noted acute tubular necrosis in two recipients. The donor serum creatinine before harvesting was 415.5 μmol/L and the sediment showed many tubular epithelial cells and pigmented coarse granular casts. A postrevascularisation graft biopsy in both recipients showed normal glomeruli with severe hydropic swelling of proximal tubular cells.

In conclusion, apparent renal injury seems relatively frequent following severe methanol poisoning. Isolated renal injury is less common than renal impairment accompanying other organs dysfunction. In our sampling, proximal tubular dysfunction, rather than glomerular, is preferentially noted. The mechanisms of nephrotoxicity are likely multifactorial. The role of direct factors remains highly speculative: possible injury to the tubular cells due to the osmotic effects of high blood methanol concentrations, and/or cytotoxic effects related to possible formate actions on proximal tubular cells. Among indirect factors, hemolysis and myoglobinuria were frequently observed.

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