

Review article

Acute alcohol intoxication

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Abstract

Acute alcohol intoxication is a clinically harmful condition that usually follows the ingestion of a large amount of alcohol. Clinical manifestations are heterogeneous and involve different organs and apparatuses, with behavioral, cardiac, gastrointestinal, pulmonary, neurological, and metabolic effects. The management of an intoxicated patient occurs mainly in the emergency department and is aimed at stabilizing the clinical condition of the patient, depending on his/her clinical presentation. One specific drug that is useful in the treatment of acute alcohol intoxication is metadoxine, which is able to accelerate ethanol excretion. In patients presenting an acute alcohol intoxication, alcohol-related disorders should be detected so that the patient can be directed to an alcohol treatment unit, where a personalized, specific treatment can be established.

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1. Introduction

Ethanol (CH₃CH₂OH) is a water-soluble compound that rapidly crosses cell membranes, resulting in ready equilibration between intra- and extra-cellular concentrations [1]. Its absorption occurs mainly in the proximal intestinal tract,

namely, in the stomach (70%) and in the duodenum (25%), while only a small percentage occurs in the remaining intestinal tracts [1]. Gastric alcohol dehydrogenase (ADH) is responsible for 10% of alcohol metabolism (so called “first pass metabolism”) and has important gender-related differences [2]. The remaining 90% of ingested ethanol is metabolized in acetaldehyde along three liver enzymatic pathways in different percentages: (1) liver ADH (90%), (2) microsomal ethanol oxidizing system (MEOS; 8–10%), and (3) catalase (0–2%) [3].

Alcohol is a substance that is widely used, mostly in western countries. It also represents the oldest and the most diffuse substance of abuse. In the United States, 20–40% of the subjects admitted to hospitals have alcohol-related problems [4] and, in elderly people, alcohol-related disorders are as common a reason for hospitalization as myocardial infarctions [5].

In Italy, some four million individuals are reported to have alcohol-related disorders; of them, approximately one million

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satisfy the Diagnostic and Statistical Manual of Mental Disorders IV edition criteria [6] for alcohol dependence [7]. The social cost of alcohol-related disorders – including alcohol-related mortality, morbidity, loss of productivity, absenteeism, and hospitalization – is estimated to be around 5–6% of the gross national product (GNP) of Italy [8]. Similarly, in the rest of Europe, the full economic cost of alcohol abuse is calculated to be around 2–5% of the GNP (corresponding to €26–66 billion in the year 2003) [8].

Of the many alcohol-related disorders present in subjects referred to emergency care departments, acute alcohol intoxication is the most frequent [9]. This condition is present not only in adults but also in adolescents. Among the teen-aged population evaluated in a recent Australian study, 29% of the subjects reported drinking to the point of intoxication [10]. It is a matter of great concern that data from the United States suggest that children of an increasingly younger age are using alcohol and that up to 32% of adolescents have difficulties with alcohol intoxication/self-poisoning or dependence [11]. In the European School Survey Project on Alcohol and Other Drugs, 7% of all males between 15 and 16 years of age and 2% of all females interviewed reported ten or more episodes of drunkenness in the previous year. Moreover, the percentage of subjects reporting three or more episodes of alcohol intoxication in the previous month increased from 3% in 1999 to 7% in 2003 [12].

The aim of the present paper is to focus attention on the main clinical aspects of acute alcohol intoxication and its pharmacological management, taking into account that this disorder is common, potentially life-threatening, and linked to other harmful conditions, such as trauma and chronic alcohol use disorders.

2. Acute alcohol intoxication

2.1. Clinical features

Acute alcohol intoxication is a clinically harmful condition that usually follows the ingestion of a large amount of alcohol. In the pediatric population, it may be the result of the ingestion of household products that contain alcohol, such as colognes, mouthwash, after shave, hair tonics, medication, and solvents.

The Diagnostic and Statistical Manual of Mental Disorders IV edition criteria [6] for acute alcohol intoxication include: (a) recent alcohol ingestion; (b) clinically significant maladaptive behavioral or psychological changes developing during or shortly after alcohol ingestion and including inappropriate sexual or aggressive behavior, unstable mood, impaired judgment, and impaired social or occupational functioning; and (c) one or more of the following signs that develop during or shortly after alcohol use: (i) slurred speech; (ii) lack of coordination; (iii) unsteady gait; (iv) nystagmus; (v) impairment of attention or memory; (vi) stupor or coma; and (vii) symptoms that are not due to a general medical condition and that cannot be accounted for by another mental disorder.

Several factors can influence the extent of acute alcohol intoxication; besides the amount of alcohol ingested, individual body weight and tolerance to alcohol, the percentage of alcohol in the beverage, and the period of alcohol ingestion seem to be particularly important [13].

Symptoms are usually related to blood alcohol concentration (BAC; Table 1). At a BAC higher than 300 mg/dl (65.1 mmol/l), there is an increased risk of respiratory depression and arrest. Death attributable to acute alcohol intoxication generally occurs at a BAC higher than 500 mg/dl (108.5 mmol/l), although the lethal dose of alcohol can be variable [14]. Specifically, death has been observed at lower BACs in “non-tolerant” subjects (300 mg/dl; 65.1 mmol/l) [14] and recovery has been reported at higher levels (> 1200 mg/dl; 260.4 mmol/l) [15,16]. However, in alcohol-dependent patients who develop tolerance to alcohol as a result of repeated exposure to ethanol, these effects may become reduced [17]. This phenomenon seems to be related to compensatory changes in excitatory *N*-methyl-D-aspartate (NMDA) and inhibitory gamma-aminobutyric acid (GABA) [17].

The clinical findings usually present in alcohol-intoxicated subjects are due to the effect of acute ingestion of alcohol on different organs and apparatuses. Acute alcohol intoxication is able to cause several metabolic alterations, including hypoglycemia, lactic acidosis, hypokalemia, hypomagnesemia, hypoalbuminemia, hypocalcemia, and hypophosphatemia [1]. Acute alcohol intoxication-related cardiovascular effects include tachycardia, peripheral vasodilation, and volume depletion; these features can contribute to the induction of hypothermia and hypotension [1]. Another possible cardiovascular effect is “holiday heart syndrome”, characterized by atrial or ventricular tachyarrhythmias and new-onset atrial fibrillation after acute alcohol ingestion

Table 1
Main clinical symptoms in acute alcohol intoxication according to blood alcohol concentration (BAC)

Symptoms	BAC
Impairment in some tasks requiring skill	BAC < 50 mg/dl (10.9 mmol/l)
Increase in talkativeness	
Relaxation	
Altered perception of the environment	BAC > 100 mg/dl (21.7 mmol/l)
Ataxia	
Hyper-reflexia	
Impaired judgment	BAC > 200 mg/dl (43.4 mmol/l)
Lack of coordination	
Mood, personality, and behavioral changes, nystagmus	
Prolonged reaction time	
Slurred speech	
Amnesia	
Diplopia	
Dysarthria	BAC > 400 mg/dl (86.8 mmol/l)
Hypothermia	
Nausea	
Vomiting	
Respiratory depression	
Coma	BAC > 400 mg/dl (86.8 mmol/l)
Death	

[18,19]. The main life-threatening respiratory consequence of acute alcohol intoxication is respiratory depression. Other respiratory effects include decreased airway sensitivity to foreign bodies, decreased ciliary clearance and aspiration, and increased risk of bacterial infection with consequent bronchitis and pneumonia [20]. Gastrointestinal effects include nausea, vomiting, diarrhea, abdominal pain secondary to gastritis, peptic ulcer, and pancreatitis [21,22]. Prolonged vomiting can lead to hyponatremia [23]. Acute alcohol intoxication can cause a dysfunction of esophageal, gastric, and duodenal motility [24] and an increase in duodenal type III (propulsive) waves in the ileum [25]; this increased transit of intestinal contents may contribute to diarrhea [22]. Acute alcohol intoxication can induce acute alcoholic hepatitis [26], usually in subjects with chronic alcohol abuse and/or in patients affected by alcoholic cirrhosis. Most often the diagnosis is suggested by a history of excessive alcohol abuse in patients with features of hepatic decompensation [26–30].

Symptoms usually include nausea, vomiting, and abdominal pain. Less frequently, fever, shivering, and jaundice can occur. Zieve syndrome has also occasionally been reported; this consists of hemolytic anemia, jaundice, and hypertriglyceridemia [31,32]. Finally, acute alcohol intoxication can be found in patients affected by such psychiatric disorders as affective disorders and antisocial personality [33]; suicide or suicidal gestures are also highly associated with alcohol intoxication [1].

An increased risk of injury has been found in individuals with alcohol intoxication [34]. An Australian study showed that conditions deriving from acute alcohol intoxication, such as trauma and violence, were responsible for 46% of potential life years lost, twice that from chronic alcohol-related conditions [35]. Although all groups of drinkers are at risk of alcohol-related injury, those who usually drink little, but on occasion drink heavily, are at the highest risk, probably because of a low alcohol tolerance [36]. Moreover, alcohol can worsen the clinical course of the injury, increasing the frequency of intubation, the duration of hospitalization, and the risk of mortality [34,37]. A correlation has been reported between the severity of injury and alcohol misuse in adults [38,39], while in children this correlation is controversial [40,41].

Finally, recent findings support a strong connection between binge drinking and violent crimes such as homicide (28–86%), assault (24–37%), robbery (7–72%), and sexual offenses (13–60%) [42].

2.2. *Diagnosis*

Although it is often difficult, history-taking is needed in order to collect important information, including the quantity of alcohol and the type of beverage consumed, the time course of the symptoms, the circumstances, and eventual injuries. Physical examination must include an analysis of vital signs as well as nutritional status [43–45], hydration, and alcoholism-related signs (capillary prominence, spider

naevi, telangiectasias, palmar erythema, and muscular atrophy) [32]. Moreover, it should include cardiac and chest examination, abdominal examination, and neurological examination. Physical examination must be repeated often in order to follow up acute alcohol intoxication-related alterations. With regard to laboratory analysis, the determination of BAC is most important [46]. However, this examination has some limitations since it does not necessarily correlate with clinical presentation and does not predict clinical severity or outcome [1]. Alcohol levels can also be determined by breath analysis [47] or with a saliva dipstick, although these methods are less reliable [48]. In addition, levels of free ethanol and ethanol conjugates can be measured in urine [49]. The determination of serum osmolality usually shows a hyperosmolality with an “osmolal gap” [1]. Specifically, serum osmolality rises about 22 mOsm/l for every 100 mg/100 ml increment in BAC [1]. Serum osmolality can be important, particularly when a BAC is not available. Taking into account the more frequent clinical alterations, it is also important to determine levels of sodium, potassium, chloride, bicarbonate, urea nitrogen, glucose, calcium, magnesium, amylase, liver parameters, toxicological screen, arterial blood gas, and blood or urine ketones. Chest radiography and electrocardiography must be performed. Moreover, computed tomography (CT) of the brain should be included when neurological symptoms are present and/or a head trauma is suspected [13].

Multiple factors can confuse the diagnostic picture and affect the choice of therapy. Therefore, patients should be evaluated by expert clinicians, bearing in mind that a diagnosis of intoxication may lead some clinicians not to search for additional severe diseases. For this reason, after breath alcohol measures or BAC determination, additional investigations should be considered, depending on the clinical features of the patient, to evaluate potentially harmful alcohol-related and non-alcohol-related diseases. Special attention should be paid to mental status changes of the patient. Alcohol-induced psychopathologic conditions in patients with alcohol intoxication can range from lethargic depression to violent delirium. For patients with a history of previous intoxication episodes, mental status changes tend to be similar with each bout of binge drinking. Mental status changes that are markedly uncharacteristic of a patient’s previous intoxication pattern are often a warning sign that more aggressive assessment is needed for head injuries, cerebral hemorrhage, electrolyte abnormalities, and consumption of illicit drugs together with alcoholic beverages [13]. Moreover, the temptation to minimize issues in pleasantly intoxicated patients or to rapidly discharge unruly ones must be avoided [13].

Several different conditions can mimic the clinical features of acute alcohol intoxication and should, therefore, be excluded (Table 2). These conditions include: other substance-related intoxication, metabolic alterations, neurological causes (including seizure and trauma), infectious diseases, hypotension, hypo- or hyperthermia, hypo- or hyperthyroidism, dehydration, hypoxia, and respiratory depression [1,13].

Table 2
Main clinical conditions that can mimic an acute alcohol intoxication and that should be considered as possible differential diagnosis

Main clinical conditions	Detailed clinical conditions
Other substance-related intoxication	Alcohol other than ethanol Methanol Isopropyl alcohol Drugs of abuse: Cocaine Opiates Tetrahydrocannabinol Barbiturates Benzodiazepine Tricyclic antidepressants Disulfiram Carbon monoxide
Metabolic causes	Hepatic encephalopathy Hypoglycemia Electrolyte abnormalities: Hyper-/hypo natremia Hyper-/hypo calcemia Alcoholic ketoacidosis Diabetic ketoacidosis Non-ketotic hyperosmolar coma Uremia Hypertensive encephalopathy
Infectious disease	Sepsis Meningitis Encephalitis
Neurological causes	Alcohol withdrawal syndrome Wernicke–Korsakoff syndrome Cerebrovascular accidents Seizure disorders
Trauma	Intracranial bleeding Subdural hematoma Concussion syndromes
Respiratory causes	Hypoxia Respiratory depression
Other	Hypotension Hyper-/hypothermia Hyper-/hypothyroidism Dehydration

2.3. Treatment

The management of an intoxicated patient occurs mainly in the emergency department and is aimed at stabilizing the clinical condition of the patient, depending on his/her clinical presentation (Table 3). Airway assessment and observation of the development of respiratory function should be done. Prevention of aspiration is also mandatory; therefore, placement of the patient in a lateral position may be helpful. Intravenous access should be obtained and an intravenous fluid solution should be administered in order to hydrate the patient as well as to correct electrolyte imbalances and hypoglycemia. In current clinical practice, a protocol intravenous solution containing dextrose, magnesium, folate, thiamine, and multivitamins is used (e.g., a premixed intravenous solution of 1 l of 5% dextrose and 0.45% sodium chloride, 2 g of magnesium sulfate, 1 mg of folate, and 100 mg of thiamine) [1]. Anti-emetic drugs may be useful in patients with nausea and/or vomiting. Prolonged vomiting can lead to

hyponatremia; this should not be corrected too rapidly since it can induce a central pontine myelinolysis [23].

In agitated and violent patients, sedative substances may be used, including droperidol or haloperidol; however, one must bear in mind the possibility of a pharmacological interaction between the sedative drugs and the alcohol that could lead to respiratory depression and hypotension. The use of physical restraints to prevent patients from escaping and/or physical trauma should be avoided, given the ethical concerns about their use; they should be considered only in extreme conditions. In some cases, mechanical ventilation and intensive care must be provided [13].

One specific drug that is useful in the treatment of acute alcohol intoxication is metadoxine (pyridoxol L-2-pyrrolidone-5-carboxilate), which is the ion pair between pyrrolidone carboxilate and pyridoxine. Pyrrolidone carboxylate is involved in amino acid metabolism through the glutathione pathway [50]. It facilitates de novo ATP synthesis [51] and prevents ATP decrease in both the brain and liver of rats acutely intoxicated with ethanol [52]. Pyridoxine increases the metabolic degradation rate of ethanol, thereby reducing the damage to cell functions caused by acetaldehyde, the first metabolite in the ethanol elimination process [53]. Metadoxine appears to be able to accelerate ethanol metabolism in both rats and humans [54] due to several mechanisms including an increase in acetaldehyde dehydrogenase activity [55], ethanol and acetaldehyde plasma clearance, and urinary elimination of ketones [56]. In animals, metadoxine inhibits the increase in fatty acid esters in the liver of ethanol-treated rats, restoring the ratio between saturated and unsaturated fatty substances [57]. Moreover, metadoxine is able to prevent glutathione depletion, lipid peroxidation damage, collagen deposition, and TNF alpha secretions induced by alcohol and acetaldehyde in hepatocytes and hepatic stellate cells [58].

Recently, the first double-blind, controlled clinical trial with metadoxine compared to placebo was performed by our group in patients with acute alcohol intoxication [59]. A single intravenous injection of metadoxine (900 mg i.v.) significantly decreased the half-life of ethanol in the blood and showed a

Table 3
Management of acute alcohol intoxication

Patient stabilization	Airway assessment Observation of respiratory function Prevention of aspiration Mechanical ventilation, if necessary Intravenous access Intravenous solution administration correction of hypoglycemia and electrolyte imbalances (dextrose + magnesium + folate + thiamine + multivitamins) Anti-emetic drugs
Patient sedation (if necessary)	Droperidol Haloperidol Physical restraints (not advised)
Acceleration of ethanol elimination	Metadoxine (300–900 mg i.v.)

faster rate of ethanol elimination. The accelerated elimination of ethanol from the blood led to a faster onset of recovery from intoxication (defined as a decrease of at least one category of intoxication according to alcohol levels) in metadoxine-treated patients with respect to the placebo (control) group. The median time to onset of recovery was 2.34 h with placebo and 0.95 h with a single dose of metadoxine (900 mg i.v.). Accordingly, parameters of toxic behavioral symptomatology, such as agitation and mental function impairment scores, decreased significantly faster in metadoxine-treated patients than in controls. Moreover, the proportion of completely symptom-free patients was significantly higher in the metadoxine-treated group than in the control group.

In line with this observation, previous animal data showed the antagonization of locomotor-stimulatory effect of ethanol by metadoxine [60]. Another double-blind, controlled clinical trial compared metadoxine to a conventional treatment (parenteral solutions, multi-vitamin preparations, BDZ, or neuroleptics, as appropriate) for acute alcohol intoxication in an emergency unit [61]. The patients received a single dose of metadoxine (300 mg i.v.); a second equal dose was administered after 1 h (only if necessary) and patients were re-examined at 2 h. Significantly greater improvement was found on a clinical scale based on somatic and psychological symptoms, as well as significantly lower BACs, in the metadoxine-treated patients compared to the control group [61]. We conclude that metadoxine is a useful drug in clinical practice since it is effective in reducing BAC within a short time and in accelerating clinical and metabolic recovery from intoxication. Moreover, it appears to be manageable and safe [54,59,62–64]. Finally, it should be stressed that metadoxine is able to improve steatosis and liver function tests [63], an effect that is due to metadoxine's ability to maintain intracellular redox homeostasis [65].

3. Acute alcohol intoxication or chronic alcohol abuse?

All patients admitted to an emergency department for acute alcohol intoxication should be examined for chronic alcohol abuse and/or dependence [6]. At an initial screening, both the daily consumption and the weekly frequency of drinking should be recorded, and one or more tests, such as the AUDIT or AUDIT-C [66,67] and/or the CAGE [68], should be administered. A positive result on either of these tests indicates the probable presence of an alcohol-related disorder and calls for further evaluation using the DSM-IV criteria for alcohol abuse or alcohol dependence [6]. Patients who abuse or who are dependent on alcohol may experience an alcohol withdrawal syndrome following detoxification. Such a syndrome, in its severe form, may be life-threatening and present with delirium tremens and seizures [69]. If these conditions appear, correct drug treatment is mandatory [70–72]. Therefore, once a patient has become stabilized and both the acute alcohol intoxication symptoms and the related clinical complications have been treated, the patient should be monitored for 72 h following a BAC of 0 mg/dl (0 mmol/l).

Alcohol administration, a practice that is still frequently adopted by some emergency departments, should be avoided [73,74] since medical and surgical treatments for alcoholic diseases and their complications have limited success when drinking continues [75]. Moreover, ethanol can reinforce the craving for alcohol, limiting the possibility of relapse prevention [76]. Finally, when a diagnosis of alcohol abuse or dependence can be established, the patient should be referred to an alcohol treatment unit so that he or she can start a multimodal treatment including a psychological and/or pharmacological approach [76,77].

If the AUDIT and/or CAGE are negative, the risk of an emerging alcohol-related disorder could be considered low. In this case, a brief intervention or a one-on-one counseling session can be provided [78,79] in order to moderate alcohol consumption and to eliminate harmful drinking practices [79]. Brief intervention usually includes personalized feedback and counseling based on the patient's risk of harmful drinking and may also include motivational interviewing [80,81]. Such interventions can be useful in reducing the costs of, and burden on, health services [82].

4. Conclusions

Acute alcohol intoxication is a clinically harmful condition that usually follows the ingestion of a large amount of alcohol. It can manifest itself clinically in various ways and have behavioral, cardiac, gastrointestinal, pulmonary, neurological, and metabolic effects. The management of acute alcohol intoxication is aimed primarily at stabilizing the patient's clinical condition, hastening the elimination of alcohol, and defining and treating all of the abovementioned clinical alterations. Metadoxine is an effective and useful drug [54]. For patients with an acute alcohol intoxication, alcohol-related disorders should be detected and the patient referred to an alcohol treatment unit for a specific, personalized treatment.

5. Learning points

- Acute alcohol intoxication is a clinically harmful condition that usually follows the ingestion of a large amount of alcohol.
- Clinical manifestations involve different organs and apparatuses. Behavioral, cardiac, gastrointestinal, pulmonary, neurological, and metabolic manifestations can occur.
- The management of an intoxicated patient occurs mainly in the emergency department and is aimed at stabilizing the clinical condition of the patient, depending on his/her clinical presentation.
- Metadoxine is an effective pharmacological treatment for patients affected by acute alcohol intoxication.

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