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Coma induced by intoxication

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Abstract

Clinicians in the emergency department are often confronted with coma patients due to poisoning. A systematic general approach involving early consultation with a neurologist is of paramount importance. A high index of suspicion, a systematic first assessment already in the prehospital phase and early stabilisation of vital functions are the essential first steps. Specific antidotes like hypertonic glucose and thiamine are part of a "coma cocktail". The opiate antagonist naloxone should be used only when clinically indicated and in a titrated way. Flumazenil should only be used with caution and in restricted cases. Clinical neurological evaluation and technical investigations like CT-scan and laboratory tests should make part of a careful diagnostic plan. Toxicological tests deserve their place in the diagnostic work up of a coma patient with suspected poisoning. Knowledge of the possibilities of the toxicology lab and optimal communication with the clinical toxicologist is important for optimal patient care.

Key words : Coma ; poisoning ; approach ; antidotes ; laboratory tests.

Introduction

Clinicians working in the emergency department are often confronted with comatose patients, who represent a vital emergency. Of all patients with coma of unknown origin 30% will be due to intoxication (Gallagher and Lewin, 1998). The prognosis of the patient is determined by early diagnosis and appropriate therapeutic intervention. In this context early consultation with the neurologist is crucial. The aim of the present paper is to discuss a comprehensive approach of the comatose patient with suspected poisoning.

General approach

First assessment and stabilisation of vital functions

When confronted with a coma patient, the very first question that should arise is whether the coma is really due to intoxication. Indeed, the emergency physician and neurologist should keep in mind that causes of altered mentation may be of toxicologic nature, but also metabolic, infectious, neurological with structural changes, or psychiatric. Moreover, the causes may be combined with for instance toxicologic combined with neurologic changes due to a fall.

Only through the systematic application of basic neurologic principles and a comprehensive approach to the patient can the correct diagnosis be obtained and a safe therapy plan be elaborated.

The approach of the patient with decreased consciousness and suspected poisoning should already start in the prehospital phase. A quick assessment of the scene may already reveal important hints. For instance, a needle with a syringe may point to a heroin overdose, empty bottles of liquor or blisters of medication can provide a clue, and the presence in the room of a coal fire may point to poisoning with carbon monoxide. In the latter case, safety measures to protect emergency personnel is needed. On the other hand, the circumstances at the scene may also suggest trauma with the possibility of head trauma.

A brief history of relatives may reveal that the patient has diabetes or depression and that hypoglycemia or an antidepressant drug overdose should certainly be considered. Bystanders may also have witnessed a traumatic event, e.g., a fall, and provide important information.

These first steps should only take a few minutes. The further approach should be straightforward to the initial management with according to the needs (A) maintenance of a free airway, (B) support of breathing with artificial ventilation and (C) support of circulation with e.g., intravenous fluids and vasopressors to maintain blood pressure and adequate cerebral perfusion. Cardiac monitoring by ambulance or mobile intensive care unit personnel is essential. Oxygenation of the patient should be considered in any comatose patient who is hypoxic.

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Hypoxemia can nowadays easily be detected with pulse oximetry also outside the hospital. However, one should realize that pulse oxymeters are totally unreliable in carbon monoxide poisoning since the apparatus cannot distinguish between oxyhemoglobin and carboxyhemoglobin and therefore mislead the clinician. The importance of these general supportive measures cannot be overemphasized. Coma induced by poisoning is in most cases indeed usually well tolerated provided secondary damage due to hypoxia, hypoperfusion, and sepsis can be avoided.

In every comatose patient with a history or findings suggestive of head trauma a cervical splint with a rigid collar should be applied until an X-ray can exclude cervical trauma.

Urgent specific antidotes

During the initial management, some antidotes should be considered. Dextrose, thiamine, and the opiate antagonist naloxone have been labeled as a coma cocktail and routinely advocated in coma patients. More recently, the benzodiazepine receptor antagonist flumazenil has also been considered as an urgent antidote. The value of these antidotes used as a "coma cocktail" deserves some comments (Hoffman and Goldfrank, 1995).

Glucose and glucagon

Any patient with an altered mental status should be suspected of hypoglycemia. Clinical diagnosis of hypoglycemia is not simple. Symptoms may range from agitation to deep coma with diaphoresis and tachycardia. However, other neurological symptoms like decerebrate and decorticate posturing may occur and even focal signs, for instance hemiplegia. Therefore, dextrose 0.5-1 g/kg (or hypertonic glucose 30 or 50%) should be given to every patient with hypoglycemia. Confirming the diagnosis with measurement of glycemia can easily be done and should become routine. Rapid bedside tests are available but it should be remembered that the accuracy of the apparatus may not always be optimal at lower glucose levels. Furthermore, diabetic patients may experience glycopenic symptoms at lower but still normal glucose levels and should receive treatment. Glucagon should only be used when an i.v. access is not available.

Thiamine

Thiamine 100 mg can safely be given in any patient with an altered mental state. It will only rarely immediately improve the mental state but routine reminds us of potential nutritional deficiencies in our patients, especially chronic alcoholics at risk of Wernicke encephalopathy. It should be remembered that glucose administration in these patients may indeed precipitate Wernicke encephalopathy. Therefore, glucose and thiamine should be given as a cocktail for comatose patients.

Naloxone

Naloxone is an antagonist with a high affinity for μ, κ, and δ opioid receptors. It therefore antagonizes the opiate effects like sedation, the life threatening respiratory depression which makes it of great value in cases of intoxication. It should be noted that it is less effective in poisoning with d-propoxyphen (Depronal®), pentazocine (Fortal®) and buprenorfine (Temgesic®). It is a pure antagonist, which means that it does not produce opiate effects by itself, and it is specific for opiate poisoning, although case reports suggest that it may antagonize central nervous system depression by valproate, ethanol, captopril, and clonidine.

It is a competitive antagonist, which implies that the dose needed to reverse the opiate effects will depend upon the amount of the opiate present in the poisoned patient, which is of course rarely known in acute poisoning.

Initially and especially in the United States, naloxone was propagated in the "coma cocktail" for diagnostic and therapeutic use in any patient with decreased consciousness. However, this indiscriminate use is questioned now because of the very poor yield of beneficial effects (only in about 3% of the population) and since studies indicate that clinical diagnosis of opiate poisoning based on respiratory rate and pupil size is quite reliable. Therefore, naloxone is indicated now in coma and/or respiratory depression (rate < 12/min) in patients showing signs of opiate poisoning. The side effects like pulmonary edema are relatively rare.

However, potentially severe withdrawal problems may occur in opiate addicts. Therefore, when naloxone is used in potentially dependent patients the use of small doses of 0.1 to 0.2 mg i.v. is recommended. This can be given by taking an ampulla containing 0.4 mg naloxone and diluting it in 10 ml saline solution, which permits administration of such low doses. After this low starting dose, subsequent doses can be given based on the clinical response like reversal of respiratory depression and decreased consciousness.

Recurrent toxicity is common after an initial good response because the half life of naloxone is short (20-30 minutes), which demonstrates the need for a continuous infusion or a repeat bolus administration, e.g. after 15 minutes. Naloxone can also be administered by the intravenous, intramuscular, intralingual, and intratracheal route.

Flumazenil

A third antagonist that can be considered in coma patients with an overdose is flumazenil

(Howland, 1998). Flumazenil is a competitive antagonist of the benzodiazepine receptor in the central nervous system, which facilitates gabaminergic transmission giving rise to the classical effects of benzodiazepines like sedation, anxiolytic, anticonvulsive and hypnotic properties. Flumazenil will reverse effects like sedation but also the anticonvulsant properties of the benzodiazepines. While the use of flumazenil is well established to counteract the effects of benzodiazepines used in diagnostic procedures like endoscopy where benzodiazepines are used for sedation, its use in patients with acute poisoning is still the subject of debate.

Opponents of the use of flumazenil in patients with suspected benzodiazepine poisoning stress that benzodiazepines rarely cause morbidity and mortality. The latter is often due not to respiratory depression (which is not always reversed with flumazenil) but to aspiration pneumonia which already occurred prior to admission to the hospital. They emphasize the importance of the risk of seizures which can be due to coingested drugs, e.g., tricyclic antidepressants, or to the acute withdrawal provoked in patients chronically taking benzodiazepines.

Proponents of the use of flumazenil stress the benefit of avoiding procedures carrying their own risks in the diagnostic work-up of a coma patient, e.g., gastric lavage.

Furthermore, they mention the benefits of avoiding the risks of endotracheal intubation and ventilation.

Many authors now agree that the indications for flumazenil in the overdose setting are pure benzodiazepine poisoning in individuals who are not tolerant to benzodiazepines, who have central nervous system depression, normal vital signs, normal ECG and otherwise normal neurologic examination. Of course, such cases are rare in adults with benzodiazepine poisoning.

Flumazenil should be given slowly and by titration (0.1 mg/min) without exceeding a total dose of 1 mg. Relapse of the sedation may occur after 20 or more minutes due to the rather short half life of flumazenil.

Flumazenil is better avoided or even contraindicated in the overdose setting in patients with a prior history of seizures or current treatment of seizures.

History of intake or ingestion of substances capable of provoking seizures (e.g., tricyclic antidepressants, theofylline) or provoking cardiac arrhythmias is also a contraindication. Patients having ingested carbamazepine, chloroquine and/or chlorinated hydrocarbons should not be treated with flumazenil. Long term use of benzodiazepines is also a contraindication. Electrocardiographic evidence of tricyclic antidepressants (i.e., terminal right-ward 40 msec axis, QRS or QT prolongation) or a history and clinical signs of tricyclic antidepressant poisoning also represent a contraindication for flumazenil.

Finally, flumazenil should never be used in patients with abnormal vital signs.

Diagnostic work-up

General aspects

In the further diagnostic work-up comes the question whether the patient may have a history or signs of associated head trauma. These signs e.g. bruises should be looked for very carefully and a Glasgow Coma Score should be obtained. Consultation with the neurologist and a low threshold for ordering a CT-scan of the head is necessary. The next step is a careful neurological assessment to distinguish between a toxic-metabolic cause for coma and structural neurologic causes, for instance cerebrovascular accidents, epi- or subdural hematomas. It is of paramount importance to examine pupillary reactivity, motor responses to noxious stimuli and ocular movements. When this examination yields symmetrical findings, intact pupillary reflexes and dissociated findings (e.g., intact and symmetrical pupillary light reflexes and absent motor responses to noxious stimuli) the patient should receive a further diagnostic work-up for toxic- metabolic causes. It should be remembered, however, that there are exceptions to this rule of pupillary light reflex. Indeed, pupillary light reflexes can be fixed to light in poisoning with anticholinergics (large pupils), hypothermia and anoxia (e.g., due to carbon monoxide poisoning) and opiate poisoning (small pupils). In the other cases, further neurologic examination is essential to detect neurological structural disease. The diagnostic work-up for metabolic and infectious causes consists of blood chemistry, ECG, lumbar puncture and CT-scan. It should be kept in mind that a subarachnoidal hemorrhage that — although it is a structural-neurologic entity — can behave much like a toxic-metabolic etiology. There are still other exceptions to the generalizations made in this approach since other structural-neurologic abnormalities do not always show focality (e.g., lesions with brainstem compression) and a toxic event like hypoglycemia may produce a clinical picture of hemiplegia. Therefore, a high degree of suspicion and careful consultation with the neurologist is of utmost importance.

Toxicological testing

The clinical usefulness of toxicological testing has been questioned because retrospective studies indicate that they only rarely influence or change the therapy which consists of decontamination, supportive measures and in some cases the use of specific antidotes. It is obvious that therapy of a patient with suspected poisoning should never be

postponed when clinically indicated until the toxicological results are known. In practice, however, many clinicians, emergency physicians as well as neurologists, feel that toxicological testing is useful. When doubt remains in a coma patient about the cause, toxicological data are of great help also when they are negative. This aspect was rarely studied.

Furthermore, identifying the toxic substance will definitely influence therapy and prevent morbidity and mortality in a few patients, which can be very important for an individual patient. For instance, knowing that the coma is due to lithium poisoning will point to the necessity of specific therapy like hemodialysis in some patients. Finally, for documentation and liability concerns, confirmation of a suspected poisoning with a toxicological analysis is preferred by most clinicians (Osterloh and Snyder, 1998).

A more important issue than whether to order tests or not is "how" to order the tests. Clinicians treating patients with coma and suspected poisoning should know the limitation of a "comprehensive tox-screen". The number of drugs detected in a screen vary from laboratory to laboratory and can be falsely negative or reassuring. Moreover, a comprehensive screen demands a lot of work in the lab and may not be cost-effective. In order to increase efficiency and reduce the cost of toxicologic analysis, it is very important that the clinician provides information on the suspected drugs and consults with the clinical toxicologist. The number of potentially involved drugs or toxins is large as illustrated in table 1 showing a non limitative list.

A complete discussion of all these drugs is out of the scope of this paper. However, some examples are given to illustrate the fact that the clinician can help the pathologist with data obtained by the history of the relatives and from observed clinical signs.

Table 1

Non limitative list of substances that may be involved in coma due to poisoning

○ Ethanol	○ β-receptor blocking agents
○ Benzodiazepines	○ Carbon monoxide
○ Barbiturates	○ Gases and fumes
○ Tricyclic antidepressants	○ Methanol
○ Sedatives, hypnotics (H_1-antihistamines)	○ Trichloroethylene
	○ Organophosphates
○ Neuroleptics	○ Illegal drugs (mixtures, ...)
○ Lithium	○ ...
○ Opioids	

A patient for instance who is known to be treated for a depression, presenting with coma and also seizures, wide pupils, tachycardia, urinary retention and cardiac arrhythmias is very suspect of suffering from a tricyclic antidepressant poisoning.

A patient known to have hypertension, brought in with bradycardia, hypotension, coma and cyanosis should be considered a candidate for a β-blocker poisoning requiring specific therapy with glucagon. Specific laboratory techniques will be requested to confirm the diagnosis of β-blocker poisoning which are not performed in routine. The clinician should be aware of this and know that therapy should start without waiting for the toxicological results.

A young patient in coma presenting with severe metabolic acidosis and papillary edema is very suspect of methanol poisoning and this requires specific analysis by the lab. A quantitative determination is essential to guide therapy in such a patient.

Conclusion

A coma patient with suspected poisoning is a challenge to the clinicians in the emergency department. The approach of these patients should start with initial stabilization and the judicious use of antidotes. Clinicians should be very alert not only for specific clinical signs of acute poisoning but also for other causes decreased consciousness. Early consultation with the neurologist is of utmost importance as is communication with the toxicology laboratory.

REFERENCES

GALLAGHER E. J., LEWIN N. A. Neurologic principles. In : *Goldfrank's Toxicologic Emergencies*. Connecticut, Appleton & Lange, 1998, pp. 309-336.

HOFFMAN R. S., GOLDFRANK L. R. The poisoned patient with altered consciousness. JAMA, 1995, **274** : 562-569.

HOWLAND M. A. Antidotes in depth - Flumazenil. In : *Goldfrank's Toxicologic Emergencies*. Connecticut, Appleton & Lange, 1998, pp. 1017-1022.

OSTERLOH J. D., SNYDER J. W. Laboratory principles and techniques to evaluate the poisoned or overdosed patient. In : *Goldfrank's Toxicologic Emergencies*. Connecticut, Appleton & Lange, 1998, pp. 63-75.

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