Therapeutics, Pharmacology and Clinical Toxicology
Vol XVI, Number 3, September 2012
Pages: 197-201

ORIGINAL PAPERS

SCORES APPLIED IN TOXICOLOGICAL PRACTICE. PROGNOSTIC ASSESMENT IN INTOXICATION BY BARBITURATES AND BENZODIAZEPINES

Opriţa B., Gabor-Postole Dana Atena, Aignatoaie B.

Emergency Clinical Hospital of Bucharest, Romania

Abstract. When determining whether to observe, admit, transfer, or discharge a person who has been poisoned, there are several factors to consider. For unstable patients, admission to an intensive care unit is appropriate, and transfer to a tertiary care facility should be considered, especially with children. For stable patients, the amount of observation time is based on the half-life of a medication, the amount ingested, and the formulation. Any patient who develops signs or symptoms of toxicity that do not reverse during the observation period should be admitted for further observation.[6] Triage is the initial assessment and sorting of patients in an emergency setting to determine clinical priority of need and, in some emergency departments (Eds), appropriate area for treatment. Overcrowding of EDs makes accurate triage category assignment a priority if patient safety and timeliness of care are to be assured.[29]. The purpose of this research consists in the formulation of a pre-therapeutic and prognostic score, correlating vital parameters of patients, toxicology and post-therapy scores, so we can decide whether to maintain the patient in the Emergency Department for treatment, to discharge him/her in safety conditions or to admit him/her in Toxicology Unit.
Keywords: intoxication, score, barbiturics, benzodiazepines, PSS.

Introduction

The term „toxicology“ is derived from the Greek words *toxikos* or *toxa* („bow“) and *toxicon* („the poison in which the arrows were dipped“). Today this term is used to define the science of poisons – their source, chemical composition, effects, tests and antidotes. Recognition of the potential toxic effects of various substances is probably as old as mankind, dating back 18,000 years to the prehistoric Masai hunters of Kenya who used poison arrows. The historic poisons were plant extracts, animal venoms and minerals. They were used for hunting, in wars, for executions and in religious rituals. Currently abused agents were also known in antiquity: cannabis in China (2200 B.C.), the hallucinogenic mushroom *Amanita muscaria* – „soma“ in India (2000 B.C.), opium in Egypt (1500 B.C.), and cocaine in South America (at least 300 B.C.). Only as late as the 19th century did the danger of opiate addiction become recognized, followed by cocaine, sedative hypnotics, hallucinogens and stimulants (the current drug epidemic).[2]

The development of toxicology as a distinct specialty began during the 18th and 19th centuries. [22] Over the last 25 years, the primary specialties of medical toxicologists have changed. The development of emergency medicine and preventive medicine as medical specialties led to the training of more physicians with a dedicated interest in toxicology. By the early 1990s, emergency physicians accounted for more than half the number of medical toxicologists.[5] The increased diversity of medical toxicologists with primary training in emergency medicine, pediatrics, preventive medicine, or internal medicine has helped to broaden the goals of poison control centers and medical toxicologists beyond the treatment of acute unintentional childhood ingestions. The broad scope of medical toxicology now includes a much wider array of toxic exposures including acute and chronic, adult and pediatric, unintentional and intentional, occupational and environmental.[8]

The barbiturates were introduced in 1903 and quickly supplanted the older xenobiotics. This class of drugs dominated the sedative-hypnotic market

Bogdan Opriţa
Emergency Clinical Hospital of Bucharest, Romania
8, Calea Floreasca, 1-st District, Bucharest
email: boprita@yahoo.com

for the first half of the 20th century. Unfortunately, because barbiturates have a relatively low therapeutic-to-toxic ratio and substantial potential for abuse, they quickly became a major health problem. By the 1950s and 1960s, barbiturates were frequently implicated in overdoses and were responsible for the majority of drug-related suicides. As fatalities from barbiturates increased, attention shifted to preventing their abuse and finding less toxic alternatives.[3] These drugs included methyprylon, glutethimide, ethchlorvynol, and methaqualone. Unfortunately, many of these drugs also had significant undesirable effects. With the introduction of benzodiazepines in the early 1960s, barbiturates and the alternative drugs were quickly supplanted.[8]

Barbiturates can produce a wide range of CNS depression, ranging from mild sedation to general anesthesia. They are categorized based on their ultra short-acting, short-acting, medium-acting, or long-acting duration of clinical effects . Barbiturates are classified as schedule II to IV drugs based on their rapid time of onset and duration and their abuse potential. They can inhibit excitatory or enhance inhibitory synaptic transmission. Barbiturates inhibit excitatory synaptic transmission by reducing glutamate-induced depolarizations[19]. Barbiturates enhance the effectiveness of GABA transmission by directly activating chloride channels and depressing synaptic transmission at virtually all synapses. Barbiturates effect the duration, not frequency, of GABA channel opening, thereby hyperpolarizing and decreasing the firing rate of neurons[14]. Onset of clinical symptoms varies (15–40 minutes) and the degree of symptoms is dose and drug dependent. Clinical effects may consist of CNS and respiratory depression, hypothermia, bullous skin lesions, aspiration pneumonia, nystagmus, dysarthria, ataxia, drowsiness hypothermia, renal failure, muscle necrosis, hypotension, hypoglycemia, coma, and death[25]. Coingestion with alcohol or other CNS depressants enhances toxic effects. Duration of effects depends on the dose and the specific drug itself[1]

Chlordiazepoxide, the first commercially available benzodiazepine, initially was synthesized by Hoffman-LaRoche in 1955 and marketed in 1960. Now more than 50 benzodiazepines are marketed, and more are being developed. In the 1980s, benzodiazepines captured >80% of the sedative market and >50% of the hypnotic market.[15,27] Compared with an overdose of barbiturates, an overdose of a benzodiazepine alone accounts for relatively few deaths.[7] Most deaths associated with benzodiazepines result from mixed overdoses of benzodiazepines and other respiratory depressants, especially alcohol[12,8].

Because of the popularity of benzodiazepines and the perception of widespread abuse, changes in local regulations and restrictions in prescribing practices for benzodiazepines led to a resurgence in the use of older sedative-hypnotic agents in specific areas. [8] Benzodiazepines are a large class of drugs that bind to specific receptor sites on g-aminobutyric acid (GABA)-mediated receptor synapses in the brain. Benzodiazepines are believed to increase GABA-mediated chloride conduction into the postsynaptic neuron, prolonging hyperpolarization of the cell and diminishing synaptic transmission, thereby producing its sedative properties.[1,24.]

Both barbiturates and benzodiazepines act on the GABA site, but barbiturates prolong the opening of the chloride ionophore, whereas benzodiazepines increase the frequency of ionophore opening[27,8].

Drugs within this class vary in their affinity and efficacy at their receptor. This variation results in differences in the degree of clinical effects, time of onset, and rate of metabolism. Ultimately, with a faster rate of onset there tends to be greater abuse potential [23]. Clinical effects may consist in dizziness, disorientation, lack of coordination, and slurred speech, which mimic alcohol intoxication. [11,1] Rapid alternation of hot and cold flashes may precipitously be followed by loss of consciousness. Large doses (O2 g) have produced aspiration, muscular hypotonia, hypotension, bradycardia, coma, and death[19, 26, 4. 16]

In the diagnosis of toxic ingestion , although the history is important, it may be unreliable or incomplete[29,20] Consider that family members, friends, and pharmacists may have additional information. In the absence of a classic presentation or toxidrome, separating patients with suspected poisoning into broad categories basedon vital signs, ocular findings, mental status, and muscle tone can help determine drug or toxin class.[21,20]

Depending on the intoxication, patients may present with hypotension or hypertension, bradyarrhythmias or tachyarrhythmias. The pathogenesis of hypotension varies and may include hypovolemia, myocardial depression, cardiac arrhythmias, and systemic vasodilation. Treatment should be individualized, but an initial strategy of rapid IV normal saline solution infusion is indicated in most instances.

Vasopressors may be required for refractory hypotension. The vasopressor of choice depends on the type of intoxication (see below). Hypertension occurs in the setting of sympathomimetic drugs, anticholinergics, ergot derivatives, phenylpropanolamine overdose, and withdrawal from nicotine, alcohol, and sedatives. Treatment of the hypertension depends on its chronicity and severity and the inciting agent (see below). Hypertension-induced (reflex) bradycardia generally should not be treated.[20]

Triage is the initial assessment and sorting of patients in an emergency setting to determine clinical priority of need and, in some emergency departments (EDs), appropriate area for treatment. Overcrowding of EDs makes accurate triage category assignment a priority if patient safety and timeliness of care are to be assured.[29] In the initial approach to a child or adult with an acute change in mental status, physicians should consider the possibility of inadvertent or intentional improper medication ingestion. Factors that would raise the level of suspicion include acute behavioral changes; concern about possible ingestion on behalf of a relative, friend, or health care professional; and evidence of ingestion, such as pills found in the patient's possession.[13,10]

The initial approach is to assess the airway, breathing, and circulation, and to take a thorough history. The purpose of airway management and breathing support in a person who has been poisoned is to correct hypoxia and acidemia while preventing aspiration. Pulse oximetry should be initiated in patients with respiratory distress or cyanosis; cardiac monitoring is indicated for patients with hemodynamic instability.[9,10]

Once the patient has been stabilized, information should be sought from the patient, friends or family members, and emergency medical services personnel when appropriate.

The most important question to answer immediately is when the ingestion occurred. Identifying the ingested medication, including the precise formulation and known or estimated amount, is also important.[6] Medication packaging can be inspected when available. [10]

When determining whether to observe, admit, transfer, or discharge a person who has been poisoned, there are several factors to consider. For unstable patients, admission to an intensive care unit is appropriate, and transfer to a tertiary care facility should be considered, especially with children. For stable patients, the amount of observation time is based on the half-life of a medication, the amount ingested, and the formulation. Any patient who develops signs or symptoms of toxicity that do not reverse during the observation period should be admitted for further observation.[6] When a patient is ready for discharge, his or her home situation must be taken into account, especially if the patient is a child.[13] Patients who have attempted suicide will need a psychiatric evaluation and will likely be admitted to a psychiatric unit. Patients with substance abuse issues should be referred for counseling.[10]

Material and methods

Prior to our study, to the SCUB (Emergency Clinical Hospital of Bucharest) came 280 patients in 2007 and 340 patients in 2008 with benzodiazebine poisoning, barbiturates or mixed poisoning. In Romania, barbiturates are still frequently used in some therapeutic schemes, both independently and as components of different pharmaceutical products, so they still constitute a significant base of study. We performed a joint analysis in the UPU-SMURD Department of the Emergency Clinical Hospital of Bucharest between 17 February 2009 and 16 July 2009 using the following historical data: sex, age, class, INN, trade name and quantity of the substance ingested, time from ingestion to presentation in the emergency department, assessing whether a single active substance was ingested, various drugs were ingested and / or such was associated with ethanol consumption, whether foods were consumed before, while or after drug ingestion, whether the patient had vomiting after drug intake, whether he/she received or not supportive treatment until admission in the emergency department.

After admission in the emergency room we observed the consciousness by assessing the Glasgow Coma Scale, the hemodynamic and respiratory parameters (BP, HR, RR, SpO2, CRT) at presentation, 1 hour later and 2 hours later. On basis thereof we calculated the REED and CRAMS scores.We conducted qualitative toxicology testing upon patient presentation in the emergency room and upon his/her discharge from hospital.

We monitored the treatment and the patient's evolution during the stay in the emergency room, as well as of those hospitalized in the intensive care unit - Toxicology. Thus was established the correlation of these parameters with Poisoning Severity Score (PSS) (calculated on admission and discharge) which currently has a prognostic value.

Purpose

The purpose of this research consists in the formulation of a pre-therapeutic and prognostic score, correlating vital parameters of patients, toxicology and post-therapy scores, so we can decide whether to maintain the patient in the Emergency Department for treatment, to discharge him/her in safety conditions or to admit him/her in Toxicology Unit. The Emergency Department is organized into several areas. With the help of the aforementioned score we will be able to decide whether the patient will be cared for in the resuscitation area, in the immediate treatment area or in the observation area, whether or not the patient requires monitoring of vital functions, or just of consciousness.

Results

Due to the fact that we were able to make a corroboration of the GCS score, PSS, REED scale,

hemodynamic and respiratory parameters, as well as BP, HR, RR, SpO2, CRT, we are entitled to believe that we can develop a score that will help us decide if the patient can be safely discharged after a short period of time, if he/she remains hospitalized in toxicology unit, or he/she shall receive specialist treatment in the ED, for a longer period of time, and only afterwards the patient will be discharged.

Discussion

We examined patients from 17 February 2009 until 16 July 2009 . From a total of 126, 89 were female and 37 were male, of which 114 patients (women + men) had 14-15 GCS score at presentation, 8 patients had 9-13 GCS score, 4 patients a GCS below 8. Of hospitalized patients - 67, 56 patients had GCS values between 14 and 15, 7 patients had GCS values between 9 and 13 and 4 patients had GCS values below 8. Regarding PSS at hospitalized patients 56 had values between 0 and 1 and 11 had values between 2 and 3. Regarding the patients who have not remained hospitalized, their number being 59, 58 had GCS score of 14 and 15 and 1 had GCS score of 13 and the PSS was 0 or 1 at 55 of them and 2 at 4 patients.

Conclusions

Given the insufficient clinical and anamnestic data obtained from the prehospital emergency crews, this data cannot allow elaboration of a pre-therapeutic and prognosis-implications score , even more as the therapeutic facilities available in prehospital are limited. Therefore, all patients with affirmative ingestion of barbiturates and benzodiazepines should be immediately transported to the closest hospital with an Emergency Department. During transportation, all the critical patient stabilization measures will be provided, as well as the ones for delaying absorption and stimulating of the elimination of toxic substances.

Once arrived in the Emergency Department, the corroboration of clinical and monitoring data allows for the elaboration of a score, based on which the gravity of the case and evolution potential can be decided. This score could estimate whether the patient requires admission in the critical care unit or in the surveillance area even if the initial evaluation of the vital signs could have suggested that due to the initial stable status, the evolution potential or the evolution wouldn't be towards aggravation.

The corroboration of the clinical data, toxicological exam and the quantification of the PSS may allow to indite the evolution potential. This way it can be decided right from the presentation in the Emergency Department which category of patients will obviously require admission, observation for a certain time period or discharging from the Emergency Department.

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