hyperinsulinemic euglycemia protocol requiring insulin infusion while maintaining acceptable serum glucose levels by exogenous glucose administration is another therapeutic choice in severe CCB overdose. To date, evidence supporting this therapy is based on case reports and one case series that demonstrates improvement in BP and metabolic acidosis. The benefit afforded by insulin appears to be due to increased cardiac carbohydrate metabolism efficiency and direct inotropic effects of insulin. Insulin infusion rates of 0.5 to 1 U/kg/hour or higher have been reported, and close monitoring for prevention of hypoglycemia and hypokalemia is imperative. Severe CCB toxicity unresponsive to therapies mentioned above may require cardiac pacing and other advanced therapies such as intra-aortic balloon pump or extracorporeal membrane oxygenation.

β-Blocker toxicity is still most commonly treated by administering high-dose glucagon therapy. A glucagon bolus of 5 to 10 mg (150 micrograms/kg) over 1 to 2 min is frequently used in this setting. Clinical effect (increased heart rate or BP) is usually noted within a few minutes; however, as glucagon has a short duration of action, a continuous infusion of 2 to 10 mg/hours is usually necessary. Nausea and vomiting can be noted as a side effect of high-dose glucagon therapy.The hyperinsulinemic euglycemia protocol, as discussed above, may also have some benefit in β-blocker toxicity.

References

1. Philip MP, Janice LZ. Toxicology in Critical Care Unit. Chest 2008; 133:1006-1013
2. Spiller HA, Krenzelok EP, Grande GA, et al. A prospective evaluation of the effect of activated charcoal before oral N-acetylcysteine in acetaminophen overdose. Ann Emerg Med 1994; 23:519-523
3. Hoiseth G, Bramness JG, Christophersen AS, et al. Carisoprodol intoxications: a retrospective study of forensic autopsy material from 1992–2003. Int J Legal Med 2006
4. Isbister GK, O'Regan L, Sibbritt D, et al Alprazolam is relatively more toxic than other benzodiazepines in overdose. Br J Clin Pharmacol 2004; 58:88-95
5. Harris NS. Case records of the Massachusetts General Hospital: case 24–2006; a 40-year-old woman with hypotension after an overdose of amlodipine. N Engl J Med 2006; 355:602-611

"Drug and Therapeutics Letter" is also available in the following webite: http://www.teachinghospital.org.np/diu.html

Chief Editor :
Prof. Kumud Kumar Kafle
Editors:
Dr. Sanu Maiya Shakya, Dr. Sangha Ratna Bajracharya, Dr. Satish Deo, Dr. Sammodavardhana K., Dr. Naba Raj Simkhada, Dr. Pradip Gyawali.
Department of Clinical Pharmacology, Drug information Unit, Room Number: 1-85 Doctors' Room Block, TU Teaching Hospital, P.O.Box: 3578, Maharajgunj, Kathmandu

Phone No.: 4412404 Extn 1093, **E-mail:** diu@iom.edu.np

DRUG & THERAPEUTICS LETTER

A Quarterly Bulletin from
Drug Information Unit (DIU)
Department of Clinical Pharmacology
Tribhuvan University Teaching Hospital
Institute of Medicine, Maharajgunj, Kathmandu

Vol. 17 No. 4 October -December 2010

Toxicology of some common drug groups in the Critical Care Unit

Early Management Issues

Critical care management of the patient with a toxicologic condition requires rapid diagnosis and appropriate specific treatment while providing supportive care. Diagnosis requires a thorough history and physical examination combined with several laboratory tests.The clinical evaluation may reveal the presence of characteristic clinical syndromes, called toxidromes, that suggest particular offending agents. However, many overdose patients treated in the ICU have used more than one agent, and toxidromes may overlap. Laboratory tests that may be of value include calculation of the anion, osmolal, and oxygen saturation gap, ECG, and quantitative toxicology assays for specific drugs. If the specific agent is unclear or multiple drugs have been ingested, an paracetamol level should be obtained because of the lack of specific signs or symptoms and the potential benefit afforded by early, appropriate therapy. Quantitative testing for other drugs or toxins should be guided by clinical and laboratory findings. Qualitative toxicology assays performed on urine detect a limited number of drugs and have little impact on patient management.

Several interventions such as cathartics, ipecac, gastric lavage, whole-bowel irrigation, urine alkalinization (pH >7.5), single-dose activated charcoal (SDAC), multiple-dose activated charcoal, renal replacement therapy have been routinely performed in patients with suspected oral overdose to decrease GI absorption or enhance elimination with little evidence of effectiveness. Of these interventions, single-dose activated charcoal (SDAC) is the most utilized. The benefit of SDAC decreases when comparing administration at 60 to 120 min after ingestion in volunteer studies with a single-agent ingestion. There is a theoretical benefit to administering charcoal at later times if there is a suspicion of delayed GI absorption.

Analgesics

Analgesics are the most common drugs that result in toxicity necessitating hospitalization throughout the world. The utility of N-acetylcysteine (NAC) as an antidote in preventing paracetamol-induced hepatotoxicity has been demonstrated since 1977. The

Rumack-Matthew nomogram uses paracetamol levels to determine the need for NAC administration in single acute ingestions of immediate-release paracetamol. Unfortunately, many patients have a history of long-term use, repeated ingestions, or use of extended-release formulations that limit the utility of the nomogram. In patients who ingest extended-release paracetamol, assessment of a second paracetamol level 4 to 6 hours after the first level is recommended if the initial level was in the nontoxic range. Regardless of the time after ingestion, therapy with NAC provides significant benefit to those patients with paracetamol-induced hepatic enzyme elevation.

NAC can be administered orally or IV with equivalent effects. However, significant experience with compounding an IV formulation from the oral preparation has developed, and the compounded product appears to be safe. The use of compounded medications is governed by local pharmacy boards; thus, clinicians need to obtain input from pharmacists regarding the legality of using compounded NAC. Either form of NAC should be administered within the first 8 hours after ingestion to prevent hepatotoxicity. Oral administration of NAC may cause vomiting due to the odor, and higher doses of antiemetics may be necessary. IV administration of NAC is associated with anaphylactoid reactions that are usually easily managed.Another therapeutic consideration when treating a single acute ingestion is the shorter dosing schedule of IV NAC compared to the oral form (20 hours vs 72 hours).

Definitive treatment guidelines are not established for patients who present with chronic or repeated ingestions of paracetamol. Transaminase elevation (> 50 IU/L) and an paracetamol level > 10 mg/L on presentation have been suggested as indications for treating with NAC. Generally, treatment with NAC, whether oral or IV, is continued in these patients until serum paracetamol levels are undetectable and liver function has normalized or is normalizing. SDAC may reduce the need for NAC treatment if used within 2 hours of acute paracetamol ingestion. A recent review suggests that the concomitant use of activated charcoal and NAC therapy improves patient outcomes. The oral NAC dose does not need to be increased if administered after activated charcoal, nor does there need to be a time lag between the two therapies.

Paracetamol-induced hepatitis may progress to fulminant hepatic failure, and appropriate referral for liver transplantation may be necessary. The King s College criteria (KCC) for prognosis in paracetamol-induced hepatoxicity are often used, but other indicators include lactate and amylase levels. Patients who fit the KCC have a predictably high mortality, but the sensitivity is not ideal; thus, liver transplant may be of benefit to some patients who do not fit the KCC.

Ingestion of opioid analgesics is increasing, and misuse may result in significant respiratory, CNS, or hemodynamic depression. Critical care management of these complications is usually based on providing supportive care. The opioid antagonist naloxone is used to reverse significant respiratory depression associated with opioids. Typically, patients respond to IV doses

of 0.04 to 0.4 mg; however, synthetic opioids such as fentanyl or buprenorphine may require doses as high as ⩾10 mg.Counteracting the respiratory depressant effect of longer-acting opioids may require a continuous infusion of naloxone. In these cases, the naloxone infusion is initiated at an hourly rate of two thirds of the IV bolus dose needed to reverse the respiratory depression and titrated to effect. Tramadol, an opioid considered to be a safer alternative to conventional opioids, should be recognized as a drug with abuse potential. Rare but significant toxicity, including death, has been associated with this drug especially when combined with other CNS depressants. Seizures are a common manifestation of tramadol intoxication and usually occur within 24 hours of ingestion. The misuse of fentanyl as a street drug that is often combined with heroin is increasingly recognized. Urine toxicology assays will not detect fentanyl as an opiate.

Sedative-Hypnotics and Muscle Relaxants

Sedative-hypnotics and muscles relaxants are agents that may lead to the need for respiratory support in the ICU. Recently, alprazolam and carisoprodol have been noted to cause significant harm to patients in overdoses. Alprazolam was specifically associated with an increased ICU length of stay when compared to other benzodiazepines. Flumazenil as a diagnostic agent in benzodiazepine overdose should be used cautiously, especially in those patients with chronic benzodiazepine use, epilepsy, or coingestion with medications that may increase the risk for seizures such as tricyclic antidepressants. Flumazenil is not indicated as a substitute for airway protection because its half-life is shorter than half-life of benzodiazepines.

Cardiovascular Medications

Significant overdoses with cardiovascular medications often require critical care support.All antihypertensives may cause harm, but overdoses with calcium-channel blockers (CCBs) and β-blockers result in the most severe hemodynamic abnormalities. Delayed and continous absorption of long actiong formulations of β -blockers and CCBs can lead to prolonged clinical presentations. Whole-bowel irrigation may be considered in patients with delayed presentations. The dihidropyridine class of CCBs (eg, amlodipine and nimodipine) usually leads to significant hypotension without bradycardia, whereas the nondihidropyridine class of CCBs (eg, diltiazem and verapamil) leads most commonly to bradycardia and, in the most severe overdoses, cardiogenic shock and sinus arrest. Therapies for CCB overdose usually require volume resuscitation and vasopressors to maintain BP and heart rate. Vasopressors such as dopamine and norepinephrine are first-line agents, but hypotension unresponsive to these agents may respond to vasopressin. IV calcium salts are also often used in supraphysiologic doses, and care must be taken to avoid extravasation during IV administration. Ionized calcium levels should be monitored when using high doses of calcium. IV glucagon is not as widely accepted for CCB toxicity as it is for β- blocker toxicity, but a review of animal studies suggests a possible beneficial effect in both toxicities. A