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Egyptian Pharmaceutical Vigilance Center (EPVC)

Pharmacovigilance Department

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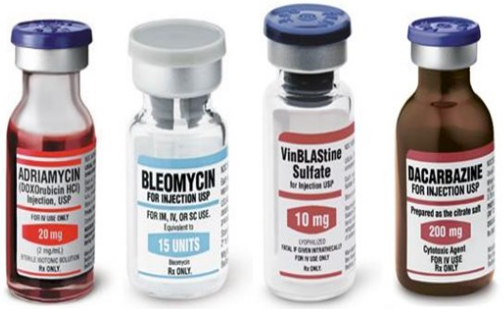
Case Report from Sohag- Cardiac Arrest and patient death After Administration of ABVD protocol



The Egyptian pharmaceutical Vigilance regional center in Sohag has received an ICSR about an adult Female patient, 45 years old , 55 Kg weight ,who Suffered from Hodgkin Lymphoma with bone marrow infiltration and cervical lymph node. At 10/07/2016 she was administered (Adriamycin 50 mg, Bloicin s 15 mg, Velbastine 10 mg and Dacarbazine 200 mg) as intravenous drip then after ending the chemotherapy set she suffered from cardiac arrest and died.

Upon search it was found that:

ABVD: is a chemotherapy regimen used in the first-line treatment of Hodgkin lymphoma, it consists of concurrent treatment with the chemotherapy drugs:

Adriamycin (also known as doxorubicin)

Routine use of doxorubicin as adjuvant therapy in any tumor category is not recommended the activity of doxorubicin in combination with other medicines is affected not only by the nature of the medicine itself, but also by the schedule of administration , Doxorubicin may potentiate the toxicity of other anticancer therapies.

Bleomycin

Vascular toxicities coincident with the use of Bleomycin in combination with other antineoplastic agents have been reposed rarely.

The events are clinically heterogeneous and may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (hemolytic uremic syndrome) or cerebrovascular arteritis.

Vinblastine

Cardiac effects such as myocardial infarction, angina pectoris and transient

abnormalities of ECG related to coronary ischemia have been reported very rarely.

Cases of unexpected myocardial infarction and cerebrovascular accidents have occurred in patients undergoing combination chemotherapy with Vinblastine, bleomycin and cisplatin

Dacarbazine:

Hemopoietic depression is the most common toxicity with dacarbazine for injection and involves primarily the leukocytes and platelets, although anemia may sometimes occur.

Recommendations For Healthcare Professionals:

1. The recommended dose of doxorubicin, when administered in combination with other chemotherapy drugs, is 40 to 75 mg/m2 intravenously every 21 to 28 days, Consider use of the lower doxorubicin dose in the recommended dose range or longer intervals between cycles for heavily pretreated patients, elderly patients, or obese patients , **Cumulative doses above 550 mg/m2 are associated with an increased risk of cardiomyopathy**.
2. When **Bleomycin is used in combination with other antineoplastic agents, pulmonary toxicities may occur at lower doses** ,

   Because of the possibility of an anaphylactoid reaction, lymphoma patients should receive test doses of between 1-5 units, for the first two treatments. If no acute allergic reaction occurs within 4-6 hours, the balance of the dose may be given. Thereafter the regular dosage schedule may be followed, if no reaction occurs

   Idiosyncratic reactions similar to anaphylaxis have been reported in 1% of patients treated with Bleomycin (5% of lymphoma patients).

   Since these usually occur after the first or second dose, careful monitoring is essential after these doses
3. In patients with malignant-cell infiltration of the bone marrow, the leukocyte and platelet counts have sometimes fallen precipitously after moderate doses of Vinblastine sulfate.

   Further use of the drug in such patients is inadvisable.

   The chemotherapy drug regimen of vinblastine, bleomycin and cisplatin appears to cause serious life- threatening cardiovascular toxicity
4. The possible bone marrow depression requires careful monitoring of white blood cells, red blood cells, and platelet levels, hemopoietic toxicity may warrant temporary suspension or cessation of therapy with dacarbazine for injection.

Leukopenia and thrombocytopenia may be severe enough to cause death.

References:

1. *FDA-Dacarbazine injection label (Click Here)*
2. *TGA-Bleomycin sulfate Product information (Click Here)*
3. *Drugs.com-Drug Interaction Report (Click Here)*

Case Report from Sohag- Extravasation Phenomenon Induced By Dopamine Hydrochloride Injection

The Egyptian pharmaceutical Vigilance regional center in Sohag has received an ICSR about neonate female, 1.5 kg, who had administrated Dopamine 200 mg/ 5 ml, and then she had infusion site extravasation (extravasation phenomenon).

The reporter said that this reaction appears with dopamine hydrochloride when the final concentration exceeds 3.2 mg/ml in the final solution and so Dopamine Hydrochloride was diluted by Normal saline or Glucose.

***Dopamine Hydrochloride*:**

Stimulates beta-1 receptors in the heart, causing more complete and forceful contractions (entropy). Also acts on alpha receptors (dose dependent) and has dopaminergic effects.

Indications and Usage:

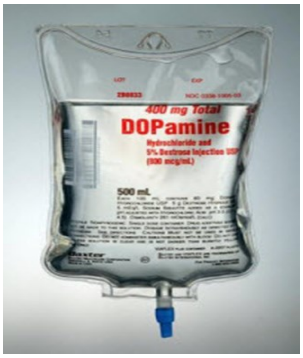
Correction of hemodynamic imbalances present in shock syndrome after MI, trauma, endotoxic septicemia, open heart surgery, and renal failure or chronic cardiac decompensation (eg, CHF).

Extravasation:

Is the leakage of intravenously (IV) infused potentially damaging medications into the extravascular tissue around the site of infusion.

Upon search it was found that:

- **Pediatric: It is not recommended for use in children as safety and efficacy in this age group has not been established.**
- Dopamine Hydrochloride and 5% Dextrose Injection, USP is administered only intravenously via a suitable I.V. catheter or needle infusion. **The less concentrated 800 mcg/mL solution may be preferred when**



fluid expansion is not a problem. The more concentrated 1600 mcg/mL or 3200 mcg/mL solutions, may be preferred in patients with fluid retention or when a slower rate of infusion is desired

- Extravasation

  Dopamine Hydrochloride and 5% Dextrose Injection, USP should be infused into a large vein whenever possible to prevent the possibility of extravasation into tissue adjacent to the infusion site. Extravasation may cause necrosis and sloughing of surrounding tissue

- Patients with a history of peripheral vascular disease should be closely monitored for any changes in color or temperature of the skin of the extremities. If a change of skin color or temperature occurs and is thought to be the result of compromised circulation to the extremities, the benefits of continued dopamine infusion should be weighed against the risk of possible necrosis. These changes may be reversed by decreasing the rate or discontinuing the infusion.
- Antidote **for peripheral ischemia following extravasations**

To prevent sloughing and necrosis in ischemic areas, the area should be infiltrated as soon as possible with 10 to 15 mL of sodium chloride

intravenous infusion 0.9% containing from 5 to 10 milligrams of phentolamine, an adrenergic blocking agent.

A syringe with a fine hypodermic needle should be used, and the solution liberally infiltrated throughout the ischemic area. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours. Therefore, phentolamine should be given as soon as possible after the extravasation is noted.

References:

1. *FDA-Dopamine Hydrochloride and 5% Dextrose Injection label (Click Here)*
2. ***TGA-*** *Dopamine Hydrochloride Product information (Click Here)*
3. ***Ireland:-*** *Dopamine Hydrochloride SPC (Click Here)*

Case report from Alexandria- Intraventricular hemorrhage related to the use of Sodium bicarbonate in a pre-mature neonate

The regional center in Alexandria has received a yellow card concerning a premature neonate (male) 26 weeks of gestation (0.9 kg weight) who was administered Sodium bicarbonate 8.4 % to treat metabolic acidosis by dose 2 meq/Kg and then he developed Intra-ventricular hemorrhage 2 days after drug administration. The physician tried to treat the reaction but he failed and the patient died on the next day.

Sodium Bicarbonate is indicated for (In neonates):

- Correction of metabolic acidosis associated with cardiac arrest in patients with pre-existing metabolic acidosis
- Cardiac arrest associated with hyperkalaemia with pre-existing metabolic acidosis
- Life threatening hyperkalaemia with pre-existing metabolic acidosis

No benefits have been demonstrated from the routine use of sodium bicarbonate in resuscitation of neonates. In neonates, sodium bicarbonate is recommended in resuscitation only in cases of prolonged cardiac arrest, irresponsive to other therapy, after establishment of adequate ventilation and circulation.

Intraventricular hemorrhage of the newborn

Intraventricular hemorrhage (IVH) of the newborn is bleeding into the fluid-filled areas (ventricles) inside the brain. The condition occurs most often in babies that are born early (premature).

Causes:

Infants born more than 10 weeks early are at highest risk for this type of bleeding. The smaller and more premature an infant is, the higher the risk for IVH. This is because blood vessels in the brain of premature infants are not yet fully developed. They are very fragile as a result. The blood vessels grow stronger in the last 10 weeks of pregnancy.

Pediatric Metabolic Acidosis Metabolic acidosis is an acid-base disorder characterized by a decrease in serum pH that results from either a primary decrease in plasma bicarbonate concentration ([HCO3-]) or an increase in hydrogen ion concentration ([H+]. It is not a disease but rather a

biochemical abnormality. The clinical manifestations of a metabolic acidosis are nonspecific, and its differential diagnoses include common and rare diseases.

Untreated, severe metabolic acidosis can lead to myocardial depression, seizures, shock, and multiorgan failure. Bicarbonate administration during treatment for diabetic ketoacidosis has been associated with an increased risk of cerebral edema

Labeled information:

According to Sodium Bicarbonate Injection 4.2%Summary of product Characteristics (SmPC) it was stated under section "4.8 Undesirable effects"

Nervous system disorders:

Intracranial hemorrhage (in neonates), hyperirritability or tetany.

According To Lexicomp Monograph of Sodium Bicarbonate (Pediatric and Neonatal Lexi-Drugs) it was stated under section Dosing:

Neonate: Usual dosage: 1 to 2 mEq/kg/dose

In older Children (>2 years) and Adolescents: 2 to 5 mEq/kg IV infusion over 4 to 8 hours; subsequent doses should be based on patient's acid-base status

Recommendations for Healthcare Professionals:

Administration of sodium bicarbonate injection:

- By slow intravenous injection or infusion.
- Plasma pH should be measured at regular intervals.
- An amount appropriate to the body - base deficiency up to 300 mmol.
- By dose in Children: The usual dose is 1mmol/kg by slow IV injection. (1ml/kg 8.4% solution)
- By concentration: In premature infants and neonates, the 4.2% solution should be used or the 8.4% solution should be diluted 1:1 with 5% dextrose
- Carefully consider clinical need before administering in Neonates because Rapid administration at a high concentration may be associated with fluctuation in cerebral blood flow and possibly ICH.

So, be cautious in use of sodium bicarbonate in premature neonate.

Other recommendation for the use of sodium bicarbonate:

- Not to be administered to patients with metabolic or respiratory alkalosis, hypocalcaemia, hypochlorhydria, hypertension, hypoventilation, chloride depletion or hyperosmolar states such as anuria or oliguria, edematous sodium retaining conditions such as hepatic cirrhosis, congestive heart failure and toxemia of pregnancy.
- Administration of sodium bicarbonate is contraindicated in patients taking diuretics known to produce hypochloremic alkalosis, such as bumetanide, etacrynic acid, furosemide and thiazides.
- Caution should be used when administering sodium ions to patients receiving corticosteroids or

corticotropin.

- Safe use during pregnancy has not been established.
- Undiluted sodium bicarbonate injection is hypertonic. Tissue necrosis, ulceration or sloughing has been reported following extravasation at the site of injection.
- Overtreatment with bicarbonate must be avoided. Frequent monitoring of serum electrolytes and acid-base status is essential.
- Excessive administration of bicarbonate may lead to metabolic alkalosis especially in patients with impaired renal function.

References:

1. *Medline Plus (Click Here)*
2. *Medscape Pediatric Metabolic Acidosis (Click Here)*
3. *emc*-Sodium Bicarbonate Injection Minijet 4.2% *(Click Here)*
4. *Onlinelexicom (Click Here)*
5. *emc-Sodium Bicarbonate Injection BP 8.4% w/v (Click Here)*