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PARAQUAT POISONING: CLINICAL CHARACTERISTICS AND BASIS FOR ITS DIAGNOSIS IN THE EMERGENCY DEPARTMENT

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ABSTRACT
Paraquat is a chemical used in several countries for the development of agricultural activities by peasants and farmers. Currently, PQ poisonings continue to be presented either by being accidentally ingested or for suicidal purposes. At the same time, most of the time it is a diagnosis that goes unnoticed by the emergency services because its initial picture is not so marked at the beginning. However, if it is not treated in time, it can lead to the death of the patient due to its high affinity with target organs such as the lung, heart and kidney. Thus causing a multiple organ failure, for this reason it is pertinent to know what in-hospital markers can help define the severity and prognosis of the patient with PQ poisoning

KEYWORDS: Paraquat poisoning, APACHE II, QT prolongation, arterial lactate, CRP.

INTRODUCTION
Paraquat is a bipyridyl herbicide that is widely used in agriculture.[1] It is classified as a highly toxic substance belonging to class II or moderately dangerous when ingested.[2] Since it produces multisystemic damage, thus mainly affecting: lungs, kidneys and liver. Being the lung the target organ, the mortality of this compound varies depending on the amount that has been ingested, the time in which the treatment is started and the age of the patient.[3] At the same time, high mortality is associated in developing countries, especially due to accidental or intentional ingestion when used as a suicide agent.[1] Mortality figures from paraquat poisoning are diverse throughout the world: in the United States, has reported a fatality of 54%, in France this has been 74% and in Asia it reached 80%. In Colombia, it was found that during 2013, 28 266 cases corresponding to acute chemical poisonings were reported, of which the group that was registered in second place and with figures of 29.2% were pesticides. It should be added that the five departments in which the most cases were reported were: Quindio, Huila, Putumayo, Meta and Caldas, thus showing the high availability of the poison in departments where rural activities are carried out[4] due to the fact that paraquat poisoning is often goes unnoticed and generates high mortality, it is convenient to describe what clinical characteristics and bases can be used for its detection in the emergency department

MATERIALS AND METHODS
A detailed bibliographic search of information published in databases such as: pubmed, Elsevier, scielo, Wiley is carried out for the search of these articles, the following descriptors were used such as: paraquat poisoing, APACHE II, Arterial lactate, QT prolongation, lung injury, metabolism of paraquat, PCR the search for articles was carried out in Spanish and English, it was not limited by year of publication.

RESULTS
Paraquat
Paraquat is a non-selective herbicide widely used in agricultural activities. Ingestion of PQ occurs frequently in farmers, either accidentally or as a suicide attempt, PQ is toxic to both humans and animals, and this intoxication causes multiple organ failure and

accelerated death due to production excessive reactant oxygen species and subsequent fulminant inflammatory response. Gastric lavage, activated catharsis, liquid infusions, charcoal hemoperfusion and immunosuppressive therapies are used to treat this type of poisoning. Currently, there is no known antidote to inhibit the toxicity and survival of PQ poisoning that is 20% to 50%.[5]

Metabolism of paraquat in the body

Several pathways are identified as causative factors for critical paraquat toxicity in the human body. First, the lungs are vulnerable to PQ poisoning, the concentrations of this chemical in the lung begin to increase constantly during the first hours after ingestion of paraquat, despite the decrease of PQ in plasma levels. Many scientists attribute this phenomenon to the high affinity of PQ for alveolar cells, the injury in pneumocytes begins with the nicotinamide adenine dinucleotide (NADH) -dependent reduction of PQ to monocationic radicals (PQ +). At the same time, the spontaneous reaction with molecular oxygen produces the superoxide radical (O2 -) and reversibly forms PQ ++, which can be reduced again. Therefore, PQ poisoning frequently causes death from respiratory failure. Second, the translation of cellular signals mediated by reactive oxygen species (ROS) causes inflammation. Consequently, the initial pathological finding is characterized by the infiltration of inflammatory cells. (Figure 1). Therefore, many doctors use drugs anti-inflammatories as a modality for the treatment of patients with acute Paraquat poisoning, third is the damage caused to the mitochondria by this chemical. In addition, PQ releases iron in free form from ferritin, aggravating ROS production.[6] It should be said that PQ is excreted in the kidney. Where its concentrations are very high, resulting in the deterioration of kidney function, if the PQ cannot be excreted normally it will tend to accumulate in the body; therefore, thus affecting several organs such as: the liver, the heart and the lung resulting in multiple organ failure (figure 2)[7], likewise animal studies indicate that PQ is a strong base cation, which is rapidly but poorly absorbed from the gastrointestinal tract. Only 5-15% manage to reach the bloodstream where it will reach the maximum concentration around 2-6 hours. The binding of paraquat to proteins is very low and it is not metabolized. Small amounts of PQ have been found in the bile of deceased patients, indicating that there is a possibility of some excretion in the bile duct. However, up to 98% of the PQ is excreted unchanged in the urine, indicating that renal function is a key factor in the elimination of paraquat.[8]

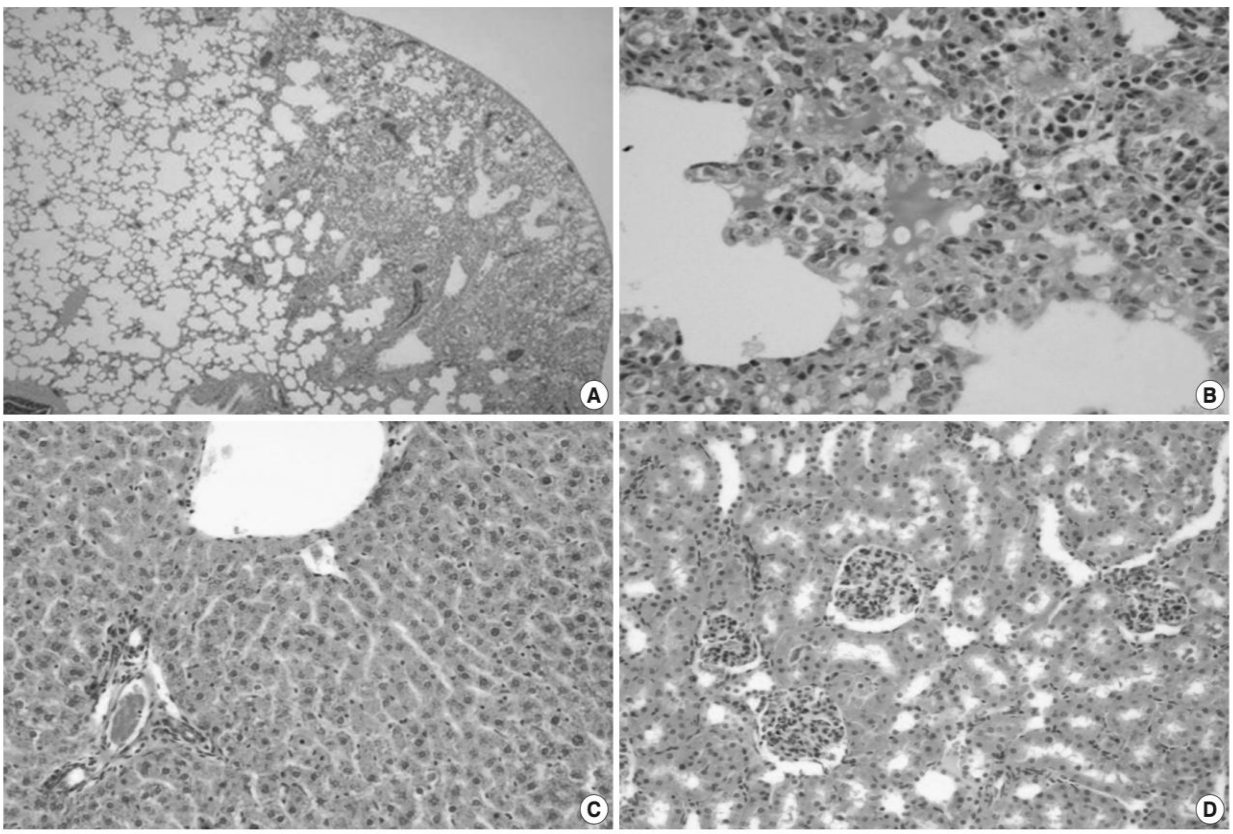

Fig. 1. Lung is a vulnerable organ in acute paraquat intoxication. Lethal dose of paraquat (25 mg/kg) was injected intraperitoneally in mice and 3 days later, the mice were sacrificed. The lung, liver and kidney were obtained and examined by light microscopy. (**A**) The lung parenchyma show interstitial widening and inflammatory infiltrates predominantly in the sub-pleural area (H&E, × 40). (**B**) High power examination of the lung reveals dense infiltration of lymphoplasma cells (H&E, ×400). The liver (**C**) and kidney (**D**) are histologically unremarkable (H&E, ×100).

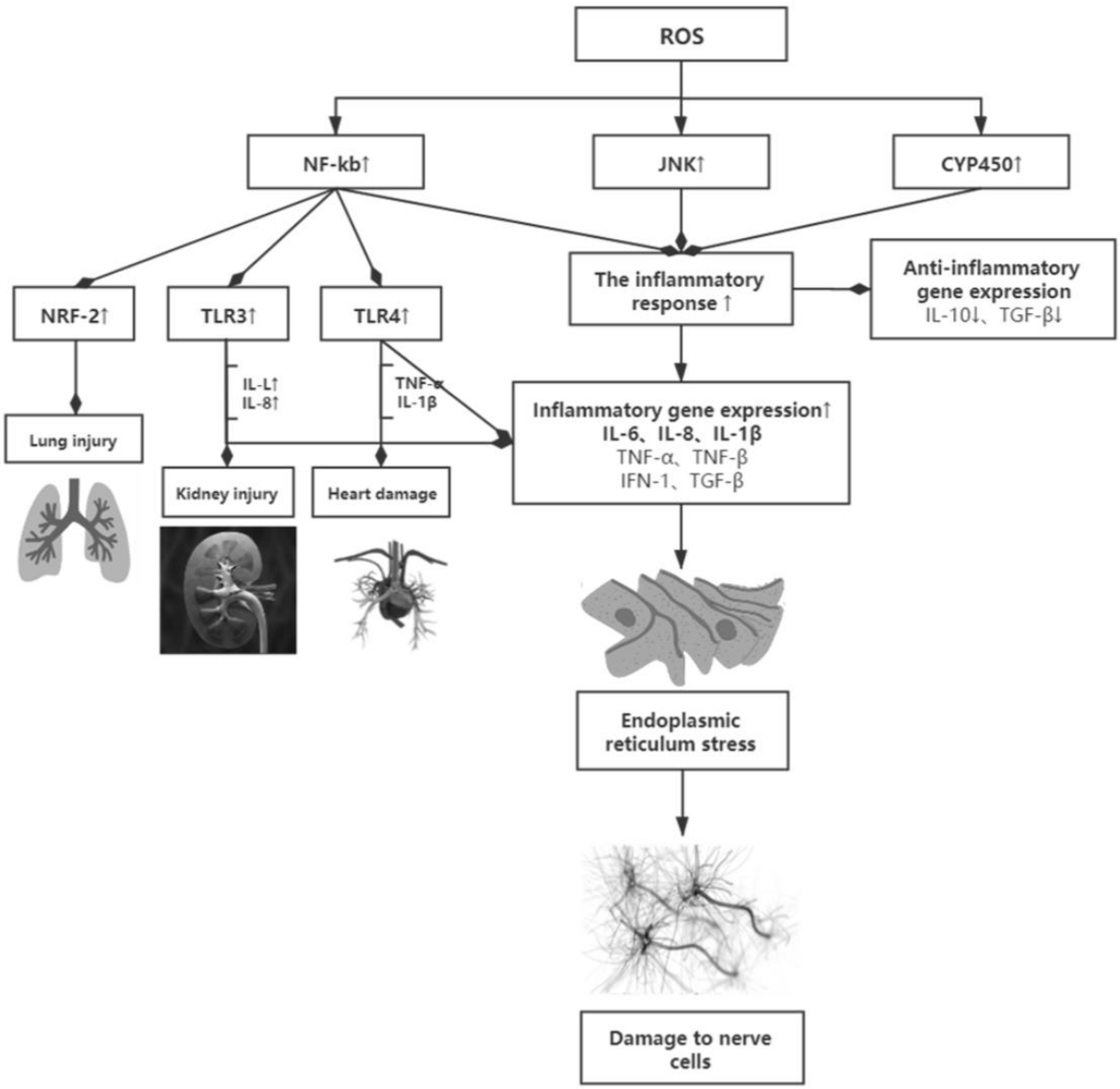

Fig. 2: The mechanism of oxidative stress products regulating inflammation.[9]

Clinical presentation of paraquat poisoning

The clinical features of acute PQ poisoning are manifested by high mortality, rapid progression, and frequent lung and kidney injury. Acute poisoning with PQ is usually considered asymptomatic when it occurs in the early stage, irritation and numbness of the tongue and oral mucosa are generally the symptoms that are reported in most cases in the first days. In (Table 1) the signs and symptoms are recorded according to the severity table of PQ poisoning, between 3 to 4 days after the ingestion of paraquat occurs dyspnea, increased respiratory rate, lethargy and confusion, as the lesion progresses at the level of the lungs in cases where it occurs moderate to severe intoxication, it has been seen that the kidney is involved in the metabolism of this chemical, which is why the susceptibility to acquiring acute kidney injury secondary to PQ poisoning has been evidenced in approximately 50% of cases. Similarly, non-oliguric renal failure is seen in less than 50% of AKI patients, especially when a large volume of fluid is administered in early treatment. The mean serum creatinine level reaches its peak around the fifth day after ingestion, this usually normalizes after 3 weeks, and a permanent loss of kidney function has not been reported after PQ poisoning. However, the risk of mortality is significantly high in patients with kidney failure.[6]

Tools to assess severity and prognosis of paraquat poisoning

APACHE II scale

Predicting the risk of death is important to prevent desperate or minimally poisoned patients from receiving unnecessary aggressive therapy. The PQ poisoning severity index is the most valuable prognostic indicator for patients with PQ poisoning. This is calculated by multiplying the time since the ingestion of the PQ in hours by the concentration in the plasma (mg / L). However, many hospitals do not have access to testing for plasma PQ levels, which limits the accurate assessment of the severity of poisoning. The Acute

Physiology and Chronic Health Evaluation (APACHE) II scale (Table 2) is widely used in the intensive care unit (ICU) and has been in use for the last 30 years or more, this APACHE II system includes the score of Acute 12-point physiology, an age point, and a chronic health assessment are readily available in most emergency departments. Furthermore, this score calculation is robust and straightforward. These scoring systems used could facilitate the emergency classification system and thus guide the treatment to be established for patients. It should be said that many studies have used the APACHE II scoring system in PQ poisoned patients to assess prognosis.[10]

C-reactive protein (CRP)

The inflammatory response is the primary and initial mechanism of tissue damage after PQ poisoning. This reactive protein is an acute phase protein that has been extensively evaluated in critical illness. CRP levels are positively correlated with the degree of inflammation during the course of the disease, consequently several studies have used CRP as a predictor of prognosis and mortality in severe diseases, such as bacterial infection in cirrhosis, avian influenza (H7N9) and in patients poisoned by phosphorous organs. Zong, et al. observed that plasma CRP levels were increased in patients with PQ intoxication, and levels were significantly high in non-surviving patients and survivors, suggesting that the inflammatory response was much higher in non-surviving patients than in those who survived. They also observed that plasma CRP levels correlated with plasma PQ levels, thus indicating that CRP could be a good marker that reflects the severity of PQ poisoning and could potentially be a prognostic marker for patients. Who get intoxicated with PQ in addition, they found that with respect to plasma PQ levels, patients whose plasma CRP level was greater than 18.0 mg / L had a poorer prognosis.[12]

QT prolongation

Corrected QT is known for its ability to predict cardiovascular mortality in various types of diagnosis. In patients poisoned by phosphorous organs, prolonged Qtc indicates a poor prognosis. When reviewing the literature, it is found that patients who suffer fulminant poisoning with PQ (for example, more than 40 mg / kg of PQ) showed a high mortality rate. These patients died between 24 and 72 hours after ingestion, with a maximum survival time of no more than 1 week. According to what has been observed in the emergency services, pulmonary fibrosis is one but not the only cause of death found in patients with high-dose PQ poisoning. Circulatory failure or vascular collapse and organ failure have been characterized as the major causes of immediate death compared to pulmonary fibrosis. Previous studies have also shown that acute PQ poisoning could cause direct myocardial injury. Therefore, it may seem reasonable to consider QTc as a prognostic factor for acute PQ poisoning.[13]

Lactate in arterial blood

Lactate estimation is a prognostic tool that can determine a mortality rate among patients who have severe sepsis and ST-segment elevation myocardial infarction, it is used in numerous patients in the intensive care unit, including patients who have recently undergone a surgical procedure and those with burns, trauma and septic shock, Lactate in arterial blood is a manifestation of organ dysfunction and has good predictive power when evaluating the prognosis of patients with acute PQ poisoning, intake of more than 15-30 ml of 20% (w / v) PQ can lead to mortality from multi-organ failure or respiratory failure within a month of poisoning. Since PQ poisonings have a dose-response relationship, it is advisable to assess the PQ dose at a given time.[14]

DISCUSSION

Poisoning with paraquat puts the lives of patients at risk because they often go unnoticed by the emergency services, thus leading to not providing rapid and timely treatment, triggering multiple organ failure and death. Paraquat enters the body through the digestive tract and from there a small amount manages to diffuse into the bloodstream, reaching the tissues with greater affinity such as the lung, heart and kidney. At the same time, (Fan et al) in a report of cases about intoxication by PQ for homicidal purposes, they found in the corpse when performing the necropsy concentrations of PQ in the tissues of the victim from high to low, presenting mainly in the lung following the brain, continuing with the kidney, liver and stomach wall. Likewise, it was found that paraquat has a high affinity with the lung. (Amin et al) discussed that the largest target organ in PQ poisoning is the lung and PQ induces lung damage associated with edema, hemorrhage, hyaline membrane formation, alveolar epithelial proliferation followed by progressive pulmonary fibrosis and eventually death, the generation of reactive oxygen species has been suggested as the main mechanism of PQ-induced lung damage. Additionally, there are several tools to assess the severity and prognosis of PQ poisoning in this study, it was found that scales such as APACHE II, C - reactive protein, QT prolongation and lactate in arterial blood were used, in terms of C-reactive protein, (Zong et al.) Observed that plasma CRP levels were increased in patients with PQ poisoning and said levels were significantly high in non-surviving patients compared to those who survived, suggesting that the inflammatory response was much higher. In non-surviving patients than in surviving patients. Therefore CRP represents an important marker for the severity and prognosis of this poisoning. In the same way, arterial blood lactate has been used as a predictive marker of organ dysfunction (Shilei et al), they systematically evaluated the prognostic value of blood lactate in 1022 patients poisoned by PQ from 6 different studies and demonstrated that arterial lactate was a favorable prognostic indicator for mortality. This prognostic value of arterial lactate in PQ poisoning obtained the same sensitivity in the prognostic of PQ poisoning in blood PQ concentration.

CONCLUSION

We can conclude that paraquat poisoning can endanger the life of the patient if it is not diagnosed and treated promptly. As is known, paraquat has an affinity for several organs, thus causing them to accumulate in their tissues causing functional deterioration in them, leading to multisystem failure and later to the death of the patient, these intoxications are characterized by their rapid progression to damage to the organs. Tissues by the production of reactive oxygen species, which causes the body to undergo an aggressive inflammatory process that leads to the functional deterioration of the target organs: lung, kidney, heart, among others. For this reason, it is important that the emergency department have an idea of what the clinical characteristics of PQ poisoning are. That is why it is convenient to know what parameters can be used for the diagnosis and treatment of these poisonings. According to the literature consulted, it has been found that the parameters that can guide us towards the severity and prognosis of the condition are: the APACHE II scale, the measurement of C-reactive protein, the prolongation of the Qt interval in ingestion by antiplagicides and the measurement of lactate in arterial blood to identify the presence of organ dysfunction in the patient.

It is recommended to carry out clinical studies that allow to know in depth what other systems and organs can be affected by paraquat poisoning and what possible management can be given to these poisonings.

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