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Unraveling the link between severe bradycardia and paraquat poisoning

Running title: Bradycardia in paraquat poisoning

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Dear Editor,

Poisoning with paraquat, a highly lethal herbicide, is often encountered in developing countries [1]. Human intoxication by paraquat typically occurs due to ingestion either accidentally or with suicidal intent and rarely following dermal exposure [2]. The high case fatality rate is due to lack of an effective antidote and the inherent cellular toxicity of paraquat, which is secondary to oxidative stress [3,4]. The typical clinical presentation includes multiorgan failure involving the gastrointestinal, hepatorenal, and respiratory systems [5]. Paraquat-induced pulmonary fibrosis has been abundantly reported in the literature, with evidence of its mechanism, clinical manifestation, and treatment strategies [6]. However, little to no evidence exists on the hemodynamic and cardiac electromechanical effects of acute paraquat poisoning [7]. Cases of extreme bradycardia following paraquat poisoning are particularly rare [8]. We report a case of bradycardia that was refractory to anticholinergics, which is an unusual clinical manifestation of acute paraquat poisoning.

A 32-year-old man with no known comorbidities had previously presented with an alleged history of approximately 30 mL of 20% paraquat consumption with an intent to commit suicide. The patient was treated elsewhere primarily with gastric lavage and arrived at our hospital 14 hours postconsumption. On arrival, the patient had typical mucosal involvement and was febrile with a temperature of 101°F. His heart rate was 110 beats/min, his respiratory rate was 28 breaths/min, and his oxygen saturation was 90% on ambient room air. Systemic examination findings were unremarkable, except for bibasal crepitations over both lung fields. Investigations revealed deranged kidney function tests suggestive of acute kidney injury and elevated transaminases. The patient was administered antioxidant therapy (N-acetylcysteine, vitamin C, vitamin E), immunosuppressants (parenteral steroids, 8 mg dexamethasone intravenously every 8 hours for the first 72 hours), antacids, and a topical local anesthetic for mucosal erosions, along with other
supportive therapy. Renal replacement therapy was initiated on day 2 of hospitalization because of declining renal function (metabolic acidosis, 7.24 pH; oliguria, urine output of 600 mL/24 hr; incremental trend in urea [96 mg/dL] and creatinine levels [4.8 mg/dL]). In addition, his oral mucosal lesions worsened, and he developed dysphagia within 48 hours of hospitalization. Enteral feeding through a nasogastric tube was established, and other supportive measures were continued. Serial evaluations of hepatorenal function with hematological testing and close monitoring of clinical conditions were carried out in the intensive care unit. On day 3 of hospitalization, the patient developed severe bradycardia, with his heart rate dropping to 35 beats/min. The chronotropic agents glycopyrrolate and atropine were administered parenterally. Although we noted a transient improvement in heart rate following the administration of these agents, the increase was not sustained. A 12-lead electrocardiogram suggested sinus bradycardia, and the echocardiogram was normal. Serum electrolytes were within normal limits. A thyroid profile was carried out and revealed T3 of 0.77 nmol/L, T4 of 102 nmol/L, and thyroid stimulating hormone (TSH) of 0.60 IU/mL.

Low-dose thyroxine therapy was initiated at a dose of 50 μg/day, and a sustained increase in heart rate was noted. The patient was subjected to three sessions of hemodialysis during hospitalization. The patient’s hypoxemia worsened by day 5 of hospitalization, with an ambient air saturation nadir of 88%, which improved on subsequent days without oxygen therapy. A chest roentgenogram revealed early lung fibrosis, although the serial evaluation did not show further clinical and radiological worsening. The patient’s heart rate normalized, oxygenation improved, and acute kidney injury resolved by day 7 of hospitalization. The patient was observed in a step-down unit for 1 week and then discharged home following an uneventful observation period after normalization of his hepatorenal functions. He was discharged normoxemic in an ambulant,
cheerful condition following psychiatric counselling. Thyroxine supplementation was stopped after 1 week. The patient was reviewed 1 week later and was asymptomatic, with normal vitals and an unremarkable systemic examination.

Paraquat is a quaternary nitrogen herbicide that triggers oxidative stress, mitochondrial damage, and multiorgan injuries, including the heart. Cardiotoxicity has been investigated in several experimental studies following paraquat exposure in rodents [7,9–10]. Acute paraquat poisoning has adverse hemodynamic and electromechanical effects on rat hearts. Decreases in heart rate, blood pressure, and cardiac contractility have been noted in a dose-dependent manner in anesthetized rodents [7].

Paraquat toxicity has both direct and indirect effects on the cardiovascular system. Significant contractile dysfunction has been observed following direct cardiac injury, as shown by reduced fractional shortening and myocardial remodeling. Reactive oxygen species exert indirect effects by causing ischemic alterations in the heart. Ventricular myocyte models in rodents have shown that altered calcium transport systems may be responsible for the cardiac dysfunction caused by paraquat [10]. Paraquat poisoning can lead to toxic myocarditis and sinus node dysfunction [11]. All these effects could have contributed to our patient’s bradycardia following paraquat poisoning. Another possible explanation is that immunosuppression with large doses of glucocorticoids may reduce basal TSH level, resulting in low thyroid hormone levels that may produce bradycardia [8]. Low thyroxine may impair ventricular function and the neuroendocrine profile in people with preexisting heart conditions [12]. Our patient developed extreme bradycardia on day 3 of hospitalization, which could be attributed to paraquat cardiotoxicity, to the glucocorticoid effects used in therapy, or to both. Failure to respond to the parasympatholytic drug atropine prompted us to initiate thyroxine therapy after evaluating the patient’s thyroid profile.
The patient made a remarkable clinical recovery following thyroxine therapy and was discharged home.

No antidote is available for paraquat poisoning, so clinicians often resort to antioxidants and immunosuppressive agents. Adverse effects of acute large doses of immunosuppressive therapy, such as infection or hyperglycemia, can occur when treating a case of acute paraquat toxicity. Physicians should have high suspicion of possible cardiotoxicity when treating such a case. They should manage these patients swiftly with symptomatic and supportive therapy, as mortality in this subset is extremely high.

ETHICS STATEMENT

The patient provided written informed consent for publication of the research details.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: AR, TM, RE; Investigation: RE, YVC, KH, SM, GR; Methodology: AR, RE, YVC, KH, SM, GR; Validation: TM; Visualization: TM; Writing–original draft: AR, RE; Writing–review & editing: all authors. All authors read and approved the final manuscript.
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