REVIEW ARTICLE DOI: https://doi.org/10.18502/fem.v6i1.7679

Potential therapeutic approaches in paraquat poisoning: a narrative review

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Published online: 2021-09-18

Abstract: Paraquat dichloride (PQ) poisoning is a relatively rare yet critical medical condition that has a high case fatality rate. Lung tissue is highly susceptible to PQ-induced injury, and respiratory failure is the leading cause of death in these patients. Unfortunately, there is a lack of an effective therapeutic approach to ameliorate outcomes. It is well-known that PQ interferes with a variety of cell signaling pathways and induces the generation of reactive oxygen species (ROS), which ultimately results in cell injury. The traditional treatment decisions have not been able to significantly change the clinical course of PQ poisoning. Moreover, novel therapeutic strategies for PQ poisoning have centered on the inhibition of PQ-induced signaling pathways. In the current review, we sought to provide a bird's-eye view of the available therapeutic approaches in patients with PQ poisoning.

Keywords: Antioxidants; Hemoperfusion; Paraquat; Poisoning; Signal Transduction

Cite this article as: Ghabousian A, Safari S, Ansari N. Potential therapeutic approaches in paraquat poisoning: a narrative review. Front Emerg Med. 2022;6(1):e7.

1. Introduction

Paraquat dichloride (PQ) is a notorious non-selective herbicide, commonly used in the agricultural setting (1). Notably, PQ is a highly noxious and lethal agent for human beings (2). The use of PQ has been banned by the European Union and many other nations but is still in great demand in developing countries (3). Given that PQ exhibits a marked tendency to accumulate in the alveolar epithelium via active transportation, respiratory failure is the leading reason for mortality in patients with PQ poisoning (4). Although the exact underlying molecular mechanisms contributing to PQ-induced lung toxicity have not yet been fully illuminated, it has been proposed that PQ poisoning provokes the generation of superoxide anions via involving in cyclic reduction-oxidation, which in turn leads to the development of inflammatory response, lipid peroxidation, mitochondrial dysfunction, leukocyte infiltration, fibroblast proliferation, and extracellular matrix expansion (5-7). The inflammatory response is thought to be mediated through the actuation of various signaling pathways (8). Despite considerable efforts in the field of toxicology with regard to PQ poisoning, therapeutic approaches are exceedingly limited, and none is supposed to be curative (9). Therefore, the treatment of PQ poisoning has remained a real challenge for emergency physicians. Currently, the focus of interest has been shifted towards cell signaling pathways that might be involved in the development of PQ-induced lung injury, with the aim of finding novel treatments. Mitogen-activated protein kinase (MAPK), nuclear factor kappa B (NF-KB), phosphatidylinositol 3 kinase (PI3K)/protein kinase B (AKT), transforming growth factor- β1 (TGF-β1), and Wnt/β-catenin signaling pathways have been demonstrated to be involved in PQ-induced lung injury (10-14). In the current review, we aimed to discuss the potential therapeutic options to manage PQ poisoning.

2. The current approach to PQ poisoning

2.1. Supportive care

The current management of patients with PQ poisoning is more supportive rather than curative. Once the patient arrives at the hospital, the initial evaluation should focus on managing life-threatening complications through the ABC approach (airway, breathing, and circulation) according to the available guidelines (15). Even though there is no sound evidence that supports the effectiveness of gastrointestinal decontamination in PQ poisoning, several studies have suggested that activated charcoal should be administered within 4 hours (h) of ingestion (15). However, given that gastric lavage can give rise to corrosive injury in the presence of PQ, it is not recommended for patients with PQ intoxication (16). More importantly, liberal oxygen therapy is thought to perpetuate cyclic reduction–oxidation and reactive oxygen species (ROS) formation, which in turn contributes to the destruction of type II pneumocytes (17). It should be pointed out that oxygen administration should be avoided unless the blood oxygen saturation drops beneath 90%; meanwhile, continuous oxygen monitoring to rapidly identify respiratory deterioration should be considered (18).

2.2. Hemoperfusion

The efficacy of hemoperfusion has been called into question, with the studies showing conflicting results. While previous retrospective studies suggested that early initiation of hemoperfusion (<4h) could be helpful and promote survival, a recent retrospective multi-center study that included 213 patients found that neither early nor sequential hemoperfusion had a statistically significant influence on 60-day survival (19-22). The crux of the matter is that previous studies, which found a beneficial effect for hemoperfusion, did not take plasma levels of PQ into account. Besides, at least two of them did not consider the possible impact of anti-oxidative and anti-inflammatory therapies on the outcomes. On the other hand, hemoperfusion has no influence on ROS formation and signaling pathways in lung tissue, which appear to be the most relevant underlying mechanisms involved in the pathogenesis of PQ-induced lung injury. However, a recent meta-analysis study conducted on 1041 patients with PQ poisoning has demonstrated that hemoperfusion in combination with continuous venovenous hemofiltration (CVVH) within 24h of ingestion can reduce overall 4-day mortality (hazard ratio= 0.52, P<0.0001) and circulatory failure (relative risk= 0.40, P<0.0001) compared with hemoperfusion alone, but has no significant impact on long-term mortality (23). Taken together, early hemoperfusion combined with CVVH could be considered as a last-ditch effort to ameliorate outcomes in PQ-poisoned patients (24).

2.3. Immunosuppressive therapy

Employing immunosuppressive agents for the management of PQ poisoning has yielded promising results (25,26). A recent meta-analysis study that included 426 patients has reported that pulse therapy with cyclophosphamide and glucocorticoids promotes survival rate (relative risk (RR)= 0.73; P<0.00001) without any significant short-term adverse effect (27). Of interest, both experimental and human studies have illustrated that prolonged methylprednisolone therapy (3-days of 15 mg/kg/day followed by every 2-days decreased by half and terminated at 0.47 mg/kg/day) can significantly reduce mortality in cases with moderate-severe PQ intoxication compared with pulse treatment (3-days of 15mg/kg/day) (28,29).

2.4. Traditional antioxidants

Although traditional antioxidants are widely being used due to their well-recognized ability in alleviating oxidative stress, displayed in experimental studies, there is a shortage of clinical data supporting their efficacy.

Vitamin C acts as a potent free radical scavenger and is believed to reduce the levels of pro-inflammatory and profibrotic molecules such as IL-6, IL-17, and TGF-β in the lung tissue (30). It should be noted that vitamin C has been shown to attenuate morphologic changes provoked by PQ in the liver (31). N-acetylcysteine (NAC) is a precursor of glutathione and exhibits antioxidant properties. Moreover, NAC can reduce the infiltration of inflammatory cells at the time of PQ intoxication (32-34). Similarly, vitamin E has been found to ameliorate the oxidative stress induced by PQ (35). Also, vitamin E is an inhibitor of ferroptosis, which has been illustrated to contribute to the development of cell injury in PQ poisoning (36).

2.5. Novel therapeutic avenues

Rosiglitazone, an insulin sensitizer, is a member of the thiazolidinediones family, which activates peroxisome proliferator–activated receptor γ (PPARγ) and exerts both antioxidant and anti-inflammatory properties (37). PPARγ has been shown to play a fundamental role in modulating inflammatory response occurring in pulmonary tissue (38,39). In a recent in-vivo study, PQ poisoning was found to be associated with a reduction in the expression of PPARγ and upregulation of TGF-β1 in the lung; however, rosiglitazone therapy reversed both of these changes (40). Doxycycline has been illustrated to mitigate PQ-mediated lung injury via modulating the inflammatory response. While PQ intoxication upregulates the expression of matrix metalloproteinase 9 (MMP9), doxycycline decreases MMP9 activity (41). MMP9 degrades extracellular matrix components and paves the way for developing pulmonary fibrosis. On the other hand, doxycycline tends to suppress pro-inflammatory TGF-β and tumor necrosis factor-α (TNF-α) signaling pathways induced by PQ poisoning (42). Febuxostat serves as an inhibitor of xanthine oxidase. In rats, febuxostat treatment has been shown to alleviate detrimental impacts of PQ on pulmonary tissue by blocking PI3K/Akt and β-catenin signaling induced by PQ and their downstream mediators (43).

In recent years, several studies have aimed to evaluate the efficacy of rapamycin in the context of PQ poisoning. Rapamycin is an immunosuppressive agent and downregulates Wnt and mTOR signaling pathways, which PQ induces in lung tissue, and upregulates the expression of nuclear factor erythroid 2–related factor 2 (Nrf2), which is reduced after PQ exposure (44-46). Nrf2 is a well-recognized transcription factor that promotes the expression of anti-oxidative proteins. Furthermore, a recent rat model of PQ intoxication has shown that fluorofenidone administration attenuates pulmonary fibrosis induced by PQ via suppressing PI3K/Akt/mTOR pathway (47). Another recent in-vitro study has indicated that while PQ leads to a significant increase in the expression of TGF-β1 and mothers against decapentaplegic homolog 3 (SMAD3) in lung tissue, tacrolimus, a calcineurin inhibitor, can halt the overexpression of the aforementioned factors and exhibit antifibrotic properties (13). A recent meta-analysis of randomized clinical trials has found that the administration of ambroxol, a mucolytic agent, which exerts anti-oxidative properties and promotes pulmonary compliance, significantly reduces in-hospital mortality (RR= 0.69, P=0.001) (48).

Even though lung injury is the most critical complication of PQ intoxication, other organs such as the kidney, liver,

and pancreas could also be adversely affected by PQ. Recently, it has been proposed that octreotide, which mimics somatostatin's function, can prevent pancreas and kidney injuries caused by PQ in animal models (49,50). In a sense, octreotide attenuates inflammatory response and ROS generation. Taken together, in spite of the shortage in clinical studies to confirm the efficacy of repurposed drugs, taking into account the fact that these agents have been shown to be safe and PQ poisoning has an extremely high mortality rate, adding these agents to traditional care of PQ poisoned patients might be helpful to ameliorate the severity of damage induced by PQ.

3. Conclusion

PQ poisoning has a high mortality rate and poses a real challenge for emergency department physicians. Unfortunately, there is a lack of antidotes for PQ. Current therapeutic approaches are extremely limited. Currently, repurposed drugs for PQ poisoning are receiving special attention. Even though there is a shortage of clinical studies to assess the efficacy of novel therapeutic opportunities, the use of these agents might be helpful in the management of PQ-poisoned patients.

4. Declarations

4.1. Acknowledgment

None.

4.2. Authors' contribution

It is worth mentioning that all authors met the criteria for authorship in accordance with the recommendations of international committee of medical journal editors.

4.3. Conflict of interest

There is no conflict of interest with regard to the current study.

4.4. Funding

The current study was performed without any funding, and the authors were in charge of all expenses.

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