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Is there a role for sildenafil in the management of paraquat-induced lung fibrosis?

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Paraquat is a herbicide. It is a highly toxic compound for humans often used for suicide, especially by farmers, and is associated with high mortality rates (1). In fact, if one consumes more than 20 millilitres of its 20 % solution, a rapid onset of multi-organ dysfunction will cause death within a few days. In contrast, consumption of smaller amounts of paraquat may respond to supportive care and the patient could survive the acute phase (2).

Unfortunately, the polyamine reuptake system, which is mainly expressed in the membrane of alveolar cells, is responsible for toxin accumulation in the lungs during the acute phase. Consequently, lung fibrosis may occur as a delayed complication, which may potentially be fatal (3, 4). However, scientists propose to use anti-inflammatory drugs as the main part of treatment for preventing pulmonary fibrosis, progression to end-stage respiratory failure, and death within 2-3 weeks after paraquat intoxication (2).

Fortunately, if the patient overcomes this phase, pulmonary fibrotic tissue remodelling can lead to functional regeneration within about 6 months (5).

To date, no clearly efficacious therapies have definitively been shown to alter fibrosis progression. Moreover, no treatment for respiratory failure due to paraquat-induced lung fibrosis till date has proven effective (6).

However, respiratory failure is the main reason for invasive mechanical ventilation, and there is no published study on the outcome of ventilator support. Nevertheless, according to recent studies evaluating the prognosis, respiratory failure and the need for respiratory support were the determinants of the fatal outcome (1). This finding is similar to those reported previously in patients with idiopathic pulmonary fibrosis (7). The probable mechanism is overdistension of relatively intact parts of pulmonary tissue and a consequent ventilator-induced lung injury or an increase in the right-to-left shunt flow in response to the prostanoid (8, 9).

In addition to fibrotic damage of the vasculature and elevation of vascular resistance, patients with lung fibrosis show decreased levels of nitric oxide (NO) production (NO being a significant pulmonary vasodilator), which contributes to pulmonary vasoconstriction and consequently impaired gas exchange (10, 11). This can explain a relatively swift progression of respiratory dysfunction in patients with moderate to severe paraquat toxicity.

It has previously been demonstrated that inhaled NO leads to preferential vasodilation in well-ventilated lung tissue, as well as bronchodilation, anti-inflammatory and antiproliferative properties (12).

Interestingly, reviewing the literature on the internet, one case report of successful treatment of massive paraquat ingestion by inhaled NO exists (13). Moreover, Cho and colleagues demonstrated that inhaled NO was associated with survival improvement in paraquat-injured rats (14).

Unfortunately, considering that fibrosis requires a long time to develop, continuous inhalation NO therapy presents technical difficulties. Sildenafil as a phosphodiesterase-5 inhibitor stabilises cyclic guanosine monophosphate, helps increase NO levels in the lungs, and has selective pulmonary vasodilatation properties for well-ventilated lung areas (15).

Ghofrani et al. (15) demonstrated a significant improvement in gas exchange in patients with severe lung fibrosis treated with sildenafil; moreover, a controlled trial conducted by the idiopathic pulmonary fibrosis clinical research network showed a significant improvement of dyspnoea and quality of life, as well as pulmonary function stabilisation, improvement of arterial blood gas, and carbon monoxide diffusion capacity at 12 weeks. However, the latter study was unable to show a significant improvement of survival rates because it enrolled too few patients (11, 15).

Moreover, it should be kept in mind that these two trials involved patients with severe idiopathic pulmonary fibrosis, which is a chronic and progressive lung disease, whereas, as mentioned earlier, the remodelling of fibrotic tissue can lead to functional regeneration in paraquat poisoning survivors.

According to the available safety and efficacy data, it seems that administration of sildenafil can theoretically improve ventilation–perfusion matching and thus gas exchange in paraquat poisoning patients (16). Therefore, a

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randomised controlled trial should be conducted in such patients.

Conflicts of interests

None declared.

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