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## Neurotoxic effects of paraquat

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Paraquat (1, 1' - dimethyl - 4, 4' - dipyridyl) is a bipyridyl compound. It was first marketed in 1962 as a broad-spectrum, non-selective and contact herbicide after having been described first by Weidel and Rosso in 1882 (1).

Paraquat is highly corrosive. It is absorbed poorly after inhalation but is extremely toxic if ingested. After paraquat ingestion, oedema, burns or ulceration may be seen in the mucosa of the mouth, oesophagus, stomach and intestines. Death usually occurs within 48 hours of ingestion of 50 mg/kg. Self-ingestion of paraquat is a serious health problem in many developing countries as it is used for suicidal attempts. It was described that 15 ml of 20% paraquat or one mouthful is a lethal dose in adults (2). An antidote for paraquat has still not been found. The World Health Organization classifies paraquat as a Class 2 moderately toxic substance but 'Pesticide Action Network Asia & Pacific' believes it to be in Class 1 due to its acute toxicity, delayed effects, and lack of antidote. There is a lag time between exposure and development of symptoms, early exposure is most deleterious. Unborn foetus and children are at more risk (3). In 2010, the California Environmental Protection Agency showed if exposed to lower doses even, during critical periods of childhood brain development is adversely affected.

At lower doses death may be delayed for several weeks (1). Toxicity is due to the pulmonary accumulation of bipyridyl compound. Paraquat is transported actively into pulmonary cells resulting in pulmonary oedema or fibrosis. Centrizonal hepatic necrosis, proximal renal tubular damage, myocardial damage, and skeletal muscle damage with focal

necrosis may also be seen after acute intoxication of paraquat (1).

The major cause of death in paraquat poisoning is respiratory failure due to an oxidative insult to the alveolar epithelium with subsequent obliterating fibrosis. Paraquat, once it accumulates in the lungs or renal cells, leads to redox cycling and generation of toxic reactive oxygen species. This can overwhelm cellular defense mechanisms and lead to lung damage and renal tubular necrosis.

Paraquat is neurotoxic *in vitro*, but the neurotoxic effect of paraquat in humans is not yet clear. It was shown that exposure of lab animals to paraquat causes reduction in neurotransmitters in brain (4). Stelmashook *et al* 2007 demonstrated that both mature and immature cerebellar granule neurons in rats are killed by paraquat (5). Kriscenski-Perry *et al* 2002 demonstrated that paraquat and thermal stress elicit synergistic effect in damaging spinal motor neurons in laboratory animals (6). *In vitro* studies by Niso-Santano M *et al.* (2006) showed low concentrations (25µM paraquat in to 5×10<sup>4</sup> cells/cm<sup>2</sup> rat brain neuroblast cells) of paraquat stimulate very early and rapid activation of intracellular signalling cascades leading to paraquat induced neural cell death (7).

Chen Q *et al.* 2010 showed that after treatment with paraquat which was given orally once daily for 28 consecutive days to mice, cells in the hippocampus were irregular, and cytoplasm was found to be condensed. Number of nissl bodies found there was reduced and apoptotic or necrotic neurons were observed. Increased response latency was also noted in animals given paraquat (8).

Peng J *et al.* (2008) demonstrated tyrosine hydroxylase (TH) positive neuronal cell death in primary mesencephalic neuron-glia in animals treated with 10 mg/kg paraquat twice per week for three weeks (9).

Animal studies by Fei Q *et al.* (2008), Kang M J *et al.* (2009) and Ren J *et al.* (2009) showed repeated doses of paraquat (10 mg/kg gavage daily for four months or 10 mg/kg intraperitoneal injection twice weekly for three consecutive weeks) induced damage to the cells in substantia nigra pars compacta (SN<sub>pc</sub>) in mid brain sections from mice (10-12). Kang M J *et al.* (2009) used 10mg/kg paraquat by intraperitoneal injection twice weekly for three consecutive weeks and showed reduction of TH-positive neurons in SN<sub>pc</sub> by 40% as compared to saline treated controls (11). They also demonstrated reduced levels of dopamine (DA) and homovanillic acid (metabolite of DA) in the SN<sub>pc</sub> of paraquat treated mice. Apart from the neurotoxic effects of paraquat on SN<sub>pc</sub>, Fei Q *et al.* demonstrated that paraquat induced neurotoxicity acts through a Bak-dependent mechanism as Bak deficient mice were resistant to paraquat induced neurotoxicity (10). Bak is constitutively present on the surface of mitochondria and trigger mitochondrial outer membrane permeabilization. Ultrastructural evidence shows astrocyte oedema, neuron apoptosis in rat brain visualized by electron microscopy (13,14).

Although paraquat elimination in laboratory animals and humans from blood and organs other than brain occurs in hours and days, Prasad K *et al.* (2007) showed that paraquat persists in the ventral mid brain of mice for a prolonged time with a half-life of approximately one month (9). This persistence may contribute to its prolonged adverse effects in the central nervous system.

To see the effect of paraquat in acute poisoning, Magnetic resonance imaging (MRI) has been performed on poisoned survived victims and two patients in acute post poisoning phase have showed abnormal signals in brain. Susceptibility weighted imaging (SWI) has elicited changes in the corrected phase values for the extrapyramidal ganglia of survivors and these values correlate with excessive iron deposition. Diffusion tensor imaging (DTI) has shown microstructural changes in the extrapyramidal ganglia and hippocampus after paraquat poisoning. Therefore neuroimaging has

indirectly demonstrated that acute paraquat poisoning exerts sustained effect during acute and recovery stages of poisoning (15).

Two case reports of facial nerve palsy following subcutaneous (SC) injection of paraquat and ingestion of minute amount of paraquat were found in the literature (16,17). One case report was on a 30 year-old farmer who injected (SC) himself approximately one ml of 20% solution of Gramoxone (16). Two days after, he was admitted to hospital with right facial nerve palsy. His abdominal reflexes were reduced on the right side. Oppenheim's sign (dorsiflexion of the big toe on stroking downwards along the medial side of the tibia, seen in pyramidal tract disease) was present on the left side. On the seventh day of administration of poison the findings were no longer elicited. The patient died on the 18<sup>th</sup> day in severe respiratory distress. The second case report was on a 49 year-old male who had rolled a cigarette with unwashed spray nozzles contaminated with paraquat and four days later developed a right lower motor neuron facial nerve palsy (17). The subsequent cause of the disease was not described and this may be entirely coincidental.

Cerebral haemorrhage following acute ingestion of paraquat has been reported (18,19). Autopsy findings of a 44 year-old male who had ingested 2-3ml of 20% paraquat concentrated solution and died on the sixth day of ingestion showed oedematous brain with purpuric haemorrhage extensively involving the cerebrum, brain stem, cerebellum and spinal cord (18). The maximum diameter of hemorrhagic foci was 5mm and there were no lesions seen in major arteries, veins or sinuses of the brain. The purpuric haemorrhage almost distributed in the white matter of the brain. Nerve fibers around the lesion were distorted and disintegrated to various extents. Glial proliferation was sparse. Degenerative changes were observed in Purkinje cells and granular cells of the cerebellum. The cerebral haemorrhage may be due to direct toxic effects of paraquat or its metabolites and anoxic anoxemia. Saeed S A M *et al.* (2001) also reported an intracerebral bleeding following acute paraquat ingestion (19). The report was based on a 52 year-old male who had ingested about 160 ml of "Weed killer". During the acute illness he developed left hemiparesis and computed tomography (CT) confirmed an intracerebral haematoma in the region

of the right basal ganglia and external capsule. The patient recovered gradually including his neurological features.

Chronic exposure to paraquat is a potential etiological factor for the development of Parkinson's disease (20,21). The paraquat structure bears a close similarity to the Parkinsonian toxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (20). It has been thought that paraquat gains access to dopaminergic neurons through dopamine transporter (22). Repeated doses of MPTP fed mice showed reduction of TH-positive neurons in substantia nigra similar to repeated dose of paraquat fed mice (12).

Peripheral burning sensation following acute paraquat ingestion reported by Gawarammana I.B. and Dawson A.H. may be due to involvement of sensory nerves (23).

In vitro and animal studies clearly show the neurotoxicity of paraquat. Deliberate ingestion of high doses of paraquat may cause neurotoxicity in humans; however detection would not be possible due to lack of survivors. Although it was suggested that chronic paraquat exposure is an etiology of sporadic Parkinson's disease, it is extremely difficult to correlate the two due to the difficulty in identifying the exposure state accurately and confirmation of damage is possible only at postmortem. The neurotoxic effects of acute paraquat exposure on humans have still not been clearly investigated.

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