

## Special Interest Articles:

- Paraquat
- GLP-1 Agonists
- Apadaz



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## Paraquat Poisoning: A Radical Generator

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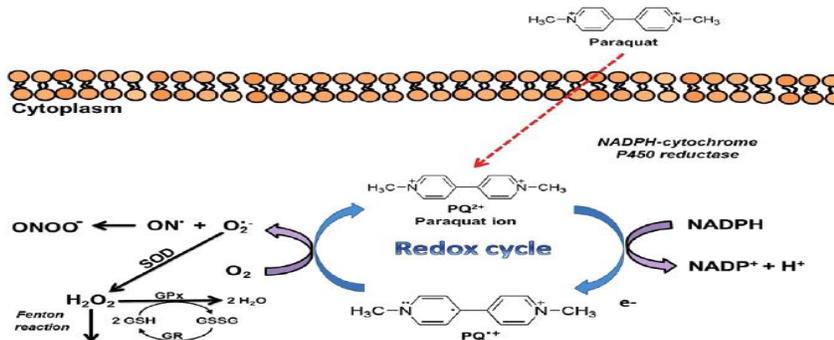
Paraquat, also known as Gramoxone®, is a rapid-acting, non-selective herbicide used primarily for weed and grass control in many agricultural and non-agricultural sites across the United States. It was first introduced in the early 1960's and is one of the most common pesticides used worldwide. Because of the high risk for toxicity and even fatality with only a small sip, the United States Environmental Protection Agency (EPA) classifies paraquat as a Restricted Use Pesticide (RUP), designating that use be limited to individuals and companies who are licensed applicators of the herbicide. It is currently banned for use in the European Union due to its toxic effects if inhaled or ingested<sup>1</sup>.

When used as an herbicide, paraquat is inactivated immediately upon reaching the ground by being tightly bound to soil particles. In the United States, available forms of paraquat are colored with a blue dye and a strong odor with some products containing an emetic agent, in hopes of keeping those who are exposed to the chemical from accidentally ingesting it. Populations most commonly exposed to paraquat are farmers who work regularly with the product.

Paraquat ingestions, accidental or deliberate, are a leading cause of fatal poisoning in many parts of Asia, Pacific nations, and the Americas with an extremely high case-fatality rate<sup>2,3</sup>. The most common and life-threatening exposure is

ingestion, often linked to storage of undiluted paraquat (concentration 30-40%) in smaller unlabeled soda bottles, causing some 17+ people (three cases involving children) since 2000 in the United States to mistake it for a drink, resulting in death. In response to the fatal toxicity of paraquat, the EPA issued new closed-system packaging requirements making it illegal to transfer the product to food, drink, or other containers. Additional types of exposure include dermal, ophthalmic, and inhalation, which have caused three deaths and several severe injuries.

Once paraquat is ingested, it is rapidly absorbed and concentrated in the tissues preferentially in the pneumocytes (which is problematic for the redox cycling because they are the highest exposed tissue to oxygen), reaching maximum concentration in six hours, where it undergoes redox cycling, utilizing paraquat and paraquat radicals. This redox cycling consumes NADPH, one of the body's antioxidant defenses (shown below)<sup>5</sup>. The by-product of the incorporation into the redox cycling is the development of a superoxide radical. This highly reactive oxygen species causes direct cellular damage and produces further nitrite radicals. The free radicals produced create oxidative stress causing cell damage and a secondary inflammatory response<sup>6</sup>. Over the next few hours to days, the ingestion leads to multi-organ failure, starting with the highest blood flow organs (lungs, heart, kidney, and liver)<sup>7</sup>. The brain is excluded because paraquat is unable to cross the blood-brain barrier<sup>8</sup>. (Continued on page 2)



***Paraquat continued from page 1***

Primary elimination is completed by the kidneys, with superoxide radicals leading to slower elimination, extending the half-life to greater than 100 hours<sup>8</sup>

If the patient survives the first 24 hours after a paraquat exposure, the patient may become progressively worse over the next few days to weeks. Prognosis is poor, as none of the current treatments have been proven effective. All ingestions should be evaluated in a hospital setting. Evaluation of dermal and inhalation exposures will depend on the extent of the exposure and symptoms. Because paraquat binds irreversibly to activated charcoal and clays (bentonite or Fuller's earth; these clays are not readily available), their use may be beneficial. Contact the Regional Poison Control Center for dosing of activated charcoal, bentonite, or Fuller's earth. Further treatment options include charcoal hemoperfusion if commenced within 4 hours of ingestion. Anti-inflammatory and immunosuppressive therapy can be utilized with dexamethasone and cyclophosphamide to prevent systemic inflammation. Many antidotes have been proposed, but efficacy and safety are lacking. Anti-oxidant therapy has been studied, but further research is needed. Oxygen therapy is not recommended due to the risk of increased oxygen free radicals, unless there is marked hypoxia and a fatal outcome is imminent. Much of the treatment becomes palliative with poor prognosis, often leading to patients being treated in the outpatient setting with adequate home-care, supplemental oxygen, and medications for pain management. Renal failure often will recover over a few weeks if the patient survives, but lung injury becomes progressively worse with supplemental oxygen therapy and progression of poisoning.

*“If the patient does not die within 24 hours from paraquat exposure, patients become progressively worse over the next few days to weeks.”*

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## Glucagon-Like Peptide-1 Receptor Agonists

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Type 2 diabetes is growing at an astonishing rate. Glucagon-like peptide-1 (GLP-1) receptor agonists mimic the effects of incretin hormone GLP-1 which is released after food intake from the intestine. GLP-1 agonists have benefits other than glucose control including weight loss, decreased blood pressure and cholesterol levels, and positive effects on beta-cell function. Their function also includes increased insulin secretion, decreased glucagon release, increased satiety, and the slowing of gastric emptying.

There are now eight GLP-1 agonists ranging from single-dose pens to multi-dose pens. The first GLP-1 receptor agonist was introduced in the market in 2005. Byetta® (exenatide) is derived from the saliva of the Gila monster, and has 53% similarity to native GLP-1. Exenatide has twice daily dosing. Newer agents with longer half-lives and extended-release formulations have since been developed allowing for once-daily, and even once weekly, dosing.

The newest GLP-1 receptor agonists are Ozempic® (semaglutide) and Bydureon® BCise™ (extended-release exenatide). Both are once-weekly injections. Other GLP-1 agonists include: Trulicity® (dulaglutide), also dosed once-weekly, Victoza® (liraglutide), dosed once-daily, Adlyxin™ (lixisenatide), dosed once-daily, Xultophy® 100/3.6. a once-daily combination of Tresiba® (insulin degludec) and Victoza (liraglutide), and Soliqua® a once-daily combination of Lantus® (insulin glargine) and Adlyxin (lixisenatide). Ozempic has an oral form in the works with plans for regulatory submission in 2019.

Overdose information is limited. The most common adverse effects seen with GLP-1 therapy include nausea, vomiting, and injection-site reactions. Case studies include three patients with type 2 diabetes experiencing severe nausea, vomiting, and hypoglycemia following a dose 10 times the maximum recommended dose with exenatide. Also, two adults developed severe nausea and vomiting following liraglutide injections 10 times the maximum recommended dose. Hypoglycemia did not develop with the liraglutide.

Many of the agents used to treat type 2 diabetes have undesirable adverse effects of hypoglycemia and weight gain. Glucagon-like peptide-1 (GLP-1) receptor agonists represent a unique approach to the treatment of diabetes.

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## Apadaz™- First Hydrocodone Prodrug and Acetaminophen Combo

Laura Read, RPh, CSPI, Regional Poison Control Center

Apadaz is an immediate-release (IR) combination of benzhydrocodone, a prodrug of the opioid agonist hydrocodone, and acetaminophen that was approved by the U.S. Food and Drug Administration (FDA) on February 23, 2018. Apadaz is approved for short-term management (no more than 14 days) of acute pain for which alternative treatments are inadequate. Apadaz is the first prodrug of hydrocodone to receive FDA approval. Benzhydrocodone is hydrocodone covalently bonded to benzoic acid, a widely used food preservative. Intestinal enzymes cleave the benzoic acid from the hydrocodone, thus activating the opioid medication.

Apadaz 6.12 mg/325 mg is equivalent to hydrocodone bitartrate/ acetaminophen 7.5 mg/325 mg and taken every 4-6 hours. Benzhydrocodone is chemically inert on its own.

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