HIGHLIGHTS

Hundreds of products

Names can confuse; check label for composition

Sometimes mixed with fertilizers

Irritate skin, eyes, respiratory & GI systems

Severe metabolic acidosis from ingesting large amounts

SIGNS & SYMPTOMS

Vomiting, diarrhea

Headache, confusion, bizarre or aggressive behavior

Peculiar odor on breath

Body temperature may be elevated

Muscle weakness, peripheral neuropathy, loss of reflexes

TREATMENT

Decontaminate skin, hair, eyes

Consider GI decontamination

IV fluids

Consider urine alkalinization

CHAPTER 10

Chlorophenoxy Herbicides

Several hundred commercial products contain chlorophenoxy herbicides in various forms, concentrations and combinations. In some cases, the same name is used for products with different ingredients. The exact composition must therefore be determined from the product label. Chlorophenoxy compounds are sometimes mixed into commercial fertilizers to control growth of broadleaf weeds. Sodium, potassium and alkylamine salts are commonly formulated as aqueous solutions, while the less water-soluble esters are applied as emulsions. Low molecular weight esters are more volatile than the acids, salts or long-chain esters.

Toxicology

Some of the **chlorophenoxy** acids, salts and esters are moderately irritating to skin, eyes and respiratory and gastrointestinal linings. In a few individuals, local cutaneous depigmentation has apparently resulted from protracted dermal contact with chlorophenoxy compounds.[1]

The chlorophenoxy compounds are well absorbed from the gastrointestinal tract.[2] They are less well absorbed from the lung. Cutaneous absorption appears to be minimal.[3] They are not significantly stored in fat. Excretion occurs almost entirely by way of urine. Apart from some conjugation of the acids, there is limited biotransformation in the body.[2,3] The compounds are highly protein bound.[3] Under normal conditions, the average half-life of **2,4-D** in humans is between 13 and 39 hours,[2,4,6] that of **2,4,5-T** about 24 hours[7] and that of **MCPP** about 17 hours.[8] However, half-life varies markedly with urinary pH, with excretion being greatly enhanced in an alkaline urine,[4,6,9] and with a half-life as prolonged as 70-90 hours with acidic urine.[9] Half-life is also longer with large doses and prolonged exposure.

A unique finding in a recent study is that chlorophenoxy herbicides, particularly 2,4-DP, 2,4-D and MCPP, inhibit the human taste receptor for sweets. Interestingly, this was not found in animal studies. While not necessarily a toxic effect, this finding could potentially be of use in diagnosing a poisoning from one of these herbicides.[10]

Ingestion of large amounts of chlorophenoxy acids has resulted in severe metabolic acidosis in humans. Such cases have been associated with electrocardiographic changes, myotonia, muscle weakness, myoglobinuria and elevated serum creatine phosphokinase, all reflecting injury to striated muscle. The medical literature contains a few reports of peripheral neuropathy, some following dermal exposures to 2,4-D[11,12,13] and another following ingestion.[14] Chlorophenoxy acids are weak uncouplers of oxidative phosphorylation; therefore, extraordinary doses may produce hyperthermia from increased production of body heat.[6]

In the manufacture of some of these herbicides, other more toxic substances can be formed at excessive temperatures. These include **chlorinated dibenzo dioxin (CDD)** and **chlorinated dibenzo furan (CDF)**. The 2,3,7,8-tetra CDD form is extraordinarily toxic to multiple mammalian tissues; it is formed only in the synthesis of 2,4,5-T. However, 2,3,7,8 tetra CDD has been found as a contaminant in samples of 2,4-D, 2,4-DB and MCPA.[15] These byproducts are discussed in **Chapter 21, *Chronic Effects***. Chloracne (a chronic, disfiguring skin condition) has been seen in workers engaged in

the manufacture of 2,4,5-T and certain other chlorinated organic compounds, although it is thought to be related to the resulting 2,3,7,8-tetra CDD exposure as opposed to acute 2,4-D or 2,4,5-T toxicity. Although chloracne along with other dermal effects has been reported in an herbicide applicator,[16] it has not been reported in other occupational exposures except the manufacture of these agents.

Signs and Symptoms of Poisoning

Human poisoning from chlorophenoxy compounds was reviewed in detail in 2000.[17] In a large case series resulting from intentional self-poisoning from MCPA, most patients (85%) had minimal signs of poisoning, with mild gastrointestinal symptoms being the most commonly reported.[18] Other non-specific, mild findings from the California pesticide illness surveillance system include nausea, abdominal pain, headache, generalized weakness and dizziness.[19]

Manifestations of systemic toxicity of chlorophenoxy compounds are known mainly from clinical experience with cases of deliberate suicidal ingestion of large quantities. While most clinical reports involve exposure to 2,4-D and mecoprop, it is reasonable to assume that all chlorophenoxy herbicides will share a similar clinical picture. Most reports of fatal outcomes involve renal failure, acidosis, electrolyte imbalance and a resultant multiple organ failure.[5,9,20] The agents most often involved in these incidents have been 2,4-D and mecoprop.

Patients will present within a few hours of ingestion with vomiting, diarrhea, headache, confusion and bizarre or aggressive behavior. In a large case series resulting from intentional self-poisoning from MCPA, most patients (85%) had minimal signs of poisoning, with mild gastrointestinal symptoms being the most commonly reported.[18] Mental status changes occur, with progression to coma in severe cases.[4,6,9,18] Moderate cerebral edema has also been reported following intentional ingestion.[21] A peculiar odor is often noticed on the breath. Body temperature may be moderately elevated, but this is rarely a life-threatening feature of the poisoning. The respiratory drive is not depressed. Conversely, hyperventilation is sometimes evident, probably secondary to the metabolic acidosis that occurs. Convulsions occur very rarely. With effective urinary excretion of the toxicant, consciousness usually returns in 48-96 hours.[4,6,9]

Muscle weakness and peripheral neuropathy have been reported after occupational exposure.[9] The presentations are variable. Myotonia and muscle weakness may persist for months after acute poisoning.[6] Additional findings include loss of reflexes and fasciculation.[4,6,8,20] Electromyography and nerve conduction studies in some recovering patients have demonstrated a mild proximal neuropathy and myopathy.

As mentioned above, there are significant metabolic changes from the chlorophenoxy compounds. Metabolic acidosis is manifest as a low arterial pH and bicarbonate content. The urine is usually acidic. Skeletal muscle injury, if it occurs, is reflected in elevated creatine phosphokinase and, sometimes, myoglobinuria. Moderate elevations of blood urea nitrogen and serum creatinine are commonly found as the toxicant is excreted. Cases of renal failure are reported, often with an accompanying hyperkalemia or hypocalcemia, and were thought to result in the cardiovascular instability that led to death.[5,20] Tachycardia is commonly observed and hypotension has also been reported.[4,5,9] T-wave flattening has also been observed.[6] Mild leukocytosis and biochemical changes indicative of liver cell injury have been reported.

COMMERCIAL PRODUCTS

2,4-D or 2,4-dichlorophenoxyacetic acid

2,4-DP or 2,4-dichlorophenoxypropionic acid (Dichlorprop)

2,4-DB, or 2,4-dichlorophenoxybutyric acid

2,4,5-T, or 2,4,5-trichlorophenoxy acid

4-chloro-2-methyl-phenoxyacetic acid (MCPA)

MCPB

MCPP (Mecoprop)

2-methyl-3, 6 dichlorobenzoic acid (Dicamba)

Confirmation of Poisoning

Gas-liquid chromatographic methods are available for detecting chlorophenoxy compounds in blood and urine. These analyses are useful in confirming and assessing the magnitude of chlorophenoxy absorption. Poisoning episodes characterized by unconsciousness have shown initial blood chlorophenoxy concentrations ranging from 80 to more than 1,000 mg per liter.[4] Urine samples should be collected as soon as possible after exposure because the herbicides may be almost completely excreted in 24-72 hours in most cases. Urine samples can also confirm overexposure. In a study of asymptomatic herbicide applicators, their urinary excretion of chlorophenoxy compounds rarely exceeded 1-2 mg/L.[22] The half-life may be much longer in cases of intoxication depending on the extent of absorption and urine pH. Analyses can be performed at competent laboratories, usually known to local poison control centers. If the clinical scenario indicates that excessive exposure to chlorophenoxy compounds has occurred, initiate appropriate treatment measures immediately, not waiting for chemical confirmation of toxicant absorption.

Treatment of Chlorophenoxy Toxicosis

1. Decontaminate skin and hair by bathing with soap and water and shampooing. Individuals with chronic skin disease or known sensitivity to these herbicides should either avoid using them or take strict precautions to avoid contact (respirator, gloves, etc.).

2. Flush contaminating chemicals from eyes with copious amounts of clean water for 10-15 minutes. If irritation persists, an ophthalmologic examination should be performed.

3. If any symptoms of illness occur during or following inhalation of spray, remove victim from contact with the material for at least 2-3 days. Allow subsequent contact with chlorophenoxy compounds only if effective respiratory protection is practiced.

4. Consider gastric decontamination procedures as outlined in **Chapter 3, *General Principles*.** If substantial amounts of chlorophenoxy compounds have been ingested, spontaneous emesis may occur.

5. Administer intravenous fluids to accelerate excretion of the chlorophenoxy compound and to limit concentration of the toxicant in the kidney. A urine flow of 4-6 mL/minute is desirable. Intravenous saline/dextrose has sufficed to rescue comatose patients who drank 2,4-D and mecoprop several hours before hospital admission.

   CAUTION: ***Monitor urine protein and cells, BUN, serum creatinine, serum electrolytes and fluid intake/output carefully to ensure that renal function remains unimpaired and that fluid overload does not occur.***

6. Alkalinize the urine to maintain a pH between 7.6 and 8.8. Urinary alkalinization has been used successfully in management of suicidal ingestions of chlorophenoxy compounds, especially when initiated early.[4,6,9] Although the term "forced alkaline diuresis" has been used previously to describe this treatment, the preferred terminology is now "urinary alkalinization" to emphasize the impor-

tance of urine pH manipulation for clearing the weak acid.[23] Alkalinizing the urine by including sodium bicarbonate (44-88 mEq per liter) in the intravenous solution accelerates excretion of 2,4-D and mecoprop excretion substantially, because the weak acid is in an ionized state in the renal tubule and thus cannot diffuse back across the tubule into the blood. Renal clearance is minimal at an acidic pH of 5.1 (0.14 mL/min) compared to clearance at a pH of 8.3 (63 mL/min).[6,23]

Controversy and lack of controlled clinical studies exist surrounding the most effective way to induce clearance of 2,4-D and mecoprop. The AACT and EAPCCT position paper recommends that urine alkalinization and high urine flow (forced diuresis) be considered.[23] A Cochrane Database of Systemic Reviews notes the lack of evidence, based on the lack of randomized, controlled trials for this treatment. The author concluded that it is "not unreasonable to attempt urinary alkalinization" given the prolonged toxicity and potential for death, and that, "well conducted randomized, controlled trials are required."[24] No patients in a large case series reported by the same author as the Cochrane Review article were treated with urinary alkalinization, although it should be noted that 85% showed signs of minimal toxicity.[18]

7. Include potassium chloride as needed to offset increased potassium losses, with 20-40 mEq of potassium chloride to each liter of intravenous solution. High urine flow, approximately 200 mL/h, improves clearance, although an even higher flow rate may be required for maximal 2,4-D clearance.[6,23] Renal failure has occurred in patients with severe intoxication despite urinary alkalinization. In one case of renal failure, the urinary alkalinization was begun 26 hours after ingestion,[9] and in another it was initiated on day 2 of the hospitalization.[20] Therefore, it is crucial to carefully monitor renal function, as well as serum electrolytes, especially potassium and calcium.

8. Consider hemodialysis in severe cases, particularly where excess fluid administration is not advised.[17] Hemodialysis has been used in four patients who survived intoxication.[25] It is not recommended as first-line therapy.

9. Include electromyography and nerve conduction studies in the follow-up clinical examination to detect any neuropathic changes and neuromuscular junction defects.

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