Review Article

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A Narrative Review of Contemporary Lethal Pesticides: Unveiling the Ongoing Threat of Pesticide Poisoning

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ABSTRACT

Following the 2011 ban on paraquat sales, South Korea has witnessed a significant reduction in the mortality rate associated with acute pesticide poisoning (1). Traditionally, paraquat and diquat, alongside several highly toxic organophosphates, carbamates, and organochlorine insecticides, have been recognized as culprits in causing fatalities among patients with acute pesticide poisoning (2,3). However, despite global efforts to curtail the use of these highly toxic pesticides, certain pesticides still exhibit a level of lethality surpassing their established clinical toxicity profiles (1-6). Understanding the clinical progression of these pesticides is paramount for physicians and toxicologists, as it holds the potential to enhance patient prognoses in cases of acute poisoning. This review aims to address the persistence of such highly lethal pesticides, which continue to pose a grave threat to victims of acute poisoning.

Keywords: Chorfenapyr, Bentazon, Glyphosate, Glufosinate, Intoxication

What is already known

Despite global efforts to curtail the use of these highly toxic pesticides, certain pesticides still exhibit a level of lethality surpassing their established clinical toxicity profiles.

What is new in the current study

Understanding the clinical progression of potentially lethal pesticides is paramount for physicia ns and toxicologists, as it holds the potential to enhance patient prognoses in cases of acute poisoning. This review would unveil the persistence of such highly lethal pesticides, which co ntinue to pose a grave threat to victims of acute poisoning.

1. Chlorfenapyr

Chlorfenapyr is an insecticide, derived from halogenated pyrroles produced by *Streptomyces spp*.. Its acute toxicity, following ingestion, is categorized as Toxicity category class I (mild toxicity) in mice (Lethal dose, LD50, of 45mg/kg) and class II (moderate toxicity) in rats (LD50 of 441mg/kg) (7,8). In humans, chlorfenapyr intoxication can be fatal and is associated with distinctive clinical and neuroradiological features (9-15).

Mechanisms of toxicity

Chlorfenapyr acts as a pro-insecticide that must undergo conversion through oxidative removal of the N-ethoxymethyl group by the microsomal monooxygenase system of target insects to produce the toxic metabolite tralopyril (16). Tralopyril, identified as the most toxic metabolite in animal studies, has an oral LD50 of 27 mg/kg in male rats (17). Possessing both lipophilic and acidic properties, tralopyril exerts its lethal effects on insects and rodent cells by causing mitochondrial uncoupling (8,18). In insect studies, inhibition of microsomal monooxygenase by the specific inhibitor pyperonyl butoxide significantly reduced the potency of chlorfenapyr, but not tralopyril (19,20). The detergents in pesticides may enhance gastrointestinal absorption of chlorfenapyr, as indicated in animal studies (21). However, knowledge regarding the pharmacokinetics of chlorfenapyr and tralopyril in mammals remains limited.

Radiologically, the involvement of the entire white matter tract is a characteristic finding, consistent with previous reports (9-11). Rats with chlorfenapyr intoxication revealed vacuolar myelinopathy and myelin sheath swelling in neurohistopathological examinations (7). Similar pathological changes in myelin and white matter necrosis have been observed in autopsies of patients with toxic leukoencephalopathy (11,14). These findings suggest that chlorfenapyr may damage the white matter of the central nervous system (CNS), resulting in neurological symptoms and signs such as blurred vision, optic neuropathy, urinary incontinence, altered mental status, seizure, and paraplegia (10-13).

Clinical features

Toxic symptoms and signs of acute chlorfenapyr poisoning include fever, diaphoresis, general fatigue, blurred vision, psychological effects, pancreatitis, and rhabdomyolysis (10, 22-25). Following oral ingestion, patients typically exhibit self-limited vomiting, diarrhea, a subjective feeling of heat, and diaphoresis within 1–14 days post-exposure (10,26,27). Restlessness and confusion may appear 4–18 days after exposure (25,28,29). High body temperature or hyperthermia (> 39°C), observed at 5–19 days post-exposure, often indicates a poor prognosis (15,30-32). Hence, heightened vigilance is essential in cases of hyperthermia (> 39°C) associated with acute chlorfenapyr poisoning, irrespective of the onset timing. The reported minimal lethal dose for oral administration stands at 10 mL of 10% chlorfenapyr in a 13-year-old girl, with a median time to death averaging 10 days (ranging from 5 to 20 days) (26,32,33). Notably, inhalation and skin contact exposure can also result in severe poisoning. For instance, a 55-year-old man involved in farming work died on day 7 shortly after spraying a diluted chlorfenapyr solution (125 mL at 10% in 500 L of water) and developing fever and seizures (34). A 49-year-old man showed various neurological toxic symptoms and signs from 1day after skin contact with a 10% chlorfenapyr solution on his arm, chest, and abdomen (28). Lee et al. (35) reported a 74-year-old male who passed away 12 days after self-injection with 20 mL of chlorfenapyr into his abdomen. The main toxic symptoms and signs and the clinical progress have been summarized in Figure 1.

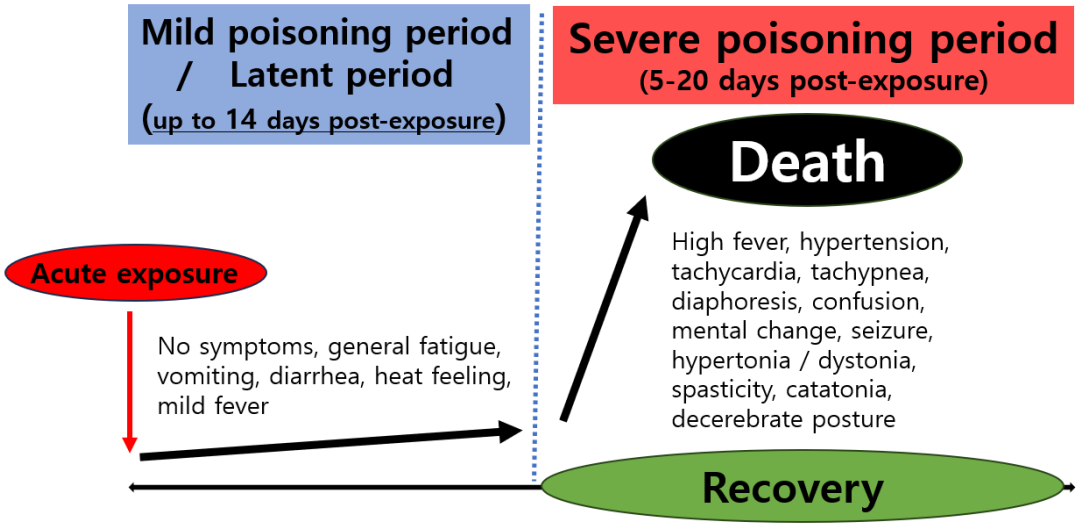

Figure 1. Clinical course of acute chlorfenapyr poisoning

In the clinical course of acute chlorfenapyr poisoning, the following should be noted: 1) the potential for fatality "even with minimal exposure", 2) the possibility of "life-threatening delayed injury" occurring after the resolution of non-specific acute poisoning, 3) the extension of this "latent period" to approximately 14 days post-exposure

Management

There are no well-established specific treatments beyond fundamental measures, such as administering activated charcoal and, if necessary, performing gastric lavage. Conservative treatment should be tailored to the patient's symptoms and clinical signs. Furthermore, it is important to exercise caution regarding the potential occurrence of secondary poisoning among healthcare providers due to contact or exposure while treating poisoned patients.

Extracorporeal removal methods may be considered due to the small molecular weight of chlorfenapyr (407.6 Da), allowing it to readily cross cellular membranes (19,20). However, the lack of comprehensive data regarding other physiochemical properties of chlorfenapyr in humans, such as protein binding, volume of distribution, and lipid solubility, hinders the justification for the use of extracorporeal removal methods. Nevertheless, considering the latest clinical reports, timely elimination of the toxicant and early organ function support can significantly enhance the prognosis. Therefore, intermittent hemodialysis (IHD) or Continuous renal replacement therapy (CRRT) can be undergone deliberately at the charged physician's discretion (27,36). It's crucial for healthcare providers to recognize that all patients exposed to chlorfenapyr, even in cases of dermal exposure, carry a potential risk of a relentless course and mortality (28). Therefore, while the reasons for varying clinical courses among patients remain unclear, extended in-hospital observation of individuals with chlorfenapyr intoxication is imperative. Lastly, considering the documented cases to date, close attention should be paid to the potential occurrence of delayed toxic symptoms following the initial alleviation of acute poisoning symptoms. Proactive treatment for such delayed toxic symptoms is strongly recommended. Regarding the management of significant hyperthermia, a standardized treatment protocol for effectively managing significant hyperthermia has not been explicitly reported. Muscle relaxants, such as benzodiazepines, and neuroleptic agents like chlorpromazine, have been utilized to mitigate shivering and act as a preventive measure against seizures. However, the uncertainty surrounding their efficacy stems from the absence of clinical trials. Dantrolene sodium has not proven effective in reducing core

temperature. Although antipyretic agents theoretically hold promise in addressing the acute phase reactant response, their specific evaluation for this purpose remains inadequately explored. Active cooling methods, encompassing cold packs or ice packs, cooling blankets, evaporative cooling, and intravenous (IV) cold saline, are considered potential strategies to facilitate temperature reduction. In exigent circumstances, the contemplation of Therapeutic Hypothermia (TTM) utilizing cooling devices may also be warranted.

2. Bentazon(e)

Bentazon(e) is a selective contact herbicide and is classified as a moderately hazardous (class II) herbicide by the World Health Organization (37,38).

Mechanisms of Toxicity

In a rat model, bentazon(e) was rapidly absorbed and mostly excreted in the urine (37). An hour after its oral administration, it was distributed to the stomach, liver, kidneys, and heart of the rat, but not to its brain or spinal cord (37,38). The substance was metabolized to 6-OH bentazon(e) and 8-OH bentazon(e) through hydroxylation (38,39). The LD50 was 1,100 mg/kg in rats and 2,918 mg/kg in pheasants (38,39). Bentazon(e) was rapidly absorbed in and distributed to the stomach, liver, kidneys, and heart. Limited information regarding the toxicokinetics of bentazon(e) in humans suggests rapid and extensive absorption following oral administration, with significant excretion in the urine, primarily in its unchanged form (37). Its mechanism of action in humans is unknown, although the clinical features of poisoning suggest that bentazon(e) may uncouple oxidative phosphorylation. It is likely that co-formulants will be responsible for some of the toxic effects of some products.

Clinical Features

The toxic symptoms and signs of acute bentazon(e) poisoning include sweating, hyperpyrexia, nausea, vomiting, diarrhea, abdominal pain, cough, tachypnea, dyspnea, apnea, tachycardia, mental change, neurological abnormalities including agitation, talking nonsense, and loss of consciousness, muscle rigidity, rigor mortis, and cardiac arrest (39-45). Although bentazon(e) is known not to cross the blood-brain barrier (BBB) in rats, neurological toxic signs and symptoms in acute bentazon(e) poisoning suggest that it may do so after consumption of large amounts. Limb rigidity was a prominent feature in severely intoxicated patients. Limb rigidity, rhabdomyolysis, hyperpyrexia, and elevated levels of AST and ALT might misdiagnose acute bentazon(e) poisoning as neuroleptic malignant syndrome (NMS) (40). Notably, the emerging pattern of fetal bentazon(e) poisoning is that the time required for the onset of features may be less than 1 hour and that death may result within as little as 2 hours. In such cases, jaw rigidity commonly occurs. The main toxic symptoms and signs and the clinical progress have been summarized in Figure 2

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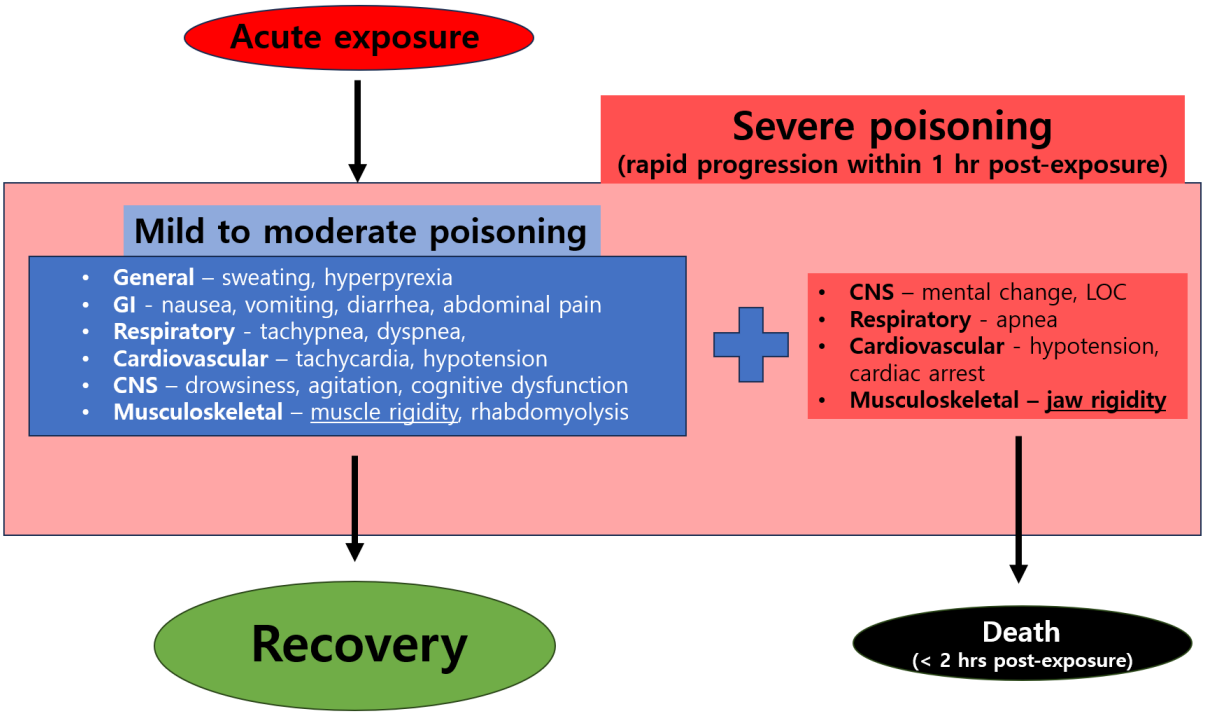

Figure 2. Clinical course of acute bentazon(e) poisoning

In the clinical course of acute bentazon(e) poisoning, the following should be noted: 1) the occurrence of musculoskeletal rigidity, 2) a very rapid progression to deterioration in cases of severe, life-threatening poisoning, 3) the development of jaw rigidity unresponsive to muscle relaxants in severely poisoned patients

Management

If the patient seeks medical attention within 1 hour of ingestion, gastric lavage is performed, and activated charcoal should be administered. Activated charcoal administration can help treat up to several hours after exposure. Furthermore, it is important to exercise caution regarding the potential occurrence of secondary poisoning among healthcare providers due to contact or exposure while treating poisoned patients. There's no specific antidote for acute bentazon(e) poisoning. The management of acute bentazon(e) poisoning is symptomatic and supportive. As illustrated in Figure 2, severe poisoning advances rapidly and is frequently accompanied by trismus. Thus, in scenarios where severe poisoning is anticipated, proactive preparation for airway management is crucial. Laboratory work-up and the ECG results should be monitored. Dantrolene sodium may be administered if muscle rigidity is severe. In cases of hypotension and loss of consciousness, crucial interventions encompass fluid resuscitation with vasopressor administration and respiratory support, including endotracheal intubation. The muscle relaxant succinylcholine might be ineffective against muscle rigidity in acute bentazon(e) poisoning, therefore, cricothyroidotomy should be needed to keep the airway open (44).

3. Glyphosate surfactant herbicide (G-SH)

It is a non-selective wide range herbicide that inhibits the sikimic acid pathway and has been widely used worldwide since its development in 1970 (46). It is mainly sold as a roundup, and glyphosate-based herbicides (GHB) are also sold a lot (47). Glyphosate isopropylamine or ammonium salts are commonly used as active ingredients, and many products also contain polyoxyethylene amine (POEA) as one of the surfactants (4,48-50). POEA often leads to harm in individuals who have been poisoned in the acute poisoning Therefore, whether POEA was used as an adjuvant in patients with acute G-SH poisoning is crucial for their treatment and prognosis prediction (48,50,51).

Mechanisms of toxicity

Ingestion of surfactants would result in causing hemodynamic changes with decreased total vascular resistance (52). Therefore, the mechanism of G-SH toxicity appears to be related to the absorption and decomposition of surfactants containing POEA. In rodents, the oral LD50 of Glyphosate is greater than 5g/kg (50). However, the LD50 of POEA is 1-2g/kg. Due to this toxicity, a notable aspect of acute G-SH poisoning is that while toxicity symptoms caused by glyphosate alone are mild, the co-formulant POEA used as an adjuvant becomes the primary cause of intoxication injury (51).

Clinical features

Symptoms and signs of acute G-SH poisoning can vary based on the type and level of exposure, but they might include 1) gastrointestinal system – oropharyngeal irritation and nausea, vomiting, abdominal irritation and pain, diarrhea, hemorrhagic gastritis, elevated hepatic enzyme, esophageal perforation, and pyloric stenosis, 2) pulmonary system - dyspnea, pulmonary congestion, pulmonary edema, and aspiration pneumonia, 3) cardiovascular system - hypotension, shock, first-degree heart block, ST-T wave change, and cardiac arrest, 4) renal system – oliguria and AKI, 5) others - skin irritation, hyperkalemia, hemolysis, mental change, seizures and coma in severe cases (46,53-63). Seeking immediate medical attention is crucial in cases of suspected G-SH poisoning, as symptoms can escalate swiftly. The main toxic symptoms and signs and the clinical progress have been summarized in Figure 3.

Considering that the severity of toxicity progresses based on the extent of adjuvant absorption, it is conjectured that the degree of systemic toxicity is closely related to the prognosis of the patient with acute G-SH poisoning. Toxic signs or diagnoses related to acute G-SH poisoning such as acute kidney injury, hypotension, and severe metabolic acidosis reflect the worsening of severe poisoning, thus requiring special attention in the management of these kinds of patients (62,64). Additionally, although not explicitly included in Figure 3, it is known that the prognosis for elderly has poor prognosis.

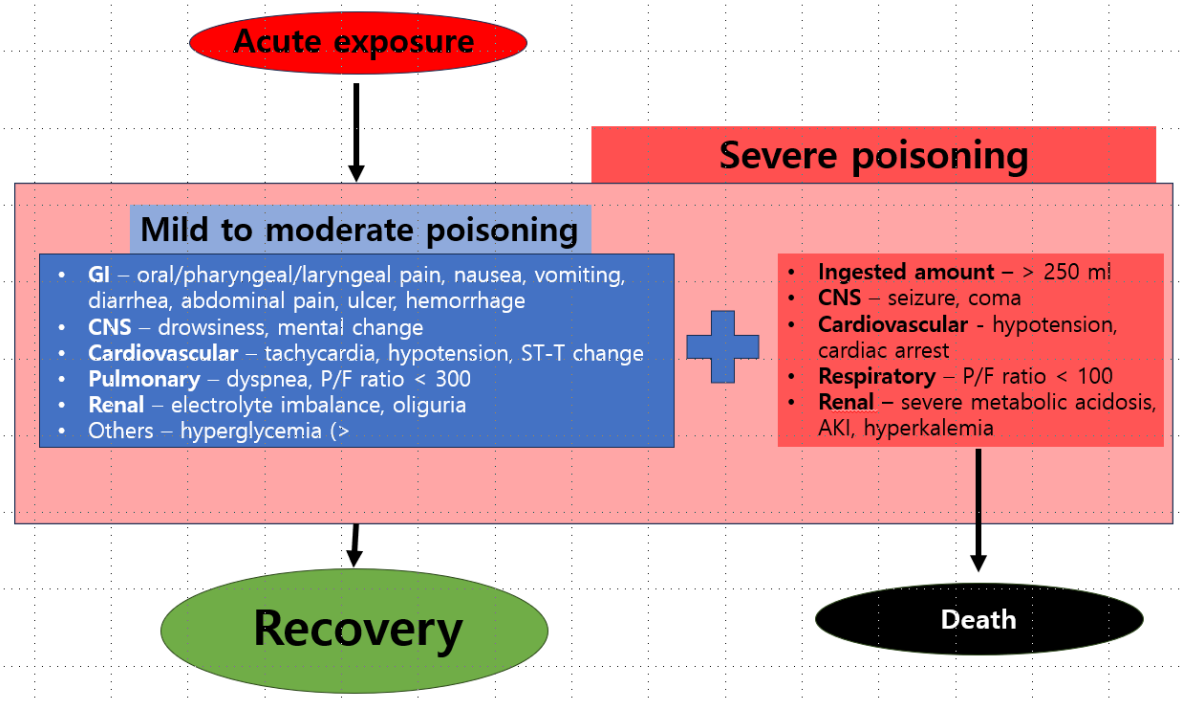

Figure 3. Clinical progress of acute G-SH poisoning

In the clinical course of acute G-SH poisoning, a large amount of ingestion (> 250ml), seizure, coma, hypotension, cardiac arrest, P/F ratio less than 100, severe metabolic acidosis, acute kidney injury, and hyperkalemia suggest severe poisoning, which will be likely to show poor prognosis.

Management

If the ingested amount is more than one sip (0.5 ml/kg) of a typical product containing 41% or higher glyphosate concentration, it is necessary to observe them for a minimum of 24 hours (53,65). If the patient seeks medical attention within 1 hour of ingestion, gastric lavage is performed, and activated charcoal should be administered. Activated charcoal administration can help treat up to several hours after exposure. Furthermore, it is important to exercise caution regarding the potential occurrence of secondary poisoning among healthcare providers due to contact or exposure while treating poisoned patients. There's no specific antidote for glyphosate poisoning. Therefore, treatment typically involves supportive care, such as keeping breathing and cardiac function proper, as well as administering medications to manage symptoms. Recently, Intravenous Lipid Emulsion (ILE) has emerged as a potential antidote for moderate to severe poisoning and may be administered based on the charged physician's discretion (66-68). The mortality rate varies among reported cases but generally falls within the range of 7.5% to 16.1% (47,53). After the active rescue, scar contractures occurred in both the esophagus and trachea, which will need reconstruction surgery (69). In cases involving a drop in blood pressure or loss of consciousness, essential measures include fluid resuscitation, which entails vasopressor administration, and respiratory support, including endotracheal intubation. If renal function remains normal after ingestion, elimination through the kidneys is a viable option. In instances of acute kidney injury, moderate to severe metabolic acidosis, pulmonary edema, hyperkalemia, a large amount of ingestion, and severe cardiovascular dysfunction or when these conditions are anticipated, extracorporeal removal methods such as IHD or CRRT or extracorporeal membrane oxygenation (ECMO) become necessary (64,70,71). When the ingestion is attributed to a product containing Glyphosate potassium, there is an increased risk of hyperkalemia, necessitating potassium level

monitoring (72). While explicit research on long-term complications or sequelae following recovery from acute poisoning is nearly lacking, caution is warranted regarding potential complications, including esophageal stricture and cancer development, carcinogenicity in the kidneys and liver, and the onset of degenerative neurological disorders.

4. Glufosinate ammonium herbicide (GAH)

Glufosinate ammonium is a herbicide commonly used to control weeds and unwanted vegetation. It works by inhibiting an enzyme that is crucial for plant growth, but it can also be harmful to humans if ingested, inhaled, or comes into contact with the skin or eyes. GAH commercially available in South Korea does not contain sodium polyoxyethylene alkyl ether sulfate (AES) as the surfactant (4). The LD50 in rats is 1.66 g/kg, and due to relatively rapid absorption through the gastrointestinal tract, it reaches peak blood concentration within one hour (73). When absorbed in combination with surfactants, it is absorbed approximately 25-30% more (73). In humans, the acute oral LD50 is 1.6-1.8 mg/kg (74). Over 90% of the absorbed compound is eliminated through the kidneys, and when renal function is maintained normally, approximately 97% of the compound is eliminated within 24 hours (73-75).

Mechanisms of toxicity

Gastrointestinal irritation and damage may occur due to the surfactants, and CNS toxicity is suspected to be attributed to N-methyl-D-aspartate (NMDA) receptor activation and a decrease in gamma-aminobutyric acid (GABA) (4,76-79). Glufosinate ammonium is a compound with high hydrophilicity and high polarity, making it challenging to penetrate the intact BBB (73). However, glufosinate has been detected in the brains of acute glufosinate poisoning patients. Typically, brain glufosinate concentrations are about one-third of the plasma concentration. When AES is used as a surfactant, caution is warranted because it can lead to significant hemodynamic changes, including vasodilation, and direct cardiac suppression at high concentrations, increasing the risk of cardiovascular complications (80).

Clinical features

Toxic symptoms and signs of acute GAH poisoning can vary depending on the route and extent of exposure, but they may include nausea, vomiting, diarrhea, abdominal pain, difficulty breathing, dizziness, headache, and in severe cases, seizures, loss of consciousness, diabetic insipidus, and apnea (81-87). Immediate medical attention is crucial when there is suspicion of acute moderate to severe GAH poisoning, as toxic symptoms and signs can rapidly worsen in severity. It's important to note that even in cases where patients with acute GAH poisoning present with an alert mental status or a normal level of GCS upon admission to the ED, severe poisoning or fatality remains a possibility. Brain lesions secondary to acute poisoning are commonly found in the splenium of the corpus callosum, bilateral posterior limbs of the internal capsule, bilateral cerebellar peduncles, bilateral cerebral peduncles of the midbrain, and the hippocampus. Fig. 4. outlines the clinical progress of acute GAH poisoning.

Hyperammonemia

In the process of GAH decomposition, ammonia is often produced, leading to elevated plasma ammonia levels in acute GAH poisoning cases. However, for CNS toxicity to occur in moderate to severe GAH poisoning, I believe that GAH or its metabolic byproducts must breach the BBB. Moderate to severe poisoning symptoms seem to emerge when GAH crosses the BBB due to overdose or other mechanisms. Predicting fatal CNS toxicity solely based on initial blood ammonia levels measured upon the ED admission, except in cases with exceptionally high levels (at least >100 μg/dL), is challenging (88). As previously mentioned, in acute GAH poisoning, severe CNS toxicity symptoms and signs likely result from the stimulation of NMDA receptors by GAH or related metabolic products that have crossed the BBB. Additionally, exceptionally high plasma ammonia levels upon the ED admission may indicate a large amount overdose of GAH or suggest specificity in GAH metabolism, warranting consideration of such factors. Therefore, while an increase in blood ammonia levels upon the ED admission may suggest exposure to a certain degree of overdose, accurately predicting severe CNS toxicity is challenging compared to other contributing factors. Given the previous diverse findings and perspectives on the

influence of hyperammonemia in the development of neurological toxicity and its role in the progression and prognosis of acute GAH poisoning, it is recommended to interpret the above information in light of these considerations. The main toxic symptoms and signs and the clinical progress have been summarized in Figure 4.

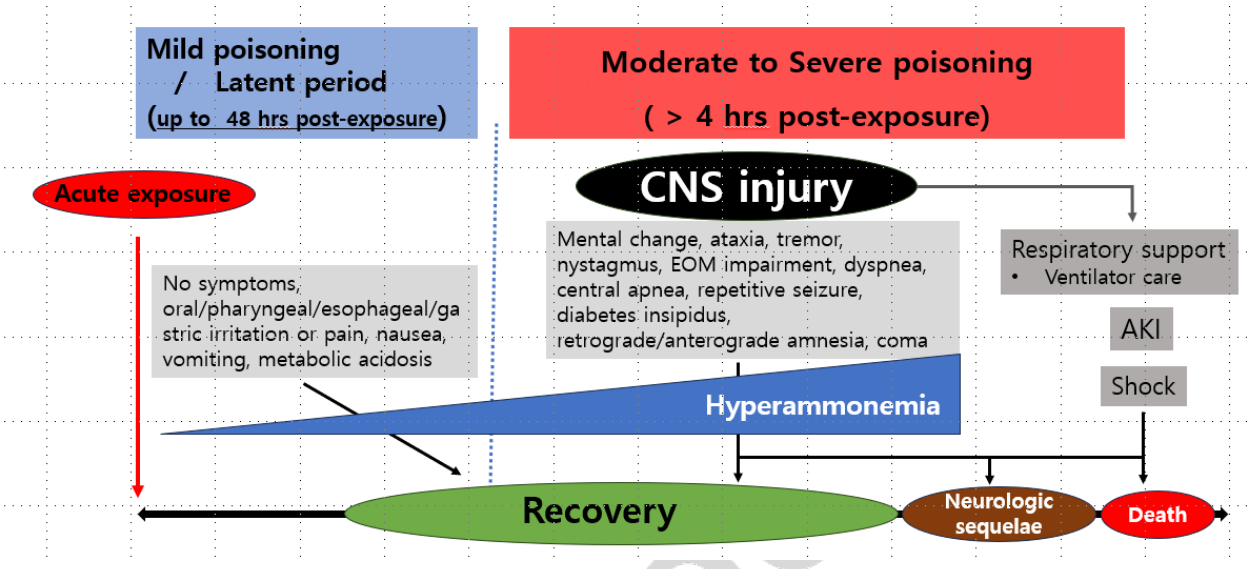

Figure 4. Clinical progress of acute GAH poisoning

In the clinical course of acute GAH poisoning (85,86,89-94), the following should be noted: 1) "Frequent elevation of plasma ammonia levels" from the early phase of poisoning, 2) The presence of "various CNS toxic symptoms and signs", necessitating critical care support in moderate to severe poisoning, 3) The potential for "a latent period up to 48 hours" following GAH exposure

Management

If the patient seeks medical attention within 1 hour of ingestion, gastric lavage is performed, and activated charcoal should be administered. Activated charcoal administration can help treat up to several hours after exposure. Furthermore, it is important to exercise caution regarding the potential occurrence of secondary poisoning among healthcare providers due to contact or exposure while treating poisoned patients. There's no specific antidote for acute GAH poisoning. Therefore, treatment typically involves supportive care, such as keeping breathing and cardiac function proper, as well as administering medications to manage symptoms. In cases where hypotension, loss of consciousness, or breathing difficulty occurs, fluid resuscitation including the administration of vasopressors and inotropic agents, and respiratory support, which includes endotracheal intubation, is necessary. At the discretion of the attending physician, IHD or CRRT may be administered in the early stages of acute poisoning to reduce plasma levels of GAH (95). However, the effectiveness of these interventions in preventing severe complications, such as seizures and respiratory arrest, remains uncertain (82, 95, 96). Additionally, considering that the renal clearance of GLA is 1.6–1.8 times larger than that of HD, it is recommended to limit HD to patients experiencing the early phase of serious toxic symptoms or those with acute kidney injury. As of now, there is no evidence supporting the administration of ILE as a potential therapeutic agent in cases of acute GAH poisoning.

Even though the blood ammonia concentration in patients with acute GAH poisoning may not accurately reflect the CNS ammonia level, it is necessary to monitor the plasma ammonia level from the ED admission (88,97-99). This is because changes in plasma ammonia concentration can provide

some estimation of the worsening or improvement of CNS toxicity symptoms in acute GAH poisoning (79,100). Therefore, it is believed that monitoring this can help assess the severity of patients with acute GAH poisoning regardless of the occurrence of CNS toxicity. Clear treatment guidelines for managing hyperammonemia in patients with acute GAH poisoning have not been reported. However, given that elevated ammonia levels can lead to changes in consciousness, cognitive function, ataxia, seizures, and even coma, treatment is deemed necessary. Non-absorbable disaccharides (lactulose, a notable example composed of the monosaccharides fructose and galactose) are considered the primary therapeutic approach for hyperammonemia. Rifaximin has emerged as the most effective antibiotic for hyperammonemia treatment due to its safety, efficacy, and tolerability. Additionally, sodium benzoate contributes to reducing blood ammonium levels by inhibiting glycine metabolism in the liver, kidney, and brain. Lastly, it's crucial to note that early symptoms or ammonia test results have limitations in predicting severity in cases of acute GAH poisoning (101). Hence, closely monitoring patients for at least 48 hours after GAH exposure appears essential. Recovery from an acute poisoned state to everyday life may be prolonged. While explicit research on long-term complications or sequelae following recovery from acute poisoning is nearly lacking, caution is warranted regarding potential complications, including reversible amnesia, prolonged overall cognitive dysfunction, psychotic features, and other neurolopsychological sequelae.

5. The others

The following substances in Korea have been discontinued due to their high fatality in cases of acute poisoning, but they continue to be used due to their utility as pesticides. Therefore, proper disposal and handling of existing stocks are crucial to prevent accidental exposures.

1) Methomyl

Methomyl is a highly toxic carbamate insecticide commonly used to control a wide range of insects on crops, vegetables, and ornamental plants. It is known for its rapid action against pests, making it effective but also potentially dangerous to humans and other non-target organisms. Regarding acute methomyl poisoning, it is important to note that liquid formulations may contain methanol as a surfactant (102). Additionally, severe and rapidly occurring symptoms, such as altered consciousness, should be closely monitored. In South Korea, methomyl was discontinued from sale and distribution in 2012. However, products containing thiocarb, which can be metabolized into methomyl, are still available in the market, often mixed with other insecticidal compounds.

Mechanism of Toxicity

Methomyl reversibly inhibits acetylcholinesterase, an enzyme that plays a crucial role in the nervous system by breaking down the neurotransmitter acetylcholine. When acetylcholinesterase is inhibited, acetylcholine accumulates in the synapse, leading to cholinergic nerve stimulation (103). This can result in a range of symptoms affecting various bodily functions.

Clinical features

Exposure to methomyl can lead to a variety of symptoms, which can vary depending on the level of exposure and the route of exposure (ingestion, inhalation, or skin contact). Representative symptoms and signs of acute methomyl poisoning are DUMBELS (Diarrhea, Urination, Meiosis, Bronchorrhea/Bronchospasm, Emesis/nausea, Lacrimation, and Salivation) (103,104). The other toxic

symptoms and signs included profound sweating, dyspnea, headache, dizziness, muscle weakness, tremor, and confusion. In moderate to severe poisoning, breathing difficulties, mental change, and hypotension should be noted (103-105). In rare instances, patients with acute methomyl poisoning did not manifest DUMBELS symptoms, emphasizing the need for caution among treating physicians.

Management

The treatment of acute methomyl poisoning involves supportive care and atropine administration to counteract the effects of the poison (103,105). Furthermore, it is important to exercise caution regarding the potential occurrence of secondary poisoning among healthcare providers due to contact or exposure while treating poisoned patients. Treatment may include: 1) Decontamination: If the exposure is recent, decontamination methods such as gastric lavage or administration of activated charcoal may be used to reduce absorption, 2) Antidotes: Atropine, an antidote to carbamate poisoning, should be administered to counteract the toxic effects of acetylcholinesterase inhibition if DUMBELS are identified. When toxic symptoms and signs are vague, the atropine challenge test can be useful to evaluate the severity of poisoning. While the administration of Pralidoxime (2-PAM) is not recommended for acute methomyl poisoning, in instances of prolonged cholinesterase inhibition associated with acute methomyl poisoning, the consideration of administering 2-PAM or obidoxime is warranted, following a similar approach as in acute organophosphate poisoning (106), 3) Respiratory Support: In cases of severe respiratory distress, patients may require oxygen supplementation or mechanical ventilation, 4) Symptomatic Treatment: Medications can be prescribed to manage specific symptoms such as seizures or muscle tremors. Furthermore, in the event of a rapid decline in mental status and severe metabolic acidosis, it may be necessary to initiate treatment for concurrent acute methanol poisoning (107).

2) Endosulfan

Endosulfan, a highly toxic organochlorine insecticide and acaricide, was commonly used to control a variety of pests on crops like fruits, vegetables, and cotton. However, due to its high toxicity, persistence in the environment, and potential to accumulate in organisms, many countries have restricted or banned its use. Therefore, incidents of acute endosulfan poisoning have decreased.

Mechanism of Action

Endosulfan acts on the nervous system by affecting the normal function of the neurotransmitter GABA. GABA is an inhibitory neurotransmitter that helps regulate nerve activity (108,109). Endosulfan inhibits GABA receptors, leading to overstimulation of nerve cells and various physiological effects (108,109).

Clinical features

Exposure to endosulfan can lead to a range of symptoms, which can vary based on the level and route of exposure (ingestion, inhalation, or skin contact). Symptoms of acute endosulfan poisoning may include (109-114): 1) Neurological Effects: Central nervous system symptoms are common and can include headache, dizziness, confusion, agitation, tremors, and intractable convulsions (seizures), 2) Gastrointestinal Distress: Nausea, vomiting, abdominal pain, and diarrhea are common gastrointestinal symptoms associated with endosulfan poisoning, 3) Respiratory Effects: Breathing difficulties, chest tightness, coughing, and wheezing can occur due to the impact on the nervous system and respiratory muscles, 4) Skin and Eye Irritation: Skin contact with endosulfan can cause irritation, redness, and itching. Eye exposure can lead to eye irritation and redness, 4) Cardiovascular Effects: Rapid heart rate (tachycardia) and hypotension may occur due to pulmonary embolism, 5) Miosis: Constricted pupils (miosis) can be a sign of endosulfan poisoning.

Management

The treatment of acute endosulfan poisoning involves immediate medical attention and supportive care. As mentioned earlier, seizures secondary to acute endosulfan poisoning are highly persistent and prolonged to about maximally 23.2 hours (115,116). Despite this, in the context of convulsions related to acute endosulfan poisoning, the prognosis is generally more favorable compared to seizures resulting from other neurological diseases (116). Therefore, active management including intravenous administration of lorazepam and antiepileptic agents and continuous electroencephalogram monitoring to control seizures is deemed necessary in cases of endosulfan-related status epilepticus (116,117). There's no specific antidote for acute endosulfan poisoning. Treatment may include: 1) Decontamination: If the exposure is recent, decontamination methods such as washing the skin and eyes thoroughly or removing contaminated clothing can help reduce exposure. In addition, considering the high lipophilicity of endosulfan, it is important to exercise caution regarding the potential occurrence of secondary poisoning among healthcare providers due to contact or exposure while treating poisoned patients, 2) Symptomatic Treatment: Medications can be prescribed to manage specific symptoms like seizures or respiratory distress, 3) Respiratory Support: In cases of severe respiratory distress, patients may require oxygen supplementation or mechanical ventilation, 4) Vigilant monitoring: Patients exposed to endosulfan should be closely monitored for the development of symptoms and complications.

In conclusion, the persistence of highly toxic pesticides, such as chlorfenapyr, bentazon(e), G-SH, and GAH, in agricultural practices poses a continuous risk of acute pesticide poisoning. These compounds exhibit variable mechanisms of toxicity and clinical manifestations, necessitating early recognition, supportive care, and appropriate management. It is highly advantageous for physicians and health providers to possess knowledge about the clinical course of these pesticides, as this understanding can substantially enhance the provision of effective treatment and ultimately lead to improved patient outcomes.

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