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PERSPECTIVE ARTICLE

Changing Trends in Agrochemical Poisoning in India: A Cautionary Note for Primary Care Physicians

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Suicidal poisoning by agrochemical substances is almost a unique problem in the eastern countries of the world. With a significant proportion of the population being engaged in agriculture, the accessibility of agrochemicals becomes more pronounced. In times of distress, individuals often turn to these readily available substances, as they attempt to end lives. The increased unintentional use of agrochemicals in India can also be partly attributed to an ill-regulated pesticide manufacture, storage, distribution and retailing systems in place.

In recent times, there has been a shift in the trend of suicidal poisoning cases in our country, particularly when it comes to the unintended use of agrochemical substances. A noticeable shift has emerged in the patterns of self-harm, marked by a distinct decrease in the prevalence of traditional agrochemical substances. For instance, in the past, Endrin was infamous as a suicide weapon, but its use declined following its ban in the 1990s, during which the abuse of Endosulfan became more prevalent. Similarly, while the use of organophosphates and rodenticides has not declined significantly, people are increasingly turning to other agrochemicals for suicide. Contemporary individuals prone to suicide increasingly favour novel agrochemicals, with paraquat emerging as a popular choice due to its lethal properties. Reported cases also encompass neonicotinoids, pyrethroids, and chloroacetanilides like pretilachlor [1].

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There is a concerning trend where individuals from various backgrounds, not limited to agriculture, are resorting to suicide by acquiring agrochemicals like paraquat through e-marketplaces. This disturbing pattern, emerging even among school students and office executives in major cities, demands urgent regulatory attention. A deeply concerning trend has emerged where individuals attempting suicide by abusing agrochemical substances intentionally consume only lesser amounts. This results in symptoms that mimic natural diseases, allowing them to disguise their suicide attempt as a death from natural causes, thereby avoiding the stigma associated with suicide. They frequently withhold this poisoning plot from healthcare providers until the situation becomes critical, leading to life-threatening consequences. It is imperative for clinicians to consider agrochemical substance poisoning as a potential differential diagnosis, particularly in common presentations such as gastrointestinal illnesses, vomiting, diarrhoea, or generalized malaise and stupor [2]. Early recognition and intervention play a pivotal role in preventing severe outcomes associated with deceptive poisoning cases. The significance of forensic nursing in such scenarios cannot be underestimated.

It is important to exercise caution when providing primary care for individuals exposed to agrochemical substances. The *agrochemical cholinergic toxidrome*, once associated exclusively with organophosphates in clinical practice, now extends to include carbamates and chloroacetanilides quite commonly. Therefore, accurate differentiation in treatment approaches becomes imperative, emphasizing the importance of utilizing point-of-care tests. An approach to identifying the aetiology of an unknown agrochemical poisoning is summarized in Figure 1.

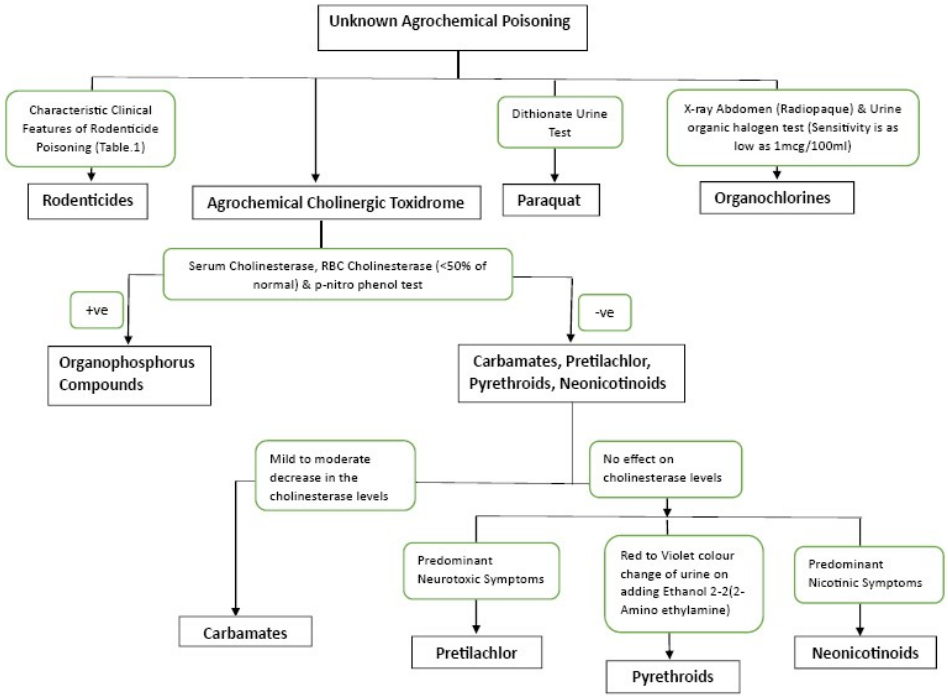

Figure 1. Approach to a Case of Unknown Agrochemical Poisoning for Identifying Aetiology

While agrochemical poisoning cases present with similar clinical manifestations, physicians must discern subtle differences among organophosphorus (OP) compounds, carbamates, pyrethroids, organochlorines, neonicotinoids and chloroacetanilides, specifically pretilachlor, for effective case management. Traditionally, carbamates were considered less fatal than organophosphate (OP) compounds; however, recent studies have shown contrasting results, indicating that fatal outcomes associated with carbamates. Both OP compounds and carbamates, including chloroacetanilides like pretilachlor, exhibit similar cholinergic symptoms, but the initial presentation of carbamate poisoning often may involve direct cardiotoxic effects like arrhythmias [3].

In organophosphate (OP) poisoning, while clinical diagnosis is often clear, measuring serum cholinesterase levels is essential for effective management of the poisoning. The treatment approach includes decontamination, atropinisation, administration of oximes (which is time-sensitive), benzodiazepines, and other supportive care. Pralidoxime is widely used in the treatment of organophosphate poisoning and remains a crucial part of the recommended management guidelines. The cause of death in these cases is respiratory failure, primarily due to bronchorrhea, bronchospasm, and muscle weakness leading to respiratory paralysis. Bradycardia and hypotension further contribute to the deterioration. Pneumonia is often a later complication, developing as a result of prolonged intubation, aspiration, or immobility leading to acute respiratory distress syndrome. (ARDS) [3,4].

It is important to note that oximes do not significantly aid in the treatment of carbamate poisoning. However, they are often given early on when the specific poison is not yet identified. In fact, oximes are contraindicated in carbamate poisoning because carbamylated oximes can become even stronger cholinesterase inhibitors than the carbamates themselves, potentially leading to fatal outcomes [5].

It is important to emphasize that the reliability of acetylcholinesterase (AChE) levels as a test for of acute cholinergic toxidrome can vary but their continuous monitoring is of importance in linking to the aetiology (agrochemical) and improving patient care. In carbamate poisoning, the transient nature of AChE inhibition may result in better-preserved enzyme activity unlike organophosphates.

In a case of chloroacetanilide poisoning (pretilachlor) [6], the clinical manifestations are exactly similar to OP poisoning. However, differentiation is possible by the absence of the characteristic garlicky odour and the presence of normal serum cholinesterase levels, which are not observed in OP poisoning [6]. The management primarily involves supportive care, and in cases of symptomatic bradycardia, correction is pursued through atropinisation. This emphasizes the importance of accurately distinguishing the type of agrochemical poison for effective management, as most of them closely resemble organophosphate (OP) poisoning.

Pyrethroids and neonicotinoids, popular groups of insecticides, are now increasingly being used as suicidal poisons. Pyrethroids affect the sodium and chloride channels of neurons and muscle cells, causing a spectrum of neurological manifestations. Neonicotinoids act at nicotinic acetylcholine receptors (nAChRs), and the spectrum of clinical features include gastrointestinal erosions,

haemorrhagic gastritis, leucocytosis, and convulsions. For both groups, the management is supportive, and knowledge of the definitive type of poison is fundamental, as they do not affect acetylcholinesterase enzymes. Administering atropine to these patients just because it mimics OP poisoning, can cause atropine toxicity including an unwarranted psychosis, worsening the condition [7]. However, it is worth mentioning that atropine is used across the spectrum of agrochemical cholinergic toxidrome to manage the muscarinic symptoms initially.

Next in the list are rodenticides that are highly potent and among the most dangerous compounds, with a high mortality rate. They consist of three groups: yellow phosphorus, aluminium, and zinc phosphide, and coumarins (Table 1). The compound should be identified before charting out treatment plan, as clinical manifestations and management also differ. It is important to note that gastric lavage should be done with caution in the case of metal phosphide poisoning, as the liberation of phosphine gas endangers the lives of medical professionals [8-10]. Instead, lavage with 1:10,000 potassium permanganate is recommended to oxidize phosphorus into less toxic compounds [11].

Table 1. Summary of Rodenticide Poisonings [8-10]

Type of compound	Clinical manifestation	Management
Yellow phosphorus Children often accidentally ingest this substance, mistaking it for toothpaste.	It is believed to affect ribosomal protein synthesis and affects major systems such as hepatic, gastrointestinal, neurological, and renal. Symptoms range from mild nausea and vomiting to acute liver failure, coagulopathy, acute kidney injury and cardiac arrythmias. The cause of death is due to direct cardiotoxicity or complications of acute liver injury.	Symptomatic care. Use of N-acetyl cysteine may help in acute liver injury. The efficacy of steroids is equivocal. Liver transplantation may be needed.
Aluminium and Zinc Phosphide These substances form phosphine gas by reacting with hydrochloric acid and water in the stomach.	They inhibit mitochondrial oxidative phosphorylation. Initial symptoms include nausea, vomiting and epigastric pain followed by circulatory collapse, hypotension, myocarditis, pericarditis etc. The cause of death is circulatory collapse.	Supportive intensive care. Correction of dyselectrolytemia and hypoglycaemia. N-acetyl cysteine is used for acute liver failure and the use of pralidoxime is being assessed.

Coumarins The second generation coumarins are about one hundred times more potent than warfarin.	They inhibit the synthesis of clotting factors and cause coagulopathy. Mild to severe bleeding can be seen across all systems. Paradoxical thrombosis can also be seen in some cases Diagnosis can be established by deranged Prothrombin time and by measuring 4-hydroxycoumarin levels.	Misdiagnosis is common in children, thinking of other haematological disorders. Vitamin K supplementation is the mainstay of treatment.

Furthermore, paraquat has emerged as the *new endrin* in the Indian agrochemical suicide landscape, often labelled as a deadly weapon, with claims that even a single sip can be fatal. It stands out as the ubiquitous choice in cases of suicidal agrochemical poisoning in India. Despite paraquat poisoning can be certainly identified through the point-of-care dithionate test, the absence of an antidote contributes to a high fatality rate.

The diagnosis of Paraquat poisoning can be relatively easily established, as it produces characteristic effects on the gastrointestinal (GI) tract, especially the tongue, commonly referred to as *"Paraquat tongue,"* which is almost universally observed. Even in small doses, GI toxicity such as mucosal lesions and perforations can be seen. Paraquat also exerts significant toxicity on the kidneys and lungs. While renal failure develops rapidly, death through this mechanism is rare. Initially, alveolitis/pulmonary oedema can develop in the lungs, later progressing to fibrosis, leading to hypoxia, multiple organ dysfunction syndrome (MODS), and ultimately death. Diagnosis can be confirmed through the urine dithionite test as mentioned earlier and measurement of plasma paraquat levels. Management involves supportive care, monitoring serum cystatin-C levels, and providing intensive respiratory care [12]. Immunosuppressive therapy and Ambroxol have been found to be efficacious in management of paraquat poisoning [13].

Organochlorine pesticides are a variety of chlorinated hydrocarbons available in forms such as dusting powders, wettable powders, emulsions, granules, and solutions. Contrary to a popular assumption among certain doctors, these pesticides do not depress cholinesterase enzymes. The mechanism of action of organochlorines involves disrupting nerve function by affecting sodium channels, inhibiting GABA-mediated chlorine channels, and interfering with calcium ATPase activity. Additionally, they induce liver drug-metabolizing enzymes, leading to liver damage. Clinical features include neurological and gastrointestinal symptoms such as seizures, tremors, confusion, headache, nausea, vomiting, abdominal pain, and diarrhoea [14].

The diagnosis of organochlorine pesticide poisoning can be aided by performing an abdominal radiograph, which may reveal the presence of certain radiopaque organochlorine compounds, particularly those with heavier chlorination. However, the diagnostic utility of this radiographic feature is limited. Additionally, measuring organic halogen compounds in urine serves as an indicator

of exposure, with a sensitivity as low as 1 mcg of organic halogen per 100 ml of urine. It is important to note that the urine halogen test is generally more useful in cases of chronic exposure rather than acute poisoning.

The importance of analytical toxicology in identifying the ingested substance is acknowledged; however, the focus of the current discussion is on improving the diagnosis of these poisonings in peripheral settings. The goal is to equip primary care practitioners with the knowledge and tools necessary to accurately diagnose cases before they reach tertiary care hospitals, thereby reducing the risk of misdiagnosis and mismanagement.

In conclusion, there is a critical need for caution and awareness regarding the diverse possibilities in agrochemical poisoning. The primary care physician should be aware of differential diagnosis (aetiology) of agrochemical cholinergic toxidrome and the importance of point of care tests. In instances of uncertainty, the first contact healthcare practitioners are advised to promptly consult the National Poison Information Centre operated by the All-India Institute of Medical Sciences, New Delhi. With the continuous introduction of new agrochemicals, it is essential for physicians to stay abreast with the several types and their distinct clinical presentations to prevent misdiagnosis, considering the variations in management approaches.

The urgent need for a National Poison Incident Database in India continues to be an unfulfilled goal to this day [15]. Additionally, there is a significant demand to ban certain herbicides, such as paraquat, which is classified among highly hazardous pesticides and has already been prohibited in many countries worldwide [16].

Nevertheless, the proper regulation of highly lethal agrochemical substances becomes imperative to mitigate risks and prevent untoward pesticide suicides. The easy accessibility of these compounds, both through e-commerce websites and over the counter, coupled with the lack of antidotes for many, poses a significant public health threat. Urgent national-level regulations are imperative for the distribution, storage, and sale of agrochemicals to address this growing concern and ensure public safety.

Statements and Declarations

Conflicts of interest

The authors declares that they do not have conflict of interest.

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