Oximes in organophosphorus poisoning

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Abstract

Acute organic insecticide poisoning is a major health problem all over the world, particularly in the developing countries, where organophosphates (OPs) are the most common suicidal poisons with high morbidity and mortality and account for a large proportion of patients admitted to intensive care units. Other insecticides less commonly used are organocarbamates, organochlorides, and pyrethroids, which are less toxic and are associated with less morbidity and mortality. Patients with poisoning present with a wide spectrum of gastrointestinal, neurological, and cardiac manifestations. A strong clinical suspicion is necessary to make an early diagnosis and to start appropriate therapy. Treatment is primarily supportive and includes decontamination, anticholinergics, protection of the airway, and cardiac and respiratory support. The use of oximes has been controversial and may be associated with higher mortality owing to a higher incidence of type-II paralysis. They may have other toxic side effects. This paper reviews the literature on OP poisoning.

Key Words: Anticholinergics, Manifestations, Organophosphate, Oximes, Poisoning

Introduction

Organophosphate (OP) compounds have been used worldwide for pest control for over 100 years. They are the insecticides of choice in the agricultural world and are the most common cause of poisoning among the organic insecticides. They are common agents of suicidal and accidental poisoning, as a result of their ready availability and easy accessibility. Several hundred people around the world die each year from OP poisoning, especially in developing countries.[1] Recently, there has been a renewed interest in OP compounds as these are agents which might be used as chemical weapons.

The WHO estimates that three million cases of poisoning occur worldwide, mostly in the developing countries.[2] There has been a change in the type of agents used for suicide attempts, with OP poisoning being seen more and more frequently as compared with phenobarbitone, diazepam, hypnotics, and antidepressants a couple of decades ago. In the Christian Medical College (CMC) and Hospital, Vellore, India, OP poisoning accounted for 12% of all admissions to the medical intensive care unit (ICU) and 29% of all poisoning in the early 1990s[3] and now accounts for over 70% of all poisonings. In another center 89.75% of patients admitted with poisoning were owing to OP.[4] OP compounds are common suicidal agents in Pakistan,[5] Sri Lanka,[6] and the other Asian and South East Asian countries.

The OP compounds are popular insecticides because of their effectiveness and nonpersistence in the environment owing to their unstable chemical nature. They do not persist in the body or environment as do organochlorides and have become the insecticide group of choice replacing DDT, an organochloride compound.[7]

OPs are common household insecticides used exten-

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sively by agricultural communities. Seasonal variations in water availability keep these communities in financial debt, driving farmers to suicide by ingestion of agricultural pesticides that are sold directly over the counter and have inadequate regulations controlling their use and storage. Early and correct diagnosis and treatment may be life-saving in OP poisoning. It is important to treat cases in hospitals with respiratory support facilities to reduce the morbidity and mortality.

Historical Perspective

The first OP compound synthesized in 1854 was tetraethyl pyrophosphate (TEPP). It came into use in Germany during World War II as an agricultural pesticide substitute for nicotine and for possible use as a nerve gas in chemical warfare. It is also the most toxic of the OP insecticides.[8] Parathion, an organic derivative of phosphoric acid, was synthesized shortly after World War II. Because it has to be converted to paraoxon by substitution of oxygen for sulfur to be physiologically active, symptoms of parathion intoxication are often delayed for 6–24 h. There have been numerous OP compounds synthesized over the years and over a hundred compounds are currently available under different brand names, making identification difficult in a given patient, unless the container is brought in by the patient's relative. Of the OP group, Parathion is the most common cause of human poisoning and fatality.[9]

Pharmacology

The OP compounds are classified in many ways; one based on clinical toxicity is as follows:[9]

1. Agricultural insecticides (high toxicity), for example, TEPP, parathion, phorate, mevinphos, and disulfoton.
2. Animal insecticides (intermediate toxicity), for example, coumaphos, chlorpyrifos, trichlorfon, and ronnel.
3. Household use or use in golf courses (low toxicity), for example, diazinon, malathion, dichlorvos, and acephate.

OPs may also be classified according to their pharmacokinetics as given below.

Pharmacokinetics

The onset, intensity, and duration of pharmacological effects that occur after poisoning are determined largely by the factors listed in Table 1.

Most OPs are well absorbed from skin, oral mucous membranes, conjunctival mucous membrane, and gastrointestinal and respiratory routes. Subsequently, most OP compounds are hydrolyzed by enzymes, the A esterases or paroxonases, which are not inhibited by OP compounds. These enzymes are found in the plasma and in the hepatic endoplasmic reticulum and split the anhydride, P–F, P–CN, or ester bonds.[10] The metabolic products are then excreted in the urine. OP compounds that bind to acetylcholinesterase block the conversion of acetylcholine to its degradation products, namely, acetic acid and choline. This leads to a build-up of excessive acetylcholine at synapses, which is the primary cause of most of the toxic effects of OP compounds.

Pathophysiology of OP Poisoning

Acetylcholine is the neurotransmitter released by the terminal nerve endings of all postganglionic parasympathetic nerves and in both sympathetic and parasympathetic ganglia. It is also released at the skeletal myoneural junctions and serves as a neurotransmitter in the central nervous system.[11] Acetylcholinesterase is present in two forms: true cholinesterase which is found primarily in the nervous tissue and erythrocytes and pseudocholinesterase which is found in the serum and liver.[9] OPs bind to the active serine residue of acetyl cholinesterase irreversibly and convert the enzyme into

Table 1: Factors determining the onset, duration, and intensity of OP poisoning

Nature of compound	Remarks
Water-soluble	Acute and shorter duration of symptoms, e.g., TEPP
Lipid-soluble	Delayed and more sustained effect, e.g., chlorfenthion
Nature of binding	
Reversible	Short-lived effects
Irreversible	Persistent effects, e.g., parathion
Mode of action	
Direct agent	Direct acetyl cholinesterase inhibition, e.g., sarin
Indirect agent	Needs to be converted to active metabolite, e.g., parathion
Route/degree of exposure	
Cutaneous	Chronic toxicity
Oral/GIT	Acute symptoms
Inhaled	May be acute or chronic depending on poison load
Relative toxicity of the compound	
Low	
Intermediate	
High	
Rate of metabolic degradation	
Malathion	

an inactive protein complex, resulting in the accumulation of acetylcholine at the receptors, leading to overstimulation and subsequent disruption of nerve impulse transmission in both the peripheral and central nervous systems.

Etiology of OP Poisoning

OP poisoning results either from suicidal or accidental poisoning or from occupational exposure such as farming. A large proportion (68%) of patients presented to the ICU following an acute suicide attempt.[6,8] Most patients are young (less than 30 years) with a male preponderance.[8,12] Occupational and accidental poisoning occur less commonly in India.[8]

Clinical Features of Poisoning

Clinical features of acute poisoning occur within 24 h of ingestion of the OP compound. These can be broadly classified as follows.

Muscuranic Effects

Cardiovascular: Bradycardia, hypotension.
Respiratory: Rhinorrhea, bronchorrhea, bronchospasm, cough.
Gastrointestinal: Increased salivation, nausea and vomiting, abdominal pain, diarrhea, fecal incontinence.
Genitourinary: Urinary incontinence.
Ocular: Blurred vision, increased lacrimation, miosis.
Dermatologic: Excessive sweating.

Nicotinic Effects

Cardiovascular: Tachycardia, hypotension.
Musculoskeletal: Weakness, fasciculations, cramps, paralysis.

Central Receptor Stimulation

Anxiety, restlessness, ataxia, absent reflexes, convulsions, insomnia, tremors, dysarthria, coma, hyperreflexia, Cheyne Stokes breathing, respiratory depression, and circulatory collapse come under this.[13]

The end-result may be multisystem manifestations involving the gastrointestinal tract, respiratory system, cardiovascular system, nervous system, skeletal muscles, as well as metabolic effects such as hypo- or hyperglycemia.

Neurological Manifestations in OP Poisoning

Neurological manifestations are the most important sequelae of OP poisoning as a large number of patients with acute OP poisoning develop neuromuscular weakness requiring prolonged ventilation. Three types of paralyses are recognized based on the time of occurrence and differ in their pathophysiology.

Type-I Paralysis or Acute Paralysis

Type-I paralysis occurs with the initial cholinergic crisis. This is postulated to be owing to the persistent depolarization at the neuromuscular junction resulting from blockade of acetylcholinesterase, and usually develops within 24–48 h. Features include muscle fasciculations, cramps, twitching, and weakness. These manifestations respond to atropine,[14] although it may not fully block the nicotinic effects. Muscle weakness may have upper motor neuron manifestations. Muscle paralysis may also involve the respiratory muscles, leading to respiratory failure, requiring ventilation. This may be further compounded by severe bronchorrhea. Acute respiratory failure has been observed in 33% of patients who presented with OP poisoning.[15]

Type-II Paralysis or Intermediate Syndrome

This was first described by Wadia as Type-II paralysis[16] and subsequently described and termed as intermediate syndrome by Senanayake.[17] Since then, there have been numerous reports of this syndrome.[14,18–21] It is a clinical entity that develops after the acute cholinergic crisis, 24–96 h after the poisoning. In the majority of patients, respiratory insufficiency draws attention to the onset of the syndrome. Cranial nerve palsies and proximal muscle weakness are observed. There is relative sparing of the distal muscle groups. The reported incidence of this syndrome varies between 8% and 49%.[20–22]

One of the earliest manifestations in these patients is the presence of marked weakness of neck flexon with the inability to lift the head from the pillow. This is a reliable test to assess if a patient is likely to develop respiratory muscle weakness and to pre-emptively manage respiratory embarrassment. The common cranial nerves involved are those supplying the extraocular muscles.

Cranial nerves VII and X are less frequently affected. Electromyographic (EMG) studies have shown a combination of pre- and postsynaptic dysfunction of neuromuscular transmission. Senanayake showed a fade on tetanic stimulation and absence of post-tetanic facilitation.[17] Nerve conduction and EMG studies in our cohort of patients have shown that the primary type of involvement is an axonal neuropathy.[23] In addition to the neuromuscular transmission defect, anterior cell or toxin-induced muscular instability appear to play a role in Type-II paralysis. This syndrome persists for approx 4–18 days and most patients survive this with ventilatory support unless infections complicate the course. More studies from CMC, Vellore, have shown that there is a myopathy as evidenced by significant elevation of muscle enzymes.[24]

Type-III Paralysis or OP-Induced Delayed Polyneuropathy

OP-induced delayed polyneuropathy (OPIDP) is a sensory-motor distal axonopathy that usually occurs after the ingestion of large doses of certain OP insecticides[25–27] or after chronic exposure. Two distinct clinical entities have been described, one being pure motor polyneuropathy and the other having a mild sensory component with a more prominent motor component. A pure sensory neuropathy has not been observed in either single or repeated acute OP poisoning.[25] Unlike the intermediate syndrome, it usually occurs 2–3 weeks after the acute poisoning episode and is characterized by distal muscle weakness with sparing of neck muscles, cranial nerves, and proximal muscles. The EMG features are those of denervation and recovery is delayed for up to 6–12 months. High-dose methyl prednisolone has been shown to be beneficial in animal studies.[28]

Other Neurologic Manifestations

Various neuropsychiatric manifestations have been described, especially in chronic poisoning.[29] These have been termed as chronic OP-induced neuropsychiatric disorder, and includes impaired memory, confusion, irritability, lethargy, and psychosis. These manifestations are usually temporary. Extrapyramidal manifestations have also been reported in acute poisoning, developing for 4–40 days following poisoning and lasting for approx 1–4 weeks, including dystonias, resting tremor, cogwheel rigidity, and choreoathetosis.[30] Neuro-ophthalmological sequelae have been documented after chronic environmental exposure including optic atrophy, degeneration of retina, defective vertical smooth pursuit movements, myopia owing to spasm, or paresis of accommodation.[31] Rare neurological manifestations include Guillian-Barré syndrome,[32] sphincter involvement,[33] isolated bilateral recurrent laryngeal nerve paralysis,[34] and ototoxicity.[35]

Cadiovascular Manifestations

Cardiac manifestations are often the cause of serious complications or fatality. A systematic analysis of patients with poisoning showed a wide variety of cardiac manifestations.[36]

Electrocardiographic Manifestations

These include prolonged Q-T corrected (QTc) interval (67%); elevated ST segment (24%); inverted T-waves (17%); prolonged PR interval (9%); rhythm abnormalities such as sinus tachycardia (35%), sinus bradycardia (28%), extra systoles (6%), atrial fibrillation (9%), ventricular tachycardia (4%); and other manifestations such as noncardiogenic pulmonary edema (43%), hypertension (22%), and hypotension (17%).

Ludomirsky et al.[37] described three phases of cardiac toxicity.

Phase 1: A brief period of increased sympathetic tone.
Phase 2: Prolonged period of increased parasympathetic activity, including atrioventricular block.
Phase 3: QT prolongation followed by torsade de points, ventricular tachycardia, and development of ventricular fibrillation.

A picture similar to myocardial infarction has also been reported.[38] In a recent study QTc prolongation at admission was found to be associated with respiratory failure and higher mortality.[39] The mechanism of cardiac toxicity includes a direct toxic effect on the myocardium, overactivity of cholinergic or nicotinic receptors, hypoxemia, acidosis, electrolyte abnormalities, and high-dose atropine therapy.

Respiratory Manifestations

In the acute phase, muscarinic effects of bronchorrhea, bronchospasm, and laryngeal spasm can result in airway obstruction. The nicotinic effects lead to weakness and paralysis of the respiratory and the oropharyngeal

muscles. Central depression of respiration owing to involvement of cholinergic systems in the brainstem finally leads to respiratory arrest.[15]

Acute respiratory failure (less than 24 h) was seen in 33% of patients with acute poisoning.[17] Most patients with intermediate syndrome develop respiratory failure, which requires mechanical ventilation.[15,17]

Gastrointestinal Manifestations

GI manifestations are the first to appear, and they respond well to atropine therapy. Rarely, acute pancreatitis has been reported.[40,41] Patients may also have hypo- or hyperglycemia.[42]

Grading the Severity of OP Poisoning

Various grading methods are available and these are helpful in grading severity and in the management of the syndrome.[43,44] We have found, however, that these do not always correlate with outcomes. Some patients who appear to recover 24 h later develop intermediate syndrome.

Diagnosis

The diagnosis of OP poisoning is made primarily based on the history and a combination of clinical features, including the typical odour of the insecticide. Some patients may present with nicotinic effects of tachycardia and mydriasis rather than the anticipated bradycardia and miosis. Some poison centers can identify the compound from the stomach contents.

Cholinesterase Estimation

True and pseudocholinesterase levels can be estimated. The levels are markedly reduced in OP poisoning. Although true cholinesterase levels correlate with severity at presentation, pseudocholinesterase levels do not.[45] Serial estimations do not correlate with clinical improvement, and hence these tests are to be used primarily to confirm the diagnosis. Other causes of low-serum cholinesterase include parenchymal liver disease, congestive cardiac failure with hepatomegaly, metastatic carcinoma, malnutrition, dermatomyositis, and acute infection. A 25% or greater depression in red-blood-cell cholinesterase level is taken as the best indicator of OP poisoning.[9]

Management

Treatment should be initiated immediately on clinical grounds without waiting for blood investigations.

General Measures
Decontamination

Decontamination of the skin is very important and it should be done very thoroughly. The patient should be stripped and washed with soap and water and then with ethyl alcohol. This will prevent further absorption through the skin. Health-care personnel should wear protective clothing and glasses.

Gastric decontamination should be done by forced emesis if the patient is fully awake or through a gastric lavage. All patients should also receive 0.5–1 g/kg activated charcoal every 4 h. Sodium sulfate or sorbitol can be used as a cathartic. A recent study has shown that the addition of serotonin adipinate, a drug that enhances the propulsive function of the gastrointestinal tract, resulted in a shortening of the toxicogenic phase and a 3.5-fold reduction of mortality.[46]

Airway and Respiration

The airway should be secured and adequate oxygenation should be ensured. Atropine can precipitate ventricular arrhythmia in hypoxic patients. On the other hand, early use of atropine will reduce respiratory secretions, improve muscle weakness, and thereby improve oxygenation. Careful observation of the respiratory status is required as these patients are prone to respiratory failure during the acute phase and intermediate syndrome. The important parameters to be monitored on a regular basis are (a) symptoms of ocular muscle involvement (e.g.; diplopia), (b) neck muscle weakness, (c) respiratory rate, (d) tidal volume or vital capacity, (e) single breath count, and (f) arterial blood gas estimation or pulse oximetry. Respiratory infections should be anticipated and treated appropriately. Theophylline is contraindicated in the management of OP poisoning.[9]

Cardiac Monitoring

Wide-ranging cardiac manifestations occur, and careful hemodynamic and electrocardiographic monitoring should be undertaken. Hypoxemia and electrolyte abnormalities contribute to cardiac complications. Some

of these may revert with atropine. Ventricular tachycardia with a prolonged QTc is best treated with electrical pacing.[39] Supraventricular tachycardia can be treated with an IV bolus of short-acting â-blockers.

Specific Therapy

Anticholinergic Agents

Anticholinergics are still the mainstay of treatment and should be started as soon as the airway has been secured. Atropine can be started initially as a 2-mg intraventricular (IV) bolus and then at doses of 2–5 mg IV bolus every 5–15 min until atropinization is achieved. The atropine dose in children is 0.05 mg/kg IV with a maintenance dose ranging from 0.02 to 0.05 mg/kg.[9] It is important to monitor these patients closely to prevent atropine toxicity and have clear end-points for atropinization. Contrary to earlier beliefs, it is no longer necessary to achieve total atropinization (i.e., full mydriasis, heart rate more than 150/min, and absent bowel sounds). In our experience a dose which keeps the heart rate at approx 100/min, pupils' midsize, and bowel sounds just present, maintains adequately atropinization without the risks of hyperexcitability, restlessness, hyperpyrexia and cardiac complications that are seen with total atropinization. Some uncontrolled studies have shown that an atropine infusion, as opposed to bolus doses at intervals, reduces mortality.[47] Bardin and Van Eden [44] have demonstrated that glycopyrrolate is equally effective with less central nervous system side effects and better control of secretions. The dose of atropine required is maximal on day 1 and tends to decrease over the next few days. The mean total dose of atropine in our series has been 140–167 mg.[48] Atropine does not reverse the effects of intermediate and Type-III paralysis.

Oximes

Oximes are nucleophilic agents that are known to reactivate the phosphorylated acetylcholinesterase by binding to the organophosphorus molecule.[10] The use of oximes in acute OP poisoning has been a controversial subject for over two decades. Initial uncontrolled studies suggested that oximes (pralidoxime, P2AM) were useful in the routine management of OP poisoning.[49,50] A subsequent report by de Silva et al.,[51] studying two periods of time (one when P2AM was available in their country and another when it was unavailable), found that P2AM did not make any difference to the outcomes. Recently, there have been a number of studies on the pharmacokinetics of these compounds and different oximes used, but these predominantly consisted of in vitro studies. A few in vivo studies, animal studies, and a few case series also exist. Reactivation has been shown to be complete when oximes are given within 1 h of exposure.[52] Its effects are different in different species,[53] and different with different OP compounds.[54] There is also variability in their potency with pH and temperature. The rate and magnitude of aging of the enzyme is also different with different OP compounds.[55,56] Once aging of the enzyme-OP complex has occurred, reactivation of the enzyme is not possible.

None of the oximes (pralidoxime, obidoxime, HI6, and Hlo7) are considered to be universal reactivators. Some are of broader spectrum and the potencies also differ. Obidoxime is the most potent with some OP compounds and HI6 against others.[55] Pralidoxime is generally less potent.[54–56] Studies have shown that obidoxime is forty, nine, and three times more potent than HI6, Hlo7, and pralidoxime, respectively.[55] Other studies have shown that Hlo7 is superior to the other oximes.[56]

Administration is an important issue, as only the powder form is stable, and once diluted, the oximes lose their potency.[57] An autoinjector that can dissolve the powder for the purpose of IM injection before admission to the hospital has also been recommended. However, in megadose poisoning, even a high dose of oxime may not be effective in reactivating the enzyme in the first few days following poisoning.[57] At least in three studies oximes have been effective when the poisoning severity was mild.[52,55,58] Cycloserin has been shown to be resistant to oxime therapy.[57] It is also possible that the response to P2AM may be different for the direct as opposed to the indirect anticholinesterase agents.

In some studies formation of methemoglobin and cyanide have been shown after IV administration of oximes to dogs especially with impaired renal function.[56,57,59] Obidoxime also leads to hepatotoxicity.[52] The reports are conflicting, though a lot work is being done in this field. Pralidoxime is the oxime available in India, is very expensive, and the least potent of all oximes.

A Medline search revealed only few randomized, controlled studies.[3,20,48,60,61] In a small, recent study, respiratory complications were more in the group treated with

obidoxime or P2AM.[62] Mortality was 9% (4/43) in the group treated with atropine, 50% (6/12) in the group treated with obidoxime and atropine, and there was no mortality in the group treated with P2AM (eight patients). Another study, small but randomized, showed that P2AM had no effect in moderate and severe poisoning.[63]

We did two major randomized, controlled studies with similar protocols using 12 g of P2AM infusion over 3 days. The first was 12 g infusion over 4 days *vs* 1 g at admission and the second was 12 g infusion over 4 days *vs* placebo.[3,48,60] A higher mortality was observed in the P2AM group in both the studies. Ventilatory requirement and incidence of intermediate syndrome was higher in the treatment group. Similar results were found when the two studies were pooled.[64] Also, a dose-response relationship was shown, especially with a higher sample size, when the two studies were pooled together (Table 2). Logistic regression analysis showed that the only independently significant variable was obtained on treatment with P2AM, with an odds ratio of 9.2 ($P < 0.006$). Age also had a significant effect on the outcome. These studies concluded that P2AM has no role in the routine management of patients with OP poisoning.

Scott[65] reported repeated cardiac asystole following P2AM in OP poisoning. A high dose of oximes can produce muscle weakness.[66]

In a more recent placebo-controlled study done by us,[67] we used the highest dose of P2AM, as one of the major criticisms was inadequate dose in the previous studies (12 g per day for 3 days for severe cases and 4 g per day for 3 days for moderate cases). It was shown that butyryl cholinesterase (BuCHE) did not correlate with the severity of poisoning, Type-I or Type-II paralysis, or other complications (Table 3). It also did not differ in cases and controls. The number of days and the total dose of atropine showed no difference in the two groups. BuCHE levels increased gradually over days in both groups and there was no difference whether patients were treated with P2AM or not. The mortality also was similar in both the groups and treatment made no difference—only two patients died, both in the severe group, and they both died of severe nosocomial infections associated with ventilation.

Thus, use of oximes in OP poisoning remains conflict-

Table 2: Dose-response relationship

	Placebo	Single dose 1g IV	High dose 12 g infusion	*P* value
Survival				
Alive	52 (94.6)	31 (68.2)	67 (73.7)	
Dead	3 (5.4)	5 (13.8)	24 (26.3)	0.001
Intermediate syndrome				
Yes	19 (13.8)	13 (36.1)	36 (61.5)	
No	36 (64.5)	23 (63.9)	23 (38.5)	0.004
Infections				
Yes	14 (25.4)	10 (27.8)	25 (43.9)	
No	41 (74.6)	26 (72.2)	30 (56.1)	0.03
Ventilation				
Yes	22 (40)	61 (67)	61 (67)	
No	33 (60)	19 (52.8)	30 (33)	0.005

ing and controversial. From the randomized, controlled trials it appears that they have no effect in moderate and severe poisoning and do more harm than good. Pralidoxime is the weaker of the oximes, is very expensive, and unstable in aqueous solution. The treatment options are anticholinergic drugs and assisted ventilation, which is often needed. Mortality rate will continue to be high as long as the patients are managed in hospitals without assisted ventilatory facilities. These patients should be transferred to a center where a proper ICU facility is available at the earliest. On a national level, a minimum pesticide list with less dangerous pesticides made available, phasing out the WHO Class-I and Class-II pesticides would be helpful. The use of safer pesticides should result in fewer deaths.

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Table 3: Cholinesterase levels by intervention, Type-I paralysis, Type–II paralysis, complications, and mortality

Variables	N	Mean cholinesterase level	SD	*P* value
Intervention				
Placebo	11	713.59	827.13	0.426
Treatment	10	886.25	959.60	
Type-I paralysis				
Yes	11	1287.73	923.63	
No	10	254.7	359.7	0.001
Type-II paralysis				
Yes	11	967.14	716.48	
No	10	607.35	1025.97	0.051
Complications				
Yes	10	1047.85	700.54	
No	11	568.68	982.63	0.024
Mortality				
Alive	19	784.32	916.61	
Dead	2	905.00	368.40	0.670

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