Respiratory failure in acute organophosphorus pesticide self-poisoning

M. EDDLESTON1,2,3, F. MOHAMED2,3, J.O.J. DAVIES2,4, P. EYER2,5, F. WOREK2,6, M.H.R. SHERIFF2,3 and N.A. BUCKLEY2,7

From the 1Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK, 2South Asian Clinical Toxicology Research Collaboration (www.sactrc.org), 3Ox-Col Collaboration, Department of Clinical Medicine, University of Colombo, Sri Lanka, 4Department of Intensive Care, St Thomas’s Hospital, London, UK, 5Walther Straub Institute of Pharmacology and Toxicology, Ludwig Maximilian’s University, Munich, 6Bundeswehr Institute of Pharmacology and Toxicology, Munich, Germany, and 7Department of Clinical Pharmacology & Toxicology, Canberra Clinical School, Canberra, Australia

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Summary

Background: Acute organophosphorus (OP) pesticide poisoning is a major clinical problem in the developing world. Textbooks ascribe most deaths to respiratory failure occurring in one of two distinct clinical syndromes: acute cholinergic respiratory failure or the intermediate syndrome. Delayed failure appears to be due to respiratory muscle weakness, but its pathophysiology is unclear.

Aim: To describe the clinical patterns of OP-induced respiratory failure, and to determine whether the two syndromes are clinically distinct.

Design: Prospective study of 376 patients with confirmed OP poisoning.

Methods: Patients were observed throughout their admission to three Sri Lankan hospitals. Exposure was confirmed by butyrylcholinesterase and blood OP assays.

Results: Ninety of 376 patients (24%) required intubation: 52 (58%) within 2 h of admission while unconscious with cholinergic features. Twenty-nine (32%) were well on admission but then required intubation after 24 h while conscious and without cholinergic features. These two syndromes were not clinically distinct and had much overlap. In particular, some patients who required intubation on arrival subsequently recovered consciousness but could not be extubated, requiring ventilation for up to 6 days.

Discussion: Respiratory failure did not occur as two discrete clinical syndromes within distinct time frames. Instead, the pattern of failure was variable and overlapped in some patients. There seemed to be two underlying mechanisms (an early acute mixed central and peripheral respiratory failure, and a late peripheral respiratory failure) rather than two distinct clinical syndromes.

Introduction

Acute organophosphorus (OP) pesticide self-poisoning is a major global problem.1–3 Although pesticide-poisoned patients make high demands on intensive care facilities in industrialized countries,4,5 it is in the developing world that practically all deaths occur.6–8 Many deaths occur within hours of pesticide ingestion during the acute cholinergic crisis.9,10
either before or soon after reaching medical care.\textsuperscript{11,12} Most result from acute respiratory failure due to central respiratory depression, respiratory muscle weakness, and/or direct pulmonary effects (bronchospasm and bronchorrhoea).\textsuperscript{9} Complications of pre-hospital respiratory arrest and unconsciousness, such as aspiration and anoxic brain damage, cause further deaths during the in-patient stay.

Deaths also occur after patients have been stabilized and treated with atropine.\textsuperscript{13–15} Some are due to cardiovascular failure,\textsuperscript{12} but others are due to sudden respiratory arrests occurring hours to days after admission. Unfortunately, in the resource-poor hospitals that admit most patients, facilities do not exist for poisoned patients to be routinely admitted to an intensive care unit (ICU) for close observation.

Wadia described the neurological features of OP poisoning, including the respiratory failure. He differentiated these features into those that occurred within 24 h (type I paralysis) and those that occurred after 24 h (type II paralysis).\textsuperscript{13} Senanayake and spelt Karalliedde subsequently reported a series of patients with a syndrome of delayed neuromuscular weakness and respiratory failure, calling it the ‘intermediate syndrome’.\textsuperscript{14} The late neurological syndrome was defined as ‘paralytic signs that appear about 24 h after admission and after atropine has already been given in large doses’,\textsuperscript{13} or ‘muscle weakness with an acute onset within 24 to 96 h after the poisoning affecting conscious patients without fasciculations or other cholinergic manifestations, with or without respiratory muscle failure’.\textsuperscript{14} Textbooks routinely describe respiratory failure associated with the acute cholinergic crisis or intermediate syndrome as two distinct clinical syndromes.\textsuperscript{10,16–19} However, while studying OP-poisoned patients in rural Sri Lanka, we noted patients whose respiratory failure did not fit into such distinct syndromes. We therefore set up a prospective observational study of respiratory failure in patients with confirmed OP poisoning to better describe its clinical features as a first step to improved understanding of its pathophysiology.

**Methods**

A large prospective cohort study of acute self-poisoned patients was established in three hospitals in the North Central and North Western provinces of Sri Lanka during 2002. A randomized controlled trial (RCT) of multiple-dose (MDAC, six 50 g doses q6h) and single-dose (SDAC, 50 g) regimens of superactivated charcoal (Carbomix; ISRCTN02920054) was nested into this cohort. Ethics review committee approval for the study was obtained from both Colombo and Oxford.

Patients with a history of self-poisoning were seen on admission, and data were recorded prospectively from 31 March 2002 to 31 December 2003 in Anuradhapura, from 4 June 2002 to 31 December 2003 in Polonnaruwa, and for two months at the end of 2002 in Kurunegala. The poison ingested was provisionally identified from the patient’s or relatives’ histories, bottles brought in to hospital, or doctor’s comments in transfer letters. A plasma sample was taken from patients who consented to enter the RCT for confirmatory identification of the ingested OP. The patients were a subset of a previously published cohort:\textsuperscript{12} intubated patients with positive blood samples for both OP and BuChE inhibition presenting before 31 December 2003.

Patients remained under the care of the hospitals’ consultant physicians. Management protocols were agreed between the ward doctors and study team. Decisions about intubation and transfer to ICU were made by the medical team independently of study doctors. All decisions were made on the basis of the patient’s clinical condition, and did not reflect the particular OP ingested, as per usual hospital practice.

Patients were assessed on admission for cholinergic features (particularly sweating, pinpoint pupils, urinary/faecal incontinence, bronchorrhoea, bronchospasm, and hypotension) and treated following a standard protocol.\textsuperscript{20} Resuscitation was performed with intubation as required and provision of oxygen. Atropine was given rapidly with intravenous fluids in doubling doses from an initial dose of 1–3 mg, until the heart rate was >80/min, bronchospasm and bronchorrhoea had resolved, and systolic blood pressure was >80 mmHg. Once this was attained, an atropine infusion was set up to keep the patient atropinized but not toxic, with frequent adjustments of dose. All symptomatic patients requiring atropine received pralidoxime chloride 1g i.v. q6h for 1–3 days, as per the standard protocol for Sri Lankan hospitals.\textsuperscript{21}

A ward round was performed twice a day to assess the patients’ condition. Patients were also seen frequently after admission while adjustments of the atropine infusion rate were required and then at least every 3 h by study doctors. Patients with any indications of respiratory failure were treated, and the event was recorded.

Seriously ill patients, as judged by the ward’s medical staff, were transferred to the ICU when a bed became available. Each hospital had 2–8 ICU beds with ventilators for medical patients; many
were filled with OP-poisoned patients and there was always difficulty in obtaining a bed. The lack of ventilators resulted in intubation and sedation being performed at the last possible moment and the patients being ambu-bagged until a ventilator became available. Early transfer of ill patients to an ICU for close observation, as would occur in hospital with more ICU beds, was usually not possible, resulting in some deaths. In this study, therefore, the need for intubation was considered to be synonymous with respiratory failure.

Intubation was primarily motivated by respiratory failure and not GCS. Criteria for intubation included: tidal volume <180 ml/breath using a Wright’s respirometer, respiratory rate <10 breaths/minute, abdominal breathing, or failure of less invasive measures to maintain airway patency. Arterial blood gases were not available to guide therapy.

**Toxicological analysis**

Admission plasma samples (taken at a median time post-ingestion of 3–4 h) were assayed for butyrylcholinesterase activity (BuChE, EC 3.1.1.8; activity <50% of the normal mean was taken to indicate substantial exposure) and concentration of chlorpyrifos, dimethoate, fenthion, or quinalphos OP. Plasma was separated, frozen at –20°C, and sent to Munich for analysis. BuChE activity was assessed as previously described.22 OPs in plasma were quantified by reversed-phase HPLC after n-hexane extraction along with an internal standard (chlorpyrifos, fenthion, and quinalphos), or deproteinization with trichloroacetic acid (dimethoate), with UV detection at 288 and 200 nm, respectively.

**Statistics**

The primary data analysis used GraphPad Prism (version 4). Clinical characteristics were summarized using counts (percentages) for categorical variables and the median (IQR) for non-normally distributed continuous variables.

**Results**

From 31 March 2002 to 31 December 2003, 4341 patients were reviewed on admission: 806 (18.6%) reported ingestion of OP pesticides, of whom 644 reported ingesting of one of the four OPs (chlorpyrifos, dimethoate, fenthion, quinalphos) for which HPLC assays were available to confirm exposure.

Plasma samples were tested for BuChE activity and OP in 455 patients recruited to the RCT. This analysis demonstrated BuChE inhibition (indicative of substantial exposure) and identified the ingested OP in 376 patients (chlorpyrifos 216, dimethoate 99, fenthion 46, quinalphos 15). The pattern of respiratory failure in these patients with confirmed OP exposure was then assessed.

**Pattern of respiratory failure**

Of the 376 patients poisoned with an identified OP, 90 (24%) required intubation and ventilatory support during their hospital admission. Forty-six (51%) of the intubated patients died.

Careful observation of patients requiring intubation revealed two major patterns of respiratory failure: (i) an early form in unconscious patients with cholinergic features (patient video 1 on website) and ii) a delayed form in conscious patients who often had few cholinergic signs (patient video 2 on website).

**Early intubation**

The majority of patients requiring intubation (52/90, 58%) were intubated on admission (or soon after) because of severe cholinergic features (Figures 1 and 2). Twenty-seven of these patients (52%) died before hospital discharge (Figure 2). In patients requiring early intubation, atropine usually treated bronchospasm and bronchorrhoea, but did not affect either GCS or respiratory rate. The effect of pralidoxime was not apparent.

Five died within 8 h of intubation: all were severely ill on admission, were never stabilized, and did not regain consciousness before death. Thirteen died 12–48 h after intubation. Most had ingested dimethoate (12/13, 92%) and all but one remained unconscious until death.

Nine patients died later during their in-patient stay, from 3 to 18 days post intubation, mostly from pneumonia that developed soon after admission, and probably resulted from pre-hospital aspiration in some cases. Five patients intermittently regained consciousness, while still requiring ventilation, before they died.

Twenty-five patients survived to discharge. Although most (67%) were extubated within 48 h, some were extubated after periods of up to 9 days. Four of this latter group regained consciousness but could not be extubated for a further 1 to 7 days. During this time, despite reductions in muscle power, the patients could move their limbs and eyes to communicate but they could not be weaned from the ventilator (patient video 3 on website).

Four patients redeveloped respiratory failure over the three days following extubation and required reintubation and ventilation for 3–15 days. Three patients had a GCS of 15/15 at the time of reintubation; the fourth had a sudden respiratory
Late intubation

Twenty-nine patients (32%) required intubation for the first time >24 h after admission. Respiratory failure occurred a median of 64 h (IQR 36–92) post-admission.

Sixteen patients (55%) survived to extubation and hospital discharge. The patients were intubated for a median of 219 h (IQR 154–276). One patient was extubated after 123 h but, 96 h later, required reintubation for a further 98 h. Eight patients were fully conscious throughout the time they were intubated (up to 14 days); a further seven regained consciousness 2–10 days before they could be extubated.

Of the 13 patients who died, four had an unexpected respiratory arrest on the ward and died rapidly following unsuccessful cardiopulmonary resuscitation. One patient, who had been intubated for 342 h, died 102 h after extubation from a sudden cardiorespiratory arrest. The other eight patients died while being ventilated. Four of these eight patients had long periods spent fully conscious while being ventilated before they died.

Intermediate timing of intubation

Nine patients required intubation between 2 and 24 h after admission. Five were unconscious, and were similar to the patients with early respiratory failure. Four patients were conscious at the time of intubation, and were therefore similar to patients with the late form of respiratory failure. Four patients died while intubated. The others were extubated 2–14 days after intubation; two subsequently died.

Relationship between timing of intubation and hours intubated

We analysed whether the timing of intubation affected the length of time that survivors required ventilatory support. Patients intubated at >24 h after admission required intubation for significantly longer than patients intubated within 24 h of admission (median time to first extubation 33 vs. 219 h, \( p < 0.0001 \); median time to final extubation 45 vs. 284 h, \( p < 0.0001 \)) (Figure 3).
Patterns of respiratory failure for particular OPs

We noticed marked variation in the pattern of respiratory failure between OPs (Figures 1 and 2). The majority of intubated patients with chlorpyrifos and dimethoate poisoning were intubated on admission. However, the dimethoate-poisoned patients had a much worse prognosis (Figure 2): 19/25 dimethoate-poisoned patients died, vs. 6/21 chlorpyrifos-poisoned patients (76% vs. 29%; RR 2.7, 95%CI 1.3–5.4). The majority of intubations following fenthion poisoning occurred late (after 24 h). There were few quinalphos-poisoned patients in the cohort but four of the six were intubated on admission.

Discussion

In this large cohort study of patients with confirmed OP poisoning, we noted two common forms of
respiratory failure: an early form, occurring at or soon after admission; and a delayed form, occurring from several hours to 5 days after admission. The early form occurred in unconscious patients with marked cholinergic features, while the delayed form occurred in conscious patients with few cholinergic features.

These syndromes are similar to the two distinct and non-overlapping syndromes of OP-induced respiratory failure described in textbooks: respiratory failure during the acute cholinergic crisis and the delayed intermediate syndrome. However, we noted many patients who did not fall cleanly into these two categories. In particular, early respiratory failure sometimes merged seamlessly with late respiratory failure, such that some patients intubated on admission regained consciousness, only to find themselves unable to breathe and requiring ventilatory support for several weeks. It may not be as easy as textbooks suggest\textsuperscript{10,16–19} to distinguish clearly between these two clinical syndromes, either clinically or temporally.

**Early respiratory failure during the acute cholinergic crisis**

Early respiratory failure occurred in unconscious patients. In all but 9% of patients, it occurred within 2 h of admission, which was a median of 3–4 h post-ingestion. As long as complications did not occur, it usually lasted for no more than 48 h. Respiratory failure lasting longer than this was normally associated with return of consciousness, unless patients were septic from pneumonia or other infections. Many intubated patients poisoned by chlorpyrifos, dimethoate or quinalphos had respiratory failure of this pattern.

The mechanism of early respiratory failure during the acute cholinergic crisis in humans is unclear, but is likely to involve three components: depression of central respiratory drive from the respiratory centre in the ventrolateral medulla, respiratory muscle weakness, and direct pulmonary effects (bronchospasm, bronchorrhoea).\textsuperscript{9,10,23}

Animal studies have suggested that the dominant component varies between OP and between species: for example, bronchospasm dominates in cats while central respiratory depression dominates in monkeys and rabbits.\textsuperscript{23,24} Bronchospasm and bronchorrhoea are probably important initially in untreated humans. However, once these features have been reversed with atropine,\textsuperscript{9,10} and oxygenation is satisfactory, these components are unlikely to be responsible for the respiratory failure seen in unconscious patients.

Definitive proof of whether central respiratory centre or neuromuscular junction (NMJ) dysfunction predominates in human poisoning will need studies using non-invasive methods to measure phrenic nerve activity.\textsuperscript{23} However, we have seen marked improvement in respiratory function and conscious level in a few Sri Lankan patients given diazepam rapidly before intubation (Eddleston, unpublished data). This suggests that disordered central activity may disrupt central respiratory function, and that reducing this disorder with benzodiazepines improves function and respiration. Rat studies have already shown such an effect of diazepam.\textsuperscript{25} If confirmed in further human studies, this will support the view that the central component predominates in the early OP-induced respiratory failure in humans.

**Type II paralysis or intermediate syndrome**

Many patients required intubation at >24 h after admission, of whom many were conscious up until intubation, suggesting a non-central cause. This pattern of delayed respiratory failure often fulfilled
the original criteria for type II paralysis or intermediate syndrome. However, there were some differences from the original descriptions in our patients. Although described as occurring from 24–96 h after admission, 10/33 (30%) patients requiring intubation for the first time while conscious were intubated either before 24 h (4/33, 12%) or after 96 h (6/33, 18%). Wadia’s original definition also indicated that patients required large amounts of atropine before developing this form of respiratory failure. However, in our series, some fenthion-poisoned patients required little if any atropine before developing delayed respiratory failure.

Type II paralysis or intermediate syndrome was particularly common in fenthion poisoning: 12/15 (80%) patients were intubated after 24 h, vs. <30% of patients ingesting the other OPs. In some patients, it occurred several days after a very mild or even absent cholinergic crisis. Fenthion is highly fat-soluble (log P = 4.3) and AChE inhibition occurs slowly. It may distribute into the fat in its thion form and then slowly leak out to be converted to the oxon, causing persistent AChE inhibition over days and delayed respiratory failure. Fat solubility alone cannot be the answer; however: chlorpyrifos is also highly soluble (log P = 5.1), but this rapidly activated thion causes delayed respiratory failure relatively rarely.

Late or peripheral respiratory failure

Not all of our cases of delayed respiratory failure fitted the original clinical descriptions by Wadia and Senanayake as being separated in time from the acute cholinergic crisis. For example, delayed respiratory failure sometimes occurred at the same time as recurrent cholinergic poisoning in fenthion poisoning.

Other patients regained consciousness from their severe acute cholinergic crisis, which had required intubation, into a form of respiratory failure that probably did not involve the CNS. Of the 34 patients still being ventilated 4 days after intubation, 24 (71%) were conscious. Among these conscious patients, it was not possible to distinguish the seven patients who had been intubated within 24 h of admission (and had developed a peripheral failure) from the 17 who had been intubated for type II paralysis/intermediate syndrome (patient video 3 on website).

The distinguishing feature of all late respiratory failure was its apparent peripheral dysfunction. After a few days, all of the patients who survived were conscious, and many could at least weakly move their arms, legs, and cranial nerve-innervated muscles, while being quite unable to breathe. It seems unlikely that localized central dysfunction affecting only the central respiratory centre would cause this respiratory failure.

Some authors have proposed that the peripheral dysfunction results from sustained overstimulation of the NMJ by high synaptic concentrations of ACh. The molecular mechanism is not known, although it may well involve down-regulation of receptors in response to sustained stimulation. There is no consensus concerning whether the dysfunction is pre- and/or post-synaptic; however, failure of the muscarinic antagonist atropine to prevent peripheral respiratory failure might favour involvement of pre- or post-synaptic nicotinic receptors over pre-synaptic muscarinic receptors.

Some researchers believe that the late respiratory failure is due to direct OP toxicity to skeletal muscle. However, there is currently little evidence to support such a mechanism. Although animal models show muscle necrosis in OP poisoning, the extent of muscle damage does not match the degree of weakness. Furthermore, small studies of patients with intermediate syndrome have failed to find either significant muscle damage or raised muscle enzymes in blood.

The report of raised blood creatinine kinase (CK) in OP patients with respiratory failure for many days is confounded by a lack of controls with similar levels of inactivity and long-term bed rest. It is possible that paralysed patients with Guillain-Barré disease or Bungarus envenoming would have had similar rises in CK. In addition, although fasciculations cause muscle damage in animals, their occurrence in their study patients was not recorded. Overall, there is little evidence that direct muscle damage causes the peripheral respiratory failure.

Relationship of the peripheral respiratory failure to oxime therapy

The delayed respiratory failure may be due to insufficient or delayed oxime therapy. The patients in our cohort often received only one day of intermittent pralidoxime treatment: significantly less than currently recommended and clearly not ideal. We have noted AChE re-inhibition in chlorpyrifos- and quinalphos-poisoned patients after 24 h, despite initial good reactivation. This late re-inhibition may account for some chlorpyrifos and quinalphos patients requiring intubation after 24 h.

A post-hoc analysis of a study from Vellore suggested that early administration of a loading 1 g dose of pralidoxime prevented late respiratory failure. It is possible that higher doses of...
pralidoxime will more effectively reanimate AChE and then prevent both early and late respiratory failure in all forms of OP poisoning. Proof may come from analysis of the RCTs of high-dose pralidoxime now underway in India and Sri Lanka.

Incidence of respiratory failure

We have found marked differences between OPs in both the form (this paper) and frequency\textsuperscript{12} of respiratory failure they cause. Many previous studies have reported the incidence for OP-induced respiratory failure or type II paralysis/intermediate syndrome.\textsuperscript{13,34,41–47} However, only Wadia’s study examined relatively large numbers of patients poisoned by a single identified OP (200 patients with diazinon poisoning\textsuperscript{13}). It is difficult to state a general incidence for OP-induced respiratory failure, since it will vary according to many factors, such as the locally common OPs, the facilities available, the time between ingestion and admission, and whether all patients are studied or just those that are admitted to ICU.

This paper clearly demonstrates how difficult OP-induced respiratory failure is to manage: it demands high levels of resources that are simply not available in the majority of hospitals seeing OP-poisoned patients. Some patients died soon after being extubated; others died from sudden unanticipated respiratory arrests. Many patients were intubated for days and weeks, using up valuable ICU beds and preventing the admission of other patients. Tragically, some patients died (from pneumonia or other complications of long-term ventilation) after they had been ventilated for several weeks, during which time they were often conscious.

Conclusions

We have not found it possible to divide up OP pesticide-induced respiratory failure into two non-overlapping clinical syndromes. Instead, it seems that respiratory failure results from two pathophysiological processes that can occur separately or together in a patient. Research is required to identify the mechanisms of both early and late respiratory failure and to translate this knowledge into prevention.

More ICU beds and more resources would have reduced the number of patients who died in this study, but this is not going to be practical in the foreseeable future in the developing world. While we wait for research to identify methods of preventing respiratory failure, it is probably worth identifying the OPs that cause most respiratory failure and banning them. It may simply be too difficult to treat their effects in a resource-poor country.

Finally, while it may not be possible to clearly distinguish the respiratory syndromes of OP poisoning, it still seems valuable to keep active the concept of type II paralysis or intermediate syndrome. It is essential that doctors are aware that patients who are apparently well may have sudden respiratory arrests many days after admission.

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References


**Appendix: Patient videos on QJM website**

Informed consent was given by patients 2 and 3 and from the relatives of patient 1 for the videos and photographs. The videos are copyright M. Eddleston, and can be accessed via the SACTRC website (http://www.sactrc.org/video/view.asp; username: video, password: letme).

**Patient 1: acute respiratory failure**

This 42-year-old male presented 4 h after ingesting dimethoate with alcohol. He had first gone to a primary hospital, where he had received atropine and pralidoxime. On admission to the district hospital, his GCS was 3/15 and required intubation during resuscitation. He never recovered and died 20 h after admission, from a cardiac arrest.

The video was taken just before intubation. It shows abdominal breathing with no movement of the chest wall – typical features of respiratory failure during the acute cholinergic syndrome. His bronchospasm and bronchorrhoea had already been treated with atropine boluses, and were not the cause of his respiratory distress.

**Patient 2: delayed respiratory failure**

This 38-year-old man presented 2 h after ingesting dimethoate with alcohol. He had first gone to a peripheral hospital, where he had received gastric lavage and atropine. On admission to the district hospital, he was alert and conscious (GCS 15/15), and he had few muscarinic features. He gradually became weaker over the next day and was intubated 46 h post admission. He remained intubated for the next 8 days, during which time he was fully conscious. He was discharged 3 days after extubation, 12 days after ingestion of the pesticide. The video shows the patient trying to lift his head off the bed while being pulled by the arms. He can be seen gesticulating and talking afterwards, explaining why his neck is so weak. Neurological examination at this time revealed neck fl exor and extensor power of 2/5, and upper limb power of 4/5. There were no cranial nerve palsies. His reflexes were present but reduced. The video shows measurement of his minute volume, which showed that his respiratory muscle function was preserved at this time. The picture shows the patient soon after he was electively intubated the next morning for generalized weakness and distress. Minute volume was satisfactory at this time; he was attached to a ventilator a few hours later.

**Patient 3: peripheral respiratory failure**

This 18-year-old woman presented 3 h after ingesting dimethoate. She had first gone to a peripheral hospital where she had received gastric lavage and atropine. Due to respiratory distress, she was intubated at the peripheral hospital. On admission to the district hospital, she was alert and had a GCS motor score of 6/6. She subsequently deteriorated before she could be extubated and had a GCS motor score of 1/6 for three days. She then regained consciousness but required intubation for a further 7 days. She was discharged 15 days after ingesting the pesticide.

The video shows her in the ICU 36 h before she could be weaned and extubated. She is asked to open and close her eyes, and to move her arms and legs. She is able to follow instructions accurately. Although she appears to have type II paralysis/intermediate syndrome, there was no interval between her cholinergic crisis and the development of the peripheral respiratory failure.