A pilot clinical study of the neuromuscular blocker rocuronium to reduce the duration of ventilation after organophosphorus insecticide poisoning

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ABSTRACT

Background: A common manifestation of organophosphorus insecticide self-poisoning is prolonged respiratory failure due to neuromuscular junction dysfunction and likely nicotinic receptor overstimulation. We aimed at collecting preliminary data on whether addition of the competitive nicotinic antagonist rocuronium to standard early therapy might be clinically feasible and associated with reduced duration of ventilation.

Methods: A pilot three-arm dose–response phase II trial was set up to compare bolus doses of rocuronium bromide titrated to produce initial >95% or 50% inhibition of neuromuscular function, measured using acceleromyography, plus standard treatment, versus standard treatment alone. After attaining inhibition, patients receiving bolus rocuronium then received rocuronium infusions for a maximum of 120 h. Primary outcome was duration of intubation; secondary outcome was case fatality. Plasma butyrylcholinesterase activity was measured throughout the inpatient stay. Blood was analysed to confirm the organophosphorus insecticide ingested.

Results: Forty-five patients were randomised to receive: rocuronium to initially attain 95% inhibition (Roc95, n = 15), rocuronium to initially attain 50% inhibition (Roc50, n = 14), or no rocuronium (control, n = 16). The most commonly ingested pesticide was profenofos (29/45, 64.4%). Butyrylcholinesterase activity remained severely inhibited for the duration of the study for most patients. Case fatality was 9/45 (20%) and similar across study arms: control 3/16 (18.8%), Roc50 4/14 (28.6%) and Roc95 2/15 (13.3%) (p = .5842). When excluding patients who died, median [IQR] duration of intubation was significantly longer in the Roc50 (259.5 [176–355] h) and Roc95 (226.8 [186–355] h) groups compared to controls (88.5 [47–160] h, p = .0162 and p = .0016, respectively).

Conclusions: In this pilot dose–response study, we found no evidence that rocuronium in addition to standard therapy reduced the duration of intubation. It is possible that it worsened neuromuscular junction function. Further clinical research, including testing of shorter duration regimens, needs to be performed before nicotinic antagonists can be used in the clinical management of OP poisoning.

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Introduction

Agricultural organophosphorus (OP) insecticides are widely used in rural regions of low- and middle-income countries [1]. Self-poisoning with these highly hazardous pesticides is responsible for >100,000 deaths, and hundreds of thousands of admissions to intensive care units (ICU) for respiratory support, every year [2–5]. OP compounds inhibit acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), causing accumulation of acetylcholine at cholinergic synapses and an “acute cholinergic crisis” that results in bradycardia, hypotension, coma and acute respiratory failure (due to a combination of neuromuscular junction [NMJ] dysfunction, loss of central respiratory drive and bronchorrhoea) [6–9]. Treatment requires the muscarinic antagonist atropine, supportive care and mechanical ventilation [10,11]. The role of oximes is unclear [12,13]. Unfortunately, despite this treatment, many poisoned patients still die.

The key issue after initial resuscitation is NMJ dysfunction (or intermediate syndrome) which prolongs respiratory failure, causing patients to need intubation for several days to weeks [14,15]. Many of those ventilated after admission do not survive to discharge from ICU [16]. The pathophysiology of NMJ dysfunction is uncertain; however, since it occurs despite adequate muscarinic receptor blockade with atropine,
the main hypothesis is that it is due to overstimulation of pre- and/or post-synaptic NMJ nicotinic receptors by excess acetylcholine causing their down regulation and neurotransmission failure [15,17,18].

Some researchers have suggested that nicotinic receptor blockade, with NMJ blocking agents (NMBAs or competitive nicotinic receptor antagonists such as rocuronium) should be added to atropine therapy [19–21]. That nicotinic antagonists are not being used routinely for treatment of these patients is likely due to the risk of inducing acute respiratory failure in patients cared for in rural district level hospitals with few mechanical ventilators and other resources [19] as well as the potential risk of critical care neuropathy [22–24]. However, when a patient does require early intubation and ventilation during the acute cholinergic syndrome (due to coma and loss of central respiratory drive), NMBAs may prevent nicotinic overstimulation and NMJ dysfunction, shortening duration of ventilation and reducing the risk of complications [21,25]. If effective, a short period of controlled N MBA-induced paralysis and ventilation – while the OP insecticide is eliminated from the body – could replace 2–3 weeks of OP insecticide-induced NMJ damage, paralysis and ventilation.

We therefore set up a small pilot randomised controlled trial (RCT) to obtain preliminary data on the efficacy of nicotinic antagonists in patients with OP insecticide self-poisoning. We selected rocuronium due to its potency at both pre-synaptic and post-synaptic nicotinic receptors [26,27] and a maximum duration of 5 days to balance the risk of neuropathy with the need for treatment when OP body load is at its highest. To investigate a dose response, we compared an initial near complete (95%) competitive inhibition of NMJ function with partial (50%) NMJ inhibition and with no inhibition.

Materials and methods

The pilot study was conducted in the toxicology ward of Teaching Hospital Peradeniya, Sri Lanka. Ethics approval was received from the Faculty of Medicine Ethics Committee, Peradeniya. Written informed consent was taken from each patient, or their relative (for unconscious patients), in their own language. The study was registered (NCT02147054) at clinicaltrials.gov.

Participants

We approached all patients with OP insecticide self-poisoning admitted to the toxicology unit who required ventilation from 07 July 2014 to 05 July 2016. The exclusion criteria were: age <16 y, known pregnancy, train-of-four (TOF) acceleromyography measurement <50% at baseline, and lack of consent. Probable ingestion of an OP was determined from the history and where available the pesticide containers brought to hospital, together with the clinical syndrome expressed by patients.

Participants remained under the care of the consultant clinicians in the toxicology ward and intensive care unit. Researchers had no say in the management of patients. TOF measurements (see later) were not used for decisions regarding extubation. The consultant intensivist decided whether a patient was clinically fit for extubation, looking for stable clinical variables (blood pressure, pulse rate and oxygenation) and a lack of aspiration pneumonia. Initially, sedation and rocuronium was switched off and ventilation subsequently converted to spontaneous mode. Those who tolerated this for about 2 h underwent a trial of extubation.

Outcome, objectives and hypotheses

The primary aim was to explore the efficacy of rocuronium at shortening the duration of ventilation (primary outcome) for OP insecticide poisoned patients requiring intubation and ventilation with at least 50% preserved NMJ function at baseline. Our hypothesis was that addition of the nicotinic antagonist rocuronium to standard care would shorten the need for ventilation. The secondary outcome was mortality.

Randomisation and allocation

Patients were randomised using closed envelopes into one of three study arms, to receive rocuronium that initially produced >95% inhibition of baseline NMJ function (Roc>95), rocuronium that initially produced 50% inhibition of baseline NMJ (Roc50), or no rocuronium (control, n=15/group). Randomisation and allocation sequence generation were done independently with a block size of six by a clinician who was not associated with the care or assessment of the patients, by means of a random number table. Allocations were concealed in sequentially numbered, opaque, sealed envelopes. Due to an error, the randomisation list was generated for 75 patients, not 45 patients as required. This resulted in a single patient imbalance between the groups.

The research clinician was not masked to dosing of rocuronium since it had to be titrated against effect. However, the primary outcome (duration of ventilation) was dependent on the intensive care staff and was not influenced by the research staff. Data analysis was done masked to allocation.

Randomisation occurred after baseline data had been entered, and after TOF acceleromyography had been performed and could not be altered by study doctors. The recruiting doctor could not predict allocation before randomisation.

Intervention and study drugs

Patients were seen by study doctors within 30 min of admission and treated as per standard management guidelines with doubling doses of atropine [28]. Data were collected using a structured case record form (CRF).

Train-of-four acceleromyography was performed on all patients, using their adductor pollicis muscle, with a TOF watch (Organon, Dublin, Ireland) at first assessment [29]. After calibration and determination of the supra-maximal threshold, a TOF reading was obtained. Any TOF reading of
less than 50%, showing substantial NMJ dysfunction, resulted in the patient being excluded from the study.

Patients randomised to the Roc>95 arm received 0.3 mg/kg bolus doses of rocuronium (Neon Laboratories Limited, Mumbai, India; 50 mg/5 mL) until the TOF measurement was 1 for the T1 spike. For the Roc50 arm, 0.3 mg/kg bolus doses were given to achieve a 50% reduction of the baseline reading on TOF testing. Control patients received no rocuronium. After the initial loading dose, we did not attempt to titrate the infusion against effect because of the confounding effect of OP-induced NMJ dysfunction. Patients in both arms allocated to rocuronium therefore received an infusion of rocuronium 1.5 mg/kg/h to maintain inhibition. This was continued until recovery and extubation, or for a maximum of 120 h to reduce the risk of critical care-induced neuropathy [30].

Blood samples were taken to assay plasma BuChE activity on recruitment and 6-hourly for the first 3 days and then twice daily. TOF measurements were collected at the same time points. BuChE activity was assessed as described [31]. The BuChE activity normal range using this assay is 2300–7000 mU/mL [32].

Sample size
No similar study has been previously performed; therefore, no data were available that could be used to generate a sample size calculation. This pilot study was designed to provide initial data on apparent efficacy and safety that would allow the design of larger phase II and III studies. Pragmatically, we aimed to enrol 15 patients with moderate-to-severe OP poisoning causing early unconsciousness and ventilatory failure into each study arm (total 45 patients), a number considered feasible within 2 years at a single site.

Analysis of blood plasma samples for confirmation of the pesticide ingested
Plasma samples were subjected to gas chromatography coupled to tandem mass spectrometry with electron ionization (GC-(EI)MS/MS) analysis for the confirmation of the ingested OP insecticide. For sample preparation, 500 μL of each plasma sample was subjected to cleanup by solid phase extraction. Following extraction, samples were dried under nitrogen flow and reconstituted in ethyl acetate. Prior to analysis, triphenyl phosphate was added as internal standard and the final volume of each sample adjusted to 350 μL with ethyl acetate.

For screening purposes, the prepared samples were analysed by combined GC-(EI)MS and dual flame photometric detector (FPD). Measurements were carried out with an Agilent 7890N GC equipped with automatic liquid injector together with an Agilent dual FPD and Agilent 5977A MSD instrument operating in full scanning mode. The capillary column was DB-5ms (Agilent, 30 m × 0.25 mm i.d., 0.25 μm film).

Statistical analysis
Graphpad Prism v7.0 was used for the main analysis. Demographic factors and clinical characteristics were summarised with counts (%) for categorical variables and median (interquartile range [IQR]) for continuous variables, as none were expected to be normally distributed. The main analysis was carried out on an intention-to-treat basis. For the non-parametric primary outcome (hours intubated), as per protocol, all groups were compared using a Kruskal–Wallis test; if significant, we then planned to perform pair wise comparisons with a non-parametric Mann–Whitney test. On the recommendation of a reviewer, we subsequently performed a post-hoc Jonckheere-Terpstra test on the primary outcome using R 3.4.0 package “clinfun” routine “jonckheere.test”, checked with SAS 6.4.1. for Windows (PROC NPAR1WAY).

Results
A total of 174 patients with OP insecticide self-poisoning were assessed on admission between 07 July 2014 and 05 July 2016. One hundred and twenty-six met exclusion criteria (TOF acceleromyography measurement <50% at baseline) while three refused consent (Figure 1). Forty-five patients (89% male) with a history of OP insecticide ingestion and features of anticholinesterase poisoning were randomised: 15 to Roc>95 arm, 14 to Roc50 arm, and 16 to the control arm. The anomaly in allocation was due to the allocation sequence being generated erroneously for 75 patients. Two patients in the Roc>95 group failed to achieve the target level of inhibition (showing more than 1 spike after bolus dosing).

The proportion of men and the OP ingested (predominantly the S-alkyl profenofos [33] [29/45, 64.4%]) were similar between groups, as was time from poisoning to intubation (Table 1). The median Peradeniya OP Poisoning (POP) score [34] and GCS score were four and three, respectively, at recruitment across all three groups (Figure 2(A,B)). There were baseline imbalances (Table 1): the control group was substantially younger, and presented later, than the other two groups. Twenty-one patients were already intubated on admission to the study hospital (6/16 [37.5%], 5/14 [35.7%]) and 10/15 (66.7%) for control, Roc50, and Roc>95 arms, respectively.

All patients in the study received a titrated atropine regimen. Patients in the Roc>95 arm received a median (IQR) initial dose of 6.0 (1.6–12.8) mg to attain atropinisation, patients in the Roc50 arm received 3.6 (2.4–9.6) mg, while control patients received 12 (4.5–19.5) mg (p = .1846 for difference across groups).

BuChE inhibition was quite similar at baseline between the three arms (Table 1) with 10/16 (62.50%), 10/14 (71.43%) and 13/15 (86.67%) fully (>95%) inhibited at baseline for control, Roc50, and Roc>95 arms, respectively. Median activity was 3% of the lower range of normal across all groups. BuChE activity remained low in many patients (Figure 3), particularly in those with initial full inhibition, indicating...
ongoing presence of the OP insecticides in blood and extracellular fluid in these patients.

Surprisingly, patients in the Roc>95 arm received a lower median (IQR) loading dose of rocuronium (21 [18–27] mg) to attain initial NMJ blockade compared to patients in the Roc50 arm (32 [19.5–38.3] mg) despite being heavier (Roc>95 mean [SD] weight 60.7 [8.2] kg; Roc50 65.5 [6.6] kg). The median duration of rocuronium infusion (continued until extubation or a maximum of 120 h) was 120 (70.5–120) h and 120 (80–120) h for Roc>95 and Roc50 arms, respectively (Figure 4(A)). Control patients did not receive rocuronium. Most patients in Roc50 (11/14, 78.6%) and Roc>95 (14/15, 93.3%) arms showed complete NMJ blockade for first 120 h (Figure 4(B)).

Case fatality was 9/45 (20%) and was similar across study arms in this small study: control 3/16 (18.8%), Roc50 4/14 (28.6%) and Roc>95 2/15 (13.3%) (p = .5842 across groups).

No dose effect of nicotinic blockade on duration of intubation and ventilation could be detected (Figure 5) – excluding patients who died, the median duration was significantly longer in the Roc50 (259.5 [176–385] h) and Roc>95 (226.8 [186–355] h) arms compared to the control arm (88.5 [47–160], p = .0162 and p = .0016, respectively). Due to the similarity of rocuronium dosing in the two rocuronium

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### Table 1. Demographic and baseline characteristics.

|                      | Roc>95 (n = 15) | Roc50 (n = 14) | Control (n = 16) |
|----------------------|-----------------|----------------|------------------|
| **Age, y, median (IQR)** | 49.0 [37.0–60.0] | 47.5 [43.8–56.7] | 26.0 [22.0–35.8] |
| **Males, n (%)**      | 14 (93.3)       | 13 (92.9)      | 13 (81.2)        |
| **OP insecticide ingested** |                 |                |                  |
| S-alkyl (profenofos)  | 9               | 8              | 12               |
| Diethyl (chlorpyrifos, quinalphos, diazinon) | 3 | 6 | 1 |
| Dimethyl (phenthoate, malathion) | 2 | 0 | 3 |
| Unknown               | 1               | 0              | 0                |
| **Baseline BuChE activity (mU/mL; median, [IQR])** | 58.5 [51.3–70.6] | 90.5 [46.4–106.3] | 87.4 [61.2–188.3] |
| **Baseline TOF score (%; median, [IQR])** | 78.0 [67.0–100] | 95.5 [81.8–100] | 70.0 [59.8–92.5] |
| **Time from poisoning to admission (hour; median, [IQR])** | 4.6 [2.9–17.5] | 2.8 [1.4–11.6] | 6.2 [2.4–31.0] |
| **Time from poisoning to intubation (hour; median, [IQR])** | 9.3 [3.8–14.5] | 11.3 [3.6–14.4] | 9.2 [3.1–21.1] |
| **Clinical status at recruitment** |                 |                |                  |
| Oxygen saturations (%; mean, SD) | 99.1 (1.0) | 98.4 (2.7) | 96.8 (4.4) |
| Heart rate (bpm; mean, SD) | 90.5 (24.8) | 92.8 (18.7) | 108.1 (24.2) |
| Systolic BP (mmHg; mean, SD) | 125.5 (23.5) | 128.3 (21.6) | 126.0 (23.4) |
| Respiratory rate (RR; mean, SD) | 15.7 (2.7) | 16.5 (3.0) | 19.1 (5.6) |
| POP score (median, IQR) | 4 (3.0–4.0) | 4 (4.0–5.3) | 4 (3.0–5.0) |
| GCS (median, IQR) | 3 (3–3) | 3 (3–3) | 3 (3–3) |
| GCS ≤13/15 (n, %) | 15 (100) | 14 (100) | 16 (100) |

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Figure 1. Trial profile as per the CONSORT guidelines. (# Two patients in the Roc>95 group failed to achieve the target level of inhibition).
groups, we also analysed them together versus the control group. Combining the two rocuronium groups, the median duration of ventilation was 157.7 h longer (Roc: 246.2 [195–353] h vs control: 88.5 [47–160] h, \( p = .0008 \)). In a post-hoc analysis, the Jonckheere–Terpstra test indicated that there was a dose–response effect of rocuronium to extend ventilation duration (\( p = .0023 \)).

Incorporating patients who died into the analysis, the median duration was insignificantly longer in the Roc50 (226.7 [76–293] h) arm but significantly longer in the Roc>95 (226.8 [170–359] h) arm compared to the control arm (124.1 [48–270], \( p = .2530 \) and \( p = .0114 \) respectively). Grouping the two rocuronium arms together, the median duration of ventilation was 102.7 h longer: rocuronium arms 226.8 [159–330] h vs control arm 124.1 [48–270] h (\( p = .0292 \)).

As a post-hoc analysis, we investigated whether persistent BuChE inhibition over the first five days was associated with ventilation duration, independent of the rocuronium treatment. Comparison of the area under curve (AUC) of BuChE inhibition over 120 h and duration of ventilation (Figure 6) showed a non-significant negative correlation (\( r = -0.00335, p = .9825 \)).

**Discussion**

This trial is the first formal comparative study of nicotinic antagonists (neuromuscular blockers) in patients with OP poisoning in need of intubation and ventilation. It shows that such a trial is possible but provides no indication that this approach offers benefit where cholinesterase inhibition persists in most patients. Indeed, the duration of ventilation was substantially longer for patients receiving rocuronium compared to patients who did not receive rocuronium. This did not seem to be related to severity at presentation as judged using GCS (a measure of severity for poisoned patients [35] and POP score [34] although the control arm included substantially younger patients, who presented later to hospital, and included patients with less severe BuChE inhibition. It is possible that the rocuronium worsened NMJ function.
The S-alkyl OP insecticide, profenofos, is currently the OP insecticide most commonly ingested in self-harm in Sri Lanka, after bans of dimethoate and fenthion [36], and most recently chlorpyrifos [37]. The fat-soluble OP causes persistent AChE and BuChE inhibition [33] meaning that nicotinic receptor stimulation likely continued for many days, past the study’s five day limit for stopping the neuromuscular blocker (aiming to reduce the risk of critical care neuropathy). A different result may occur where OP insecticides with low fat solubility, and shorter half-lives, such as dimethoate or monocrotophos are the most commonly ingested insecticides. However, we did not find a significant relationship between sustained BuChE (and likely AChE) inhibition and longer duration of intubation, which goes against this hypothesis.

The longer duration ventilation noted with rocuronium does raise the possibility that NMBA themselves, or their combination with OP insecticides, produced a critical care neuromyopathy, worsening NMJ function, when administered for up to five days. Administration for only 36 or 48 h may decrease the risk but the duration selected would need to be balanced against the speed of elimination of the OP insecticide since the NMBA needs theoretically to be present in the body for longer than the OP insecticides to work.

We only included patients in the study who had more than 50% NMJ function at baseline, indicating the presence of NMJ function that could theoretically be preserved with the NMB blockade. However, more than 70% of patients at baseline (an average of around four hours post-poisoning) showed greater than 50% inhibition of NMJ dysfunction. This suggests that only a minority of patients may be able to benefit from this approach if an effective dosing regimen can be established.

We previously assessed the effect of prophylactic administration of rocuronium in an experimental pig model of dimethoate EC40 poisoning and found some evidence of benefit (Eddleston et al., unpublished). A pig model of para-thion poisoning is also being developed to test the efficacy
of nicotinic antagonists [21], although no results have yet been published. A different NMBA, pancuronium, has previously been studied in OP insecticide poisoned patients [20,38,39]. A neurophysiological study of two patients showed transient improvement in compound muscle action potentials; a second study, of nine patients, suggested some partial improvement of NMJ block with single bolus doses of pancuronium. A subsequent study in a different group of seven patients showed a good response to a single dose of pancuronium but a deteriorating NMJ transmission when pancuronium followed pralidoxime therapy [40]. Administration of pancuronium to OP poisoned patients has not been reported since these studies.

We selected rocuronium for this study over pancuronium due to its good safety profile, potential ability to be reversed with sugammadex [41], and its potent antagonist action at both pre-synaptic and post-synaptic adult NMJ receptors [26]. It is possible that other nicotinic antagonists working at only post-synaptic or pre-synaptic receptors will offer differing effects on NMJ function.

Limitations

This study was a feasibility study assessing whether it might be possible to carry out an RCT assessing the effectiveness of NMBA. As a result, it was small with clear and expected differences between groups at baseline, including the pesticides ingested, patients’ ages, and time to presentation. It is possible that less severe poisoning in the control group explains the effect of the rocuronium treatment; however, the patient groups were similar according to the POP and GCS scores. Small feasibility RCTs in OP poisoning are difficult to interpret fully due to variation between arms; however, they are essential if larger trials are to be designed and performed.

The intensive care facilities were basic in the Sri Lankan study hospital; it is possible that a better resourced ICU would have been able to offer additional supportive care to the patients to reduce the risk of neuromyopathy. However, most patients presenting to hospital worldwide with OP insecticide self-poisoning are treated in hospitals similar to this one, supporting the relevance of this study and the hospital’s available resources to their care. Sugammadex was unavailable in the study hospital to pharmacologically stop inhibition at 120 h. Nicotinic block may therefore have persisted for longer than 120 h with implications for recovery of NMJ function.

We used BuChE as a measure of OP persistence in the body, expecting it to start rising as the OP was eliminated – since we did not have the resources to quantitively measure OP concentrations in the study. However, the relationship between plasma BuChE and AChE inhibition in tissues (CNS and NMJ) is unclear. We could have used red cell AChE as a marker of OP persistence but again the association with its activity on red cells and in tissues is unclear [33,42].

Conclusions

We were able to study NMBAs in OP insecticide poisoned patients but found no apparent benefit from rocuronium administration in profenofos OP insecticide poisoned patients requiring early intubation and ventilation with at least 50% preserved NMJ function. It is possible that this was due to the ongoing cholinesterase inhibition and nicotinic receptor overstimulation outlasting the duration of nicotinic antagonists. It is also possible that the rocuronium caused additional NMJ damage. The administration of rocuronium for up to five days may have increased the risk of inducing critical care neuromyopathy. Further studies may consider recruiting patients poisoned with short acting OP insecticides due to low fat solubility, and more rapid elimination, and using NMBAs for 48 h or less. Much more research needs to be carried out before NMBA can be used in clinical practice for OP poisoning.

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