British Journal of Clinical Pharmacology

DOI:10.1111/bcp.12839

Pharmacological management of anticholinergic delirium - theory, evidence and practice

Andrew H. Dawson[1,2] & Nicholas A. Buckley[1,3]

[1]NSW Poisons Information Center, Westmead Childrens Hospital, Sydney, [2]Central Clinical School, Royal Prince Alfred Hospital, University of Sydney, Sydney, [3]School of Pharmacology, Sydney Medical School, University of Sydney, D06 - Blackburn Building, Sydney, NSW 2006, Australia

Correspondence
Professor Andrew Dawson, Drug Health, King George V Building, Royal Prince Alfred Hospital, Camperdown NSW 2050 Australia.
Tel.: +61 (2) 9515 6419
Fax: +61 (2) 9515 5779
E-mail: andrew.dawson@sydney.edu.au

Keywords
antidotes, delirium, physostigmine

Received
20 October 2015

Accepted
16 November 2015

Accepted Article Published Online
21 November 2015

The spectrum of anticholinergic delirium is a common complication following drug overdose. Patients with severe toxicity can have significant distress and behavioural problems that often require pharmacological management. Cholinesterase inhibitors, such as physostigmine, are effective but widespread use has been limited by concerns about safety, optimal dosing and variable supply. Case series support efficacy in reversal of anticholinergic delirium. However doses vary widely and higher doses commonly lead to cholinergic toxicity. Seizures are reported in up to 2.5% of patients and occasional cardiotoxic effects are also recorded.

This article reviews the serendipitous path whereby physostigmine evolved into the preferred anticholinesterase antidote largely without any research to indicate the optimal dosing strategy. Adverse events observed in case series should be considered in the context of pharmacokinetic/pharmacodynamic studies of physostigmine which suggest a much longer latency before the maximal increase in brain acetylcholine than had been previously assumed. This would favour protocols that use lower doses and longer re-dosing intervals. We propose based on the evidence reviewed that the use of cholinesterase inhibitors should be considered in anticholinergic delirium that has not responded to non-pharmacological delirium management. The optimal risk/benefit would be with a titrated dose of 0.5 to 1 mg physostigmine (0.01–0.02 mg kg^{-1} in children) with a minimum delay of 10–15 min before re-dosing. Slower onset and longer acting agents such as rivastigmine would also be logical but more research is needed to guide the appropriate dose in this setting.

Anticholinergic toxins

The use of anticholinergics has a long history that predates medical science. This includes ritual, recreational and therapeutic use of plants containing atropine, hyoscyamine and scopolamine [1]. *Atropa belladonna*'s name reflected its use by Italian renaissance women as a beauty aid to cause their eyes to dilate and sparkle and their cheeks to gain colour.

Common anticholinergic agents should be more accurately referred to as an antimuscarinics, as these agents do not generally block nicotinic receptors. They are typically responsible for 15–20% of acute poisoning admissions [2–6], up to 40% of poisoning admission to intensive care units [7, 8] and 16% of poison centre calls [9]. 'Anticholinergic' agents are diverse and can be considered broadly as being within three categories (Table 1).

All may lead to the development of an anticholinergic toxidrome that may have both peripheral and central nervous system components. Cholinergic deficiency is recognized as a likely contributing feature to all causes of delirium [10]. Consequently, antimuscarinic agents are used to create animal models of dementia and delirium. This in turn has fostered extensive research into the pharmacokinetics and pharmacodynamics of physostigmine and other therapeutic oral and transdermal cholinesterase inhibitors [11–13].

Anticholinergic toxidrome: clinical features and diagnosis

Mechanisms

The classical anticholinergic clinical syndrome is a manifestation of competitive antagonism of acetylcholine at peripheral and central muscarinic receptors. There are at least five muscarinic subtypes, with distinct but overlapping tissue distributions [14]. M1 receptors are located primarily in the central nervous system and are involved in perception, attention and cognitive functioning. Delirium is only associated

Table 1

Mechanisms contributing to anticholinergic delirium. Adapted from [10]

Mechanism	Examples
Predominant muscarinic antagonists	Atropine, scopolamine, hyoscine, benztropine Includes many plants
Muscarinic antagonists with other mixed effects	Antihistamines, tricyclic antidepressants, antipsychotics
Decrease ACh release	Carbamazepine, opiates, cannabinoids, ethanol, clonidine
Decrease ACh synthesis	Thiamine deficiency

with the antagonism of post-synaptic M1 receptors and to date other receptor subtypes have not been implicated [15]. Peripheral muscarinic receptors are part of the autonomic nervous system and innervated by postganglionic cholinergic nerves. M2 receptors are located in the brain and heart, M3 receptors are in salivary glands and M4 receptors are in the brain and lungs [14].

There is considerable heterogeneity in the clinical expression of the 'anticholinergic toxidrome'. The main individual patient factor/modifier is reduced baseline cholinergic function associated with increasing age or central nervous system (CNS) disease. The peripheral syndrome includes dry mouth, difficulty in swallowing, blurred vision and photophobia (due to dilated pupils that only weakly constrict with light). Some other drug actions (i.e. from drugs with multiple actions or from co-ingested agents) lead to reduced pupil size but pupillary reactions will generally still be sluggish. The skin, including axilla and groin, may be dry. Bowel sounds may be absent and patients may even present with a paralytic ileus (pseudo-obstruction). Reduced gastrointestinal motility may lead to prolonged absorption, delayed peaks and prolonged effects [16, 17]. Urinary retention is common and will exacerbate the delirium. Sinus tachycardia is common. Blood pressure may be either low secondary to peripheral vasodilation or elevated due to agitation. Fever correlates with severity of delirium. It is unclear if this is due to fever exacerbating delirium or simply that it is a measure of anticholinergic effects. Mechanisms for fever include decreased heat loss (due to absent sweating), increased heat production (due to agitation and activity) and CNS dopamine mediated temperature dysregulation [18, 19].

The central anticholinergic syndrome is most commonly manifested as agitation that may progress to a hyperactive (agitated) delirium, often with pressured, incoherent speech, and visual and/or auditory hallucinations. Patients may have visual perceptual abnormalities and be seen to be picking at objects on their bed sheets. This may be precipitated by asking the patient to pick up small pieces of white tissue. They will either be unable to distinguish the tissue or continue to pick at non-existent tissue. Hypoactive and mixed delirium syndromes also occur although it is usual for most patients to have a period of hyperactive delirium. The diagnosis of hypoactive delirium is not always obvious and may only be picked up consistently in patient populations by systematic use of screening tools such as the Confusion Assessment Method [20]. Even in the presence of an agent strongly associated with anticholinergic delirium the diagnosis of other underlying causes of delirium needs to be considered. The likelihood of a different diagnosis or multifactorial delirium increases with age and comorbidity.

The clinical diagnosis of anticholinergic delirium may be supported by the presence of peripheral anti-muscarinic effects but it is common for delirium to persist when many or all of the peripheral effects have resolved [21, 22]. A relatively common scenario is anticholinergic delirium that is only noted following extubation, often with minimal or no peripheral anticholinergic signs. This phenomenon might be attributed to development of greater tolerance at peripheral receptors, higher M1 affinity and longer persistence at CNS receptors [23], and relatively greater CNS susceptibility due to age or disease related CNS cholinergic dysfunction. Significant pharmacodynamic variation at receptors is supported by healthy volunteer studies that show a poor correlation between concentration and peripheral antimuscarinic effects [24].

The anticholinergic syndrome may be accompanied by sedation, coma, seizures and/or cardiovascular toxicity not mediated by muscarinic antagonism but secondary to other drug effects on other receptors or ion channels. In particular the assessment for evidence of cardiotoxicity such as QT or QRS prolongation is important both for general management and for risk assessment for the use of cholinesterase inhibitors.

Only one study has attempted to quantify severity of the central syndrome. A scale was adapted from one used for amphetamine toxicity using published descriptors of anticholinergic toxicity (Table 2) [21]. Other studies have used delirium as a categorical outcome [25] or, even more vaguely, simply reported physician assessed improvement without describing the prior state [26].

Cholinesterase inhibitors

The ideal antidote for the anticholinergic syndrome would be a selective M1 receptor agonist. Some are in development

Table 2

Scale used for grading the severity of CNS stimulation [21]

Severity score	Clinical findings
0	Relaxed, cooperative
1	Anxious, irritable, tremulous
2	Intermittently or mildly disoriented, confused, and hallucinating, moderate agitation and motor hyperactivity
3	Incomprehensible speech, marked agitation and motor hyperactivity (requiring restraints)
4	Seizures, deep coma (unresponsive to voice or pain)

but none is in clinical use [27]. However, there is also a strong mechanistic rationale for the use of titrated doses of CNS active cholinesterase inhibitor. Physostigmine is the prototypical therapeutic cholinesterase inhibitor and the most commonly reported in therapeutic use for anticholinergic delirium.

Physostigmine was introduced following observations of the trial by ordeal conducted by the Efik people in West Africa. The suspect swallowed the physostigmine-containing Calabar bean (*Physostigma venenosum*) resulting in a cholinergic crisis. They were declared innocent if they survived [28]. The plant was imported to Europe and physostigmine was isolated in 1864. It was subsequently noted to antagonize the effects of atropine and curare. The earliest use of physostigmine to reverse anticholinergic delirium was in 1864 by Kleinwachter who treated prisoners who had mistakenly consumed atropine [29].

Acetylcholinesterase (AChE) inhibitors such as physostigmine reduce the breakdown of synaptic acetylcholine. Increased concentrations of synaptic acetylcholine compete for binding with the muscarinic antagonist but also stimulate unblocked nicotinic receptors. Further, some cholinesterase inhibitors such as physostigimine are direct nicotinic receptor agonists at the same concentrations that produce cholinesterase inhibition but independent of AChE inhibition [30–33]. Stimulation of hippocampal nicotinic receptors is both directly proconvulsant and also facilitates the generalization of seizures from other toxins [34–36].

Inhibition of erythrocyte cholinesterase is strongly correlated with brain AChE inhibition in humans and mice [37] and thus is often used to quantify anticholinesterase activity. There is a linear relationship between physostigmine dose and cholinesterase inhibition until a ceiling effect of maximum inhibition is reached [38]. This ceiling effect has been demonstrated for brain AChE, erythrocyte AChE and plasma AChE [31]. The rate (as opposed to extent) of cholinesterase inhibition has been suggested to correlate with adverse effects [13].

After intravenous administration physostigmine has a very rapid distribution and plasma elimination (distribution half-life of 2.3 min and elimination half-life of 22 min) [39]. This is shorter than the half-life of most causative anticholinergic agents. However, there is substantial evidence that both the onset and offset of effects are much slower than might be expected from these kinetic parameters (i.e. hysteresis).

Positron emission tomography studies of [^{11}C]-labelled physostigmine in primate brains show regional variation in physostigmine distribution with peak CNS radioactivity achieved 2 to 3 min after injection [40]. Increased cortical acetylcholine is inversely related to cholinesterase inhibition [41]. However, following attainment of peak AChE inhibition there was a delay of 25 min in achieving peak whole brain acetylcholine concentrations in a rat model [42, 43]. Similarly effects persist beyond the time frame expected for a 22 min half-life. Fifty percent inhibition of acetylcholine esterase recovered to baseline only after 100 min [44, 45].

Current practice: variations in management

General principles of non-pharmacological delirium management including frequent orientation and explanation to the patient, involvement of friends/family and nursing in a low stimulus environment, all still apply in this situation and may be effective in less severe cases. Benzodiazepines may have an adjunctive role in patients whose predominant symptom is mild to moderate agitation without hallucinations or thought disorder (severity score 1, Table 2). However escalating doses of benzodiazepines as primary treatment for severe delirium is associated with increased need for intubation [21] and disinhibited delirium [46]. In patients with severe agitated delirium in the general emergency medicine setting the most appropriate non-specific symptomatic treatment is droperidol, which has lower M1 antagonism and seizure risk than other neuroleptics and been shown not to cause QT prolongation at doses of 10 to 20 mg [47]. In the context of anticholinergic delirium this would correlate with a clinical severity score of 2 or 3 (Table 2), a severity when many clinicians would consider the use of physostigmine.

Internationally there is considerable variation in physostigmine's registration and supply status and therefore local clinical experience. In the US, there is a consensus that physostigmine is an essential antidote but not in the UK [48]. Elsewhere, there is not even much support for routine availability in emergency departments [XREF editorial on antidotes]. This contributes to a diverse set of viewpoints on the role of physostigmine in anticholinergic delirium and its efficacy and safety. It is our view that this might partly reflect some misconceptions about the selectivity and time course of pharmacological effects, unintended consequences of variations in dosing strategies and poor documentation of efficacy data in this heterogenous syndrome.

There is a significant variation in clinical practice. In one multicentre series of units with attending clinical toxicologists, 815 consecutive patients with anticholinergic toxidromes were analyzed. Within this cohort of patients 47% received no pharmacological treatment, 29% received benzodiazepines alone, 9% received both physostigmine and benzodiazepines, 12% were given physostigmine alone and 2.7% were given antipsychotics [49]. However, just 4/29 centres were responsible for 63% of cases where physostigmine was used. In another series 32% of all poisoned patients received physostigmine for either diagnostic or therapeutic uses [26]. This exceeded the numbers ingesting recognized anticholinergic agents. It is thus clear that vastly differing local practices or guidelines for physostigmine use exist. The variation greatly exceeds the modest diversity that might reflect differing patient acuity or causal agents

(which could in turn influence treatment decisions), or access to physostigmine [50].

A note on evidence for patient selection

Underpinning evidence in relation to efficacy, optimal dosage regimens and the risk of adverse reactions is a need to have defined patients who are likely to have a favourable risk/benefit. There is very substantial variation in described or implied treatment thresholds, contraindications and dosing protocols in published case reports and case series [22]. The most explicit indications are suggested by Burns' severity score 2 and 3 (Table 2) [21]. Some case series have such broad or ill-defined indications for physostigmine, that it appears likely that physostigmine has been used as an analeptic in comatose patients [26, 51]. Such series are hard to use to assess efficacy or optimal doses in the treatment of delirium, but all case series provide evidence relevant for assessment of safety.

Evidence for efficacy

Anyone who has used physostigmine will have observed that there can be dramatic, complete and rapid initial and repeated responses in the mental state of some patients with anticholinergic delirium. In retrospective or prospective case series of patients who have taken drugs with known anticholinergic activity (Table 3) positive clinical responses to physostigmine range from 83 to 100%. In pure anticholinergic delirium, physostigmine appears superior to benzodiazepines, controlling agitation and reversing delirium in 96% and 87%, respectively. Benzodiazepines alone controlled agitation in only 24% of patients and had no effect on delirium. Patients who received physostigmine compared with benzodiazepines had a lower rate of complications (primarily need for intubation), faster resolution of delirium and a shorter length of stay [21]. Variable methods have been used to record response including retrospective scoring systems [21, 25], descriptive physician assessment [26, 51] and prospective grading of delirium [52]. The time course of response is also poorly described in many studies, a consideration of which is critical to when further doses should be tried.

In complete responders the rate of delirium recurrence requiring repeated doses of physostigmine ranges from 31 to 90% [21, 25, 53]. The frequency and timing of relapse appears to be due to the shorter half-life and duration of action of physostigmine compared with many anticholinergic agents. Longer acting agents might thus be regarded as preferable. There is limited evidence for such agents, although generally the expected response is also reported with such agents. For example, in a tightly controlled prospective crossover study in army volunteers it was demonstrated that the intravenous (but not oral) administration of the potent cholinesterase inhibitor VX reversed the anticholinergic toxidrome [54]. Other longer acting cholinesterase inhibitors such as galantamine, donepezil and tacrine have shown efficacy in the treatment of anticholinergic delirium [55–59]. A prospective dose escalation study of 15 to 60 mgs intravenous tacrine in 11 patients with anticholinergic delirium suggested a dose related response [57] with maximal doses lower than those used in dementia [60, 61]. This is as expected but highlights the need for dose-ranging studies before sensible treatment guidelines can be made which incorporate these other cholinesterase inhibitors.

Physostigmine dosing regimens

When physostigmine was suggested to be potentially life-saving, reported doses were large and fairly rapid; for example '2 mg over 3 to 5 min' [62] and '1–4 mg slowly intravenously' [63]. There are at least four different approaches to physostigmine dosing described in larger series (Table 3). Some persist to this day with the rapid bolus method (e.g. '2 mg over 4 min' [26]), while some suggest titration of dosing with 5 min between doses, either to a similar maximum dose [25] or with no maximum dose [21]. Interestingly, the rate of titration substantially determines the reported final effective dose. Physostigmine at 1 to 2 mg over 3 to 5 min with additional titrated doses of 0.5 to 1 mg every 5 min until delirium resolved or cholinergic signs appeared, resulted in a 2.2 mg mean dose before response. [21]. A titration regimen with roughly 50% of these doses at the same intervals had a mean 1.3 mg dose before response [25]. The similar time to response but much lower mean dose with lower dose titration suggests that 5 min may be insufficient time to determine if the previous dose is effective before re-dosing. Median doses of 0.8 and 1.2 mg of physostigmine were effective in reversal of post-operative anticholinergic delirium in two case series [51, 52]. The dose of physostigmine was titrated to be twice the dose of the pre-operative scopolamine or atropine medication.

Evidence on safety and adverse effects

Excessive cholinesterase inhibition (for example by physostigmine) would lead to cholinergic toxicity including peripheral muscarinic effects (hypersecretion, bronchospasm, bradycardia, nausea, vomiting), peripheral nicotinic effects (e.g. neuromuscular weakness) and CNS effects (coma and seizures). The major safety concern arises because many drugs causing anticholinergic delirium also cause seizures or cardiovascular toxicity. In the 1970s physostigmine was suggested to be potentially life-saving in tricyclic antidepressant (TCA) toxicity [64, 65]. This suggestion overrated the anticholinergic contribution to the tricyclic toxidrome and also likely contributed to excessive doses. Subsequently, deaths and other serious adverse effects associated with the use of physostigmine within hours following tricyclic antidepressant ingestion prompted a

Table 3

Summary of clinical case series using physostigmine

Study	Physostigmine pprotocol	Response dose (mg)	Response rate %	Cholinergic events % (95% CI)	Seizures % (95% CI)	Cardiac adverse events % (95% CI)
[26]¶ *n* = 329	2 mg over 4 min, repeat doses 1–2 h as needed. Wide range of agents including non-muscarinic antagonists	Not reported	>90 §	6.4 (4.2, 9.6)	0.61 (0.17, 2.19)*	0.3 (0.5, 1.7)
[26] ** *n* = 868		Not reported	>90 §	Not reported	0.8 [0.39, 1.66]*	0.12 (0.2, 0.65)
[25] ** *n* = 39	0.5 mg every 6–7 min titrated against response in patients with a clinical diagnosis of anticholinergic delirium	Mean 1.3 Median 1	100 (19/19])§	0 (0, 9)	2.56 (0.45, 13.18)	0 (0, 9)
[21] ** *n* = 45	1–2 mg over 3 to 5 min, with repeated doses of 0.5–1 mg every 5 min until delirium resolved or cholinergic signs occurred. Restricted to patients known to have taken muscarinic antagonists	Mean 2.2 (IQR 0.5–6)	92	11.1 (4.8, 23.5)	0 (0, 7.9)	0 (0, 7.9)
[51] ** *n* = 183	Titrated dose of physostigmine to double the known dose of atropine or scopolamine. Postoperative patients† (27 with delirium and 156 prolonged drowsiness)	Median 1.2	100 (27/27)	50 increased salivation ‡	0 (0, 12.5)	0 (0, 12.5)
[52]¶ *n* = 31	Titrated dose of physostigmine to double the known dose of atropine or scopolamine. Post-operative patients (30 with delirium and one prolonged drowsiness)	Median 0.8 (IQR 0.6–1)	84 (25/30)	0 (0, 11.4)	0 (0, 11.4)	0 (0, 11.4)

*Protocol includes pretreatment with benzodiazepines. †Received barbiturate with anaesthetic. ‡No other cholinergic signs reported it is not clear if this is reporting a return to normal salivation, no treatment was required. §Response in those drugs with known muscarinic antagonism. ¶Prospective study. **Retrospective.

major reappraisal of indications and contra-indications by many clinicians [62]. A causal interpretation that events are adverse effects of physostigmine is tempered by the major contribution of the TCA overdose [66]. However, it is plausible that excessive cholinergic effects could cause seizures, bradycardia or tachycardia, or increase the rate of TCA absorption.

Some cases series exclude higher risk groups, in particular patients with QRS prolongation indicating possible sodium channel blocking drug ingestion [21, 25]. Others have used physostigmine regardless of ECG findings [26] and reported no serious cardiac events. In this series, no toxicity was seen in 315 patients with TCA poisoning (rate 0%, 95% CI 0, 1.2%) [26]. No cardiac toxicity was seen in 111 patients whose baseline QRS was greater than 100 ms. Just one patient developed premature ventricular ectopic beats following physostigmine and this was in diphenhydramine overdose [26].

Seizures (generally self-limited) are reported in many series (Table 3), with an overall rate of around 1%. This is likely influenced by patient selection and dosing protocols. The largest series reports a seizure rate of 0.6% in patients with a wide range of ingestions. However patients who had taken known proconvulsant drugs were pretreated with lorazepam [26]. Physostigmine use was associated with higher rates of seizures (OR 8.7, 95% CI 1.4, 53.9) in a series of 43 cases of maprotiline poisoning suggesting a causal relationship [67].

Treatment protocols with a target dose of 2 mg administered within 5–10 min commonly report signs of cholinergic excess, for example 6.4% 95% CI 4.2, 9.6 [26] and 11.1% [21] (Table 3). As physostigmine can cause bronchospasm a history of asthma is a relative contraindication but exacerbations of asthma have not been reported in these case series. Overall authors considered cholinergic symptoms to be mild, and these adverse effects are more an indication of probable excessive doses rather than an established safety concern. Much lower rates of cholinergic adverse effects in those studies with regimens resulting in lower doses [25, 51, 52] further suggest that faster administration protocols are commonly overshooting the required dose, perhaps due to failure to account for pharmacokinetic delay in response.

Is a better strategy evident?

Substantial clinical experience supports the efficacy of anticholinesterases, such as physostigmine, in treating anticholinergic delirium that has not responded to non-pharmacological delirium management. Further, antidotal efficacy is supported by a plausible biological mechanism and numerous controlled animal and human volunteer studies. The safety concerns are real but may have been over-stated, particularly in regard to cardiovascular toxicity. They may also be largely avoidable by better patient selection and more conservative dosing strategies. Other therapeutic cholinesterase inhibitors with different administration routes and kinetics might prove better alternative treatment options with reduced need for repeat dosing. However, these postulated improvements in treatment need better evidence to

Table 4

Pharmacokinetic characteristics of marketed anticholinesterases with CNS activity

Name	Route	Bioavailability	t_{max}	$t_{1/2}$	Metabolism/Elimination
Physostigmine	i.v., oral	3–22%	3 min	22 min	Cholinesterase-mediated hydrolysis
Tacrine	Oral	17–33%	1–2 h	1.3–2.0 h	CYP1A2, CYP2D6
Donepezil	Oral	100%	3–5 h	70–80 h	CYP2D6, CYP3A4
Rivastigmine	Dermal, oral	40%	0.5–2 h	2 h	Cholinesterase-mediated hydrolysis
Galantamine	Oral	85–100%	0.5–1 h	5–7 h	CYP2D6, CYP3A4

support them if they are to then become widely adopted. In particular it is a problem that a clear description of indications, responses, adverse effects and dosing strategies is lacking even for many of the most widely used physostigmine dosing regimens.

Despite that caveat, we believe rapid intravenous dosage protocols that administer 1–2 mg and give further doses every 5 min are a suboptimal legacy of the original recommendations. These are not consistent with the known timeframe for maximal pharmacodynamic response. While maximal brain concentrations are rapidly achieved, this ignores the much longer lag to increase brain acetylcholine. Such protocols would be expected to lead frequently to excessive doses and toxicity. As the dose leading to response is frequently reported to be less than 2 mg there is also little justification for 2 mg being a starting dose. Slower dosing may also reduce adverse effects due to unopposed nicotinic stimulation, by allowing time for desensitization. Early nicotinic effects may contribute to seizures. In anticholinesterase poisoning, seizures are much more common with agents that rapidly achieve high CNS AChE inhibition (such as nerve agents) and quite rare in agents that take hours to reach peak effects [68–70].

Most clinical studies exclude patients who are known to be at high risk of cardiotoxicity and cardiac toxicity was uncommon and not life-threatening in these series. However, we have no evidence to suggest that excluding such patients is unnecessary and would recommend that ECG screening and monitoring for a short period is optimal.

Slower onset and longer acting agents are in widespread use and appear to be more logical for many settings where prolonged delirium is expected (Table 4). It may make sense to reserve these for those with a clear diagnosis or where a relapse has occurred following a response to physostigmine. We believe there are good grounds for clinical toxicologists to experiment cautiously with such agents but would encourage them to document and report carefully their favourable and unfavourable experience. Such documentation requires the prospective use of clinically meaningful scoring systems (Table 2) [21] to describe patient severity and outcomes and treatment associated adverse events.

Conclusions

Physostigmine is an effective and relatively safe agent to use in anticholinergic delirium. It should be avoided in those at very high risk of seizures or with evidence of cardiac toxicity. A titrated dose of 0.5 to 1 mg (0.01–0.02 mg kg^{-1} in children) with a minimum delay of 10–15 min before re-dosing is likely to have similar response rates but greater safety than most current dosing strategies. Other sedatives and non-drug strategies are important in many patients, especially those with non-cholinergic factors possibly contributing to toxicity or delirium.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

REFERENCES

1 López-Muñoz F, Alamo C, García-García P. Psychotropic drugs in the cervantine texts. J R Soc Med 2008; 101: 226–34.

2 Buckley NA, Whyte IM, Dawson AH, Isbister GK. A prospective cohort study of trends in self-poisoning, Newcastle, Australia, 1987–2012: plus ça change, plus c'Est la même chose. Med J Aust 2015; 202: 438–42.

3 Hiles S, Bergen H, Hawton K, Lewin T, Whyte I, Carter G. General hospital-treated self-poisoning in England and Australia: comparison of presentation rates, clinical characteristics and aftercare based on sentinel unit data. J Psychosom Res 2015; 78: 356–62.

4 Kara H, Bayir A, Degirmenci S, Kayis SA, Akinci M, Ak A, Agacayak A, Azap M. Causes of poisoning in patients evaluated in a hospital emergency department in Konya, Turkey. J Pak Med Assoc 2014; 64: 1042–8.

5 Hendrix L, Verelst S, Desruelles D, Gillet J. Deliberate self-poisoning: characteristics of patients and impact on the emergency department of a large university hospital. Emerg Med J 2012; 30: e9.

6 Lund C, Teige B, Drottning P, Stiksrud B, Rui T, Lyngra M, Ekeberg Ø, Jacobsen D, Hovda K. A one-year observational study of all hospitalized and fatal acute poisonings in Oslo: epidemiology, intention and follow-up. BMC Public Health 2012; 12: 858.

7 McMahon A, Brohan J, Donnelly M, Fitzpatrick GJ. Characteristics of patients admitted to the intensive care unit following self-poisoning and their impact on resource utilisation. Ir J Med Sci 2013; 183: 391–5.

8 Clark D, Murray DB, Ray D. Epidemiology and outcomes of patients admitted to critical care after self-poisoning. J Intensive Care Soc 2011; 12: 268–73.

9 Bronstein AC, Spyker DA, Cantilena LR, Rumack BH, Dart RC. 2011 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 29th annual report. Clin Toxicol 2012; 50: 911–1164.

10 Hshieh TT, Fong TG, Marcantonio ER, Inouye SK. Cholinergic deficiency hypothesis in delirium: a synthesis of current evidence. J Gerontol A Biol Sci Med Sci 2008; 63: 764–72.

11 Bartus R, Dean R, Beer B, Lippa A. The cholinergic hypothesis of geriatric memory dysfunction. Science 1982; 217: 408–14.

12 Nordberg A, Svensson AL. Cholinesterase inhibitors in the treatment of Alzheimer's disease: a comparison of tolerability and pharmacology. Drug Saf 1998; 19: 465–80.

13 Darvesh S, Walsh R, Kumar R, Caines A, Roberts S, Magee D, Rockwood K, Martin E. Inhibition of human cholinesterases by drugs used to treat Alzheimer disease. Alzheimer Dis Assoc Disord 2003; 17: 117–26.

14 Brann MR, Jørgensen HB, Burstein ES, Spalding TA, Ellis J, JonsS SVP, Hill-Eubanks D. Studies of the pharmacology, localization, and structure of muscarinic acetylcholine receptorsa. Ann N Y Acad Sci 1993; 707: 225–36.

15 Pratico C, Quattrone D, Lucanto T, Amato A, Penna O, Roscitano C, Fodale V. Drugs of anesthesia acting on central cholinergic system may cause post-operative cognitive dysfunction and delirium. Med Hypotheses 2005; 65: 972–82.

16 Green R, Sitar DS, Tenenbein M. Effect of anticholinergic Drugs on the efficacy of activated charcoal. J Toxicol Clin Toxicol 2004; 42: 267–72.

17 Livshits Z, Sampson BA, Howland MA, Hoffman RS, Nelson LS. Retained drugs in the gastrointestinal tracts of deceased victims of oral drug overdose. Clin Toxicol (Phila) 2015; 53: 113–8.

18 Balthazar CH, Leite LH, Ribeiro RM, Soares DD, Coimbra CC. Effects of blockade of central dopamine D 1 and D 2 receptors on thermoregulation, metabolic rate and running performance. Pharmacol Rep 2010; 62: 54–61.

19 Schwartz PJ, Erk SD. Regulation of central dopamine-2 receptor sensitivity by a proportional control thermostat in humans. Psychiatry Res 2004; 127: 19–26.

20 Inouye SK, Van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method: a new method for detection of delirium. Ann Intern Med 1990; 113: 941–8.

21 Burns MJ, Linden CH, Graudins A, Brown RM, Fletcher KE. A comparison of physostigmine and benzodiazepines for the treatment of anticholinergic poisoning. Ann Emerg Med 2000; 35: 374–81.

22 Isbister G, Oakley P, Dawson AH, Whyte IM. Presumed angel's trumpet (brugmansia) poisoning: clinical effects and epidemiology. Emerg Med 2003; 15: 376–82.

23 Bolden C, Cusack B, Richelson E. Antagonism by antimuscarinic and neuroleptic compounds at the five cloned human muscarinic cholinergic receptors expressed in Chinese hamster ovary cells. J Pharmacol Exp Ther 1992; 260: 576–80.

24 Guthrie SK, Manzey L, Scott D, Giordani B, Tandon R. Comparison of central and peripheral pharmacologic effects of biperiden and trihexyphenidyl in human volunteers. J Clin Psychopharmacol 2000; 20: 77–83.

25 Schneir AB, Offerman SR, Ly BT, Davis JM, Baldwin RT, Williams SR, Clark RF. Complications of diagnostic physostigmine administration to emergency department patients. Ann Emerg Med 2003; 42: 14–9.

26 Rasimas JJ, Sachdeva KK, Donovan JW. Revival of an antidote: bedside experience with physostigmine. J Assoc Emergency Psychiatry 2014; 12: 5–24.

27 Ragozzino ME, Artis S, Singh A, Twose TM, Beck JE, Messer WS. The selective M1 muscarinic cholinergic agonist CDD-0102A enhances working memory and cognitive flexibility. J Pharmacol Exp Ther 2011; 340: 588–94.

28 Rygnestad T. Development of physostigmine from a poisonous plant to an antidote. One of the most important drugs in the development of modern medicine? Tidsskr Nor Laegeforen 1992; 112: 1300–3.

29 Nickalls RWD, Nickalls EA. The first use of physostigmine in the treatment of atropine poisoning. Anaesthesia 1988; 43: 776–7.

30 Aracava Y, Deshpande SS, Rickett DL, Brossi A, Schönenberger B, Albuquerque EX. The molecular basis of anticholinesterase actions on nicotinic and glutamatergic synapses. Ann N Y Acad Sci 1987; 505: 226–55.

31 Triggle DJ, Filler R. The pharmacology of physostigmine. CNS Drug Rev 1998; 4: 87–136.

32 Hamouda AK, Kimm T, Cohen JB. Physostigmine and galanthamine bind in the presence of agonist at the canonical and noncanonical subunit interfaces of a nicotinic acetylcholine receptor. J Neurosci 2013; 33: 485–94.

33 Esterlis I, Hannestad J, Bois F, Seibyl J, Laruelle M, Carson R, Cosgrove K. Imaging acetylcholine effects on [123I] 5IA-85380 binding to beta2-nicotinic acetylcholine receptors: Physostigmine studies in human subjects. J Nucl Med 2012; 53: 411.

34 Trivisano M, Terracciano A, Milano T, Cappelletti S, Pietrafusa N, Bertini ES, Vigevano F, Specchio N. Mutation of CHRNA2 in a family with benign familial infantile seizures: potential role of nicotinic acetylcholine receptor

in various phenotypes of epilepsy. Epilepsia 2015; 56: e53–7.

35 Gholami M, Saboory E, Zare S, Roshan-Milani S, Hajizadeh-Moghaddam A. The effect of dorsal hippocampal administration of nicotinic and muscarinic cholinergic ligands on pentylenetetrazol-induced generalized seizures in rats. Epilepsy Behav 25: 244–9.

36 Salas R, Cook KD, Bassetto L, De Biasi M. The alpha3 and beta4 nicotinic acetylcholine receptor subunits are necessary for nicotine-induced seizures and hypolocomotion in mice. Neuropharmacology 2004; 47: 401–7.

37 Thomsen T, Kaden B, Fischer JP, Bickel U, Barz H, Gusztony G, Cervos-Navarro J, Kewitz H. Inhibition of acetylcholinesterase activity in human brain tissue and erythrocytes by galanthamine, physostigmine and tacrine. Eur J Clin Chem Clin Biochem 1991; 29: 487–92.

38 Sherman KA, Messamore E. Blood cholinesterase inhibition as a guide to the efficacy of putative therapies for Alzheimer's dementia: comparison of tacrine and physostigmine. In: Current Research in Alzheimer Therapy. New York: Taylor & Francis, 1988; 73–86.

39 Hartvig P, Wiklund L, Lindström B. Pharmacokinetics of physostigmine after intravenous, intramuscular and subcutaneous administration in surgical patients. Acta Anaesthesiol Scand 1986; 30: 177–82.

40 Tavitian B, Pappata S, Planas AM, Jobert A, Bonnot-Lours S, Crouzel C, DiGiamberardino L. In vivo visualization of acetylcholinesterase with positron emission tomography. Neuroreport 1993; 4: 535–8.

41 Liang YQ, Tang XC. Comparative effects of huperzine a, donepezil and rivastigmine on cortical acetylcholine level and acetylcholinesterase activity in rats. Neurosci Lett 2004; 361: 56–9.

42 Hallak M, Giacobini E. A comparison of the effects of two inhibitors on brain cholinesterase. Neuropharmacology 1987; 26: 521–30.

43 Hallak M, Giacobini E. Relation of brain regional physostigmine concentration to cholinesterase activity and acetylcholine and choline levels in rat. Neurochem Res 1986; 11: 1037–48.

44 Herkert NM, Schulz S, Wille T, Thiermann H, Hatz RA, Worek F. Pre- and post-treatment effect of physostigmine on soman-inhibited human erythrocyte and muscle acetylcholinesterase in vitro. Toxicol Appl Pharmacol 2011; 253: 7–13.

45 Herkert NM, Thiermann H, Worek F. *In vitro* kinetic interactions of pyridostigmine, physostigmine and soman with erythrocyte and muscle acetylcholinesterase from different species. Toxicol Lett 2011; 206: 41–6.

46 Breitbart W, Marotta R, Platt MM, Weisman H, Derevenco M, Grau C, Corbera K, Raymond S, Lund S, Jacobson P. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. Am J Psychiatry 1996; 153: 231–7.

47 Isbister GK, Calver LA, Page CB, Stokes B, Bryant JL, Downes MA. Randomized controlled trial of intramuscular droperidol versus midazolam for violence and acute behavioral disturbance: the DORM study. Ann Emerg Med 2010; 56: 392–401.e1.

48 Thanacoody RH, Aldridge G, Laing W, Dargan PI, Nash S, Thompson JP, Vale A, Bateman N, Thomas S. National audit of antidote stocking in acute hospitals in the UK. Emerg Med J 2013; 30: 393–6.

49 Watkins JW, Schwarz ES, Arroyo-Plasencia AM, Mullins ME, Toxicology Investigators Consortium investigators. The use of physostigmine by toxicologists in anticholinergic toxicity. J Med Toxicol 2015; 11: 179–84.

50 Dart RC, Goldfrank LR, Chyka PA, Lotzer D, Woolf AD, McNally J, Snodgrass WR, Olson KR, Scharman E, Geller RJ, Spyker D, Kraft M, Lipsy R. Combined evidence-based literature analysis and consensus guidelines for stocking of emergency antidotes in the United States. Ann Emerg Med 2000; 36: 126–32.

51 Holzgrafe RE, Vondrell JJ, Mintz SM. Reversal of postoperative reactions to scopolamine with physostigmine. Anesth Analg 1973; 52: 921–5.

52 Greene LT. Physostigmine treatment of anticholinergic-drug depression in postoperative patients. Anesth Analg 1971; 50: 222–6.

53 Rosenbaum C, Bird SB. Timing and frequency of physostigmine redosing for antimuscarinic toxicity. J Med Toxicol 2010; 6: 386–92.

54 Sidell FR, Aghajanian GK, Groff WA. The reversal of anticholinergic intoxication in man with the cholinesterase inhibitor VX. Exp Biol Med 1973; 144: 725–30.

55 Cozanitis DA. Galanthamine hydrobromide, a longer acting anticholinesterase drug, in the treatment of the central effects of scopolamine (hyoscine). Anaesthesist 1977; 26: 649–50.

56 Aysın NM. Donepezil for anticholinergic drug intoxication: A case report. Prog Neuropsychopharmacol Biol Psychiatry 2003; 27: 885–7.

57 Oakley P, Isbister G, Whyte IAOP. Tacrine in the treatment of anticholinergic delirium. J Toxicol Clin Toxicol 2003; 41: 412–3.

58 Thompson JC, Nathan PJ, Stough C, Ames D, Ritchie C, Silberstein RB. The effects of donepezil on nicotinic and muscarinic blockade in healthy humans: a functional brain electrical imaging study. Eur Neuropsychopharmacol 1999; 9: 355–6.

59 Isbister GK, Oakley P, Whyte I, Dawson A. Treatment of anticholinergic-induced ileus with neostigmine. Ann Emerg Med 2001; 38: 689–93.

60 Knapp MJ, Knopman DS, Solomon PR, Pendlebury WW, Davis CS, Gracon SI. A 30-week randomized controlled trial of high-dose tacrine in patients with Alzheimer's disease. The Tacrine Study Group. JAMA 1994; 271: 985–91.

61 Farlow M, Gracon SI, Hershey LA, Lewis KW, Sadowsky CH, Dolan-Ureno J. A controlled trial of tacrine in Alzheimer's disease. The Tacrine Study Group. JAMA 1992; 268: 2523–9.

62 Pentel P, Peterson CD. Asystole complicating physostigmine treatment of tricyclic antidepressant overdose. Ann Emerg Med 1980; 9: 588–90.

63 Rumack BH. Anticholinergic poisoning: treatment with physostigmine. Pediatrics 1973; 52: 449–51.

64 Slovis TL, Ott JE, Teitelbaum DT, Lipscomb W. Physostigmine therapy in acute Tricyclic Antidepressant Poisoning. Clin Toxicol 1971; 4: 451–9.

65 Tobis J, Das BN. Cardiac complications in amitriptyline poisoning: successful treatment with physostigmine. JAMA 1976; 235: 1474–6.

66 Suchard J. Assessing physostigmine's contraindication in cyclic antidepressant ingestions. J Emerg Med 2003; 25: 185–91.

67 Knudsen K, Heath A. Effects of self poisoning with maprotiline. Br Med J (Clin Res Ed) 1984; 288: 601–3.

68 Dawson AH, Eddleston M, Senarathna L, Mohamed F, Gawarammana I, Bowe SJ, Manuweera G, Buckley NA. Acute human lethal toxicity of agricultural pesticides: a prospective cohort study. PLoS Med [Internet]. Public Library of Science;2010; 7: 1000357. doi:10.1371%2Fjournal.pmed.1000357.

69 Feiner A-S, Yersin B, Stettbacher A, Bankoul S, Baumberger C, Carron P-N. Seizures and Other Neurological Symptoms Induced by Organophosphates, Including Warfare Nerve Agents. In: Chemical-Induced Seizures: Mechanisms, Consequences and Treatment. United Arab Emirates UAE: Bentham Science Publishers 2011; 29.

70 Eddleston M, Singh S, Buckley N. Organophosphorus poisoning (acute). Clin Evid 2005; 13: 1744–55.