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CLINICAL RESEARCH



## Rivastigmine for the management of anticholinergic delirium

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### ABSTRACT

**Introduction:** Anticholinergic agents are commonly taken in overdose, often causing delirium. The spectrum of anticholinergic delirium ranges from mild agitation to severe behavioural disturbance. Physostigmine is an effective treatment for anticholinergic delirium, but its availability is limited. As rivastigmine is readily available, it has been used to manage anticholinergic delirium; however, there is limited research investigating its use.

**Method:** This was a retrospective review of patients with anticholinergic delirium treated in two toxicology units with rivastigmine (oral capsule or transdermal patch) from January 2019 to June 2023. The primary outcome was the use of further parenteral treatment (sedation or physostigmine) for delirium post rivastigmine administration.

**Results:** Fifty patients were administered rivastigmine for the management of anticholinergic delirium. The median age was 36 years (interquartile range: 25–49 years) and 27 (54 per cent) were females. Features consistent with anticholinergic toxicity included tachycardia in 44 (88 per cent) and urinary retention requiring catheterisation in 40 (80 per cent). Forty-three patients (86 per cent) were treated with physostigmine before rivastigmine administration. Twenty-two were managed with transdermal rivastigmine (most commonly 9.5 mg/24 hour patch), and 28 with oral rivastigmine 6 mg. Further parenteral sedation and/or physostigmine treatment were required more often in patients given transdermal than oral rivastigmine [16/22 (73 per cent) versus 9/28 (32 per cent),  $P=0.010$ ]. No patients had bradycardia or gastrointestinal symptoms following rivastigmine administration. One patient with a history of epilepsy had a seizure, 1.5 hours post physostigmine administration and 7 hours post transdermal rivastigmine.

**Discussion:** Rivastigmine has been increasingly used for the management of patients with anticholinergic delirium, due to the lack of availability of physostigmine. In this case series, rivastigmine transdermal patch appeared to be less effective than oral rivastigmine capsules, likely due to its slow onset of action and/or insufficient dose.

**Conclusion:** Rivastigmine can be used to treat anticholinergic delirium. In our case series oral rivastigmine appeared more effective than transdermal rivastigmine.

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## Introduction

Anticholinergic agents are commonly taken in overdose. An anticholinergic syndrome results from competitive antagonism of acetylcholine at central and peripheral muscarinic receptors [1]. Central anticholinergic toxicity can result in delirium characterised by confusion, restlessness, agitation, mumbling speech and picking at imaginary objects. Anticholinergic delirium represents a spectrum of disease ranging from mild agitation to severe behavioural disturbance. The management of patients with anticholinergic delirium may require sedation, and severe cases often require large doses of sedatives such as benzodiazepines to settle their delirium [1,2].

Physostigmine is an acetylcholinesterase inhibitor that crosses the blood-brain barrier and reduces the breakdown of synaptic acetylcholine. An increased concentration of

synaptic acetylcholine competes for binding with the muscarinic antagonist [1,3]. Physostigmine is effective in the management of anticholinergic delirium [1,4]. Physostigmine has a higher success rate with fewer complications to achieve resolution of delirium than benzodiazepines for the management of anticholinergic delirium [2,4,5]. However, physostigmine is underutilised due to concerns of adverse effects (particularly after reports of sudden cardiac arrest following its administration in tricyclic antidepressant overdose) and, more recently due to its lack of availability [5–9]. Physostigmine has a short duration of action (< 30 min), in some cases repeated doses or an infusion is required for management of delirium.

These factors have led to an increasing interest in using rivastigmine for the management of anticholinergic delirium [6,7,10–12]. Rivastigmine is used for the treatment of patients with Alzheimer dementia. It is a centrally acting pseudo-irreversible noncompetitive carbamate inhibitor of both

acetylcholinesterase and butyrylcholinesterase with far greater inhibition in the central nervous system than in the periphery [13–15]. However, it is only available as a transdermal patch and oral capsule, with no intravenous preparation. There are a few case reports and a recent case series of using the transdermal patch, oral capsule, or both to successfully manage patients with anticholinergic delirium [6,7,10–12].

The objective of this study was to report a case series of patients with anticholinergic delirium managed with rivastigmine (oral capsule or transdermal patch) from two toxicology units and compare their effectiveness.

## Methods

### Study design and setting

This was a retrospective review of patients with anticholinergic delirium, who were managed with rivastigmine (transdermal patch or oral capsule) between January 2019 and June 2023. Patients presented to one of two units, the South Eastern Area Toxicology Service (SEATS) and the Princess Alexandra Toxicology Service (PATS), which manage approximately 1,000 and 2,000 patients per year, respectively. Both toxicology units prospectively collect data on all telephone consults and admissions. Patient details are entered into purpose-built databases. Routine data collected includes demographic and ingestion information, clinical effects, treatments, complications, and outcomes. Ethics approval was obtained from respective Human Research and Ethics Committees at both hospitals (HREC/12/184:LNR/12/POW/355 and HREC/14/QPAH/308).

### Case identification

The toxicology unit databases were searched for any patient who was treated with rivastigmine for the management of anticholinergic delirium. No patients were excluded. Delirium was defined as an acute disturbance of consciousness characterized by confusion, agitation, disorientation, and/or hallucinations. Data were extracted from these databases and electronic medical records and collected onto a standardized Excel spreadsheet by researchers (clinical toxicologists) at each site (AC, KI, AH). Data collected included demographics (age, sex, weight), ingestion details (agent, dose, ingestion, time), clinical assessment at presentation, sedation and/or physostigmine received, dose and formulation of rivastigmine administered, further sedation or management with physostigmine post rivastigmine administration, adverse effects of rivastigmine administration (i.e., documentation of vomiting, bradycardia, or seizures). Sedation drugs were defined as those medications used to manage delirium/agitation and included benzodiazepines, antipsychotics, ketamine, propofol and dexmedetomidine. The dose and route of administration of rivastigmine and whether physostigmine was administered was decided by the treating toxicologist and was dependent on factors such as drug availability and patient factors.

## Outcomes

The primary outcome examined was the use of parenteral sedation or physostigmine post rivastigmine administration for the treatment of delirium. The secondary outcome examined was adverse effects of rivastigmine administration such as vomiting, bradycardia and seizures.

### Statistical analysis

Data analysis was primarily descriptive. Non-normally distributed data were presented as medians and interquartile ranges (IQR). The differences in the medians were assessed by the Mann-Whitney U test and the 95% confidence interval (CI) calculated. Categorical variables were presented as numbers (%) and were compared using the Fisher's exact test. A *P* value of < 0.05 was considered statistically significant. All analysis was performed using GraphPad PRISM® software version 10.0.2.

## Results

We identified 50 patients (median age 36 years, 27 females) who were administered rivastigmine to manage anticholinergic delirium (Table 1). The median time to presentation post-ingestion was 3.9 h (IQR: 2.1–12.6 h, *n* = 37). A variety of drugs with anticholinergic effects were ingested in this cohort (Table 2), with seven patients ingesting more than one anticholinergic agent. The majority of patients co-ingested another agent (32, 64%), most commonly ethanol (eight), benzodiazepine (12), baclofen (three) or serotonin reuptake inhibitor (three).

### Clinical presentation and management prior to rivastigmine

On hospital presentation, 33 patients were noted to be delirious, with the remainder developing delirium during their presentation. Prior to administration of rivastigmine, 47 patients received other treatments for their delirium, including sedation (parenteral or oral) and/or physostigmine. Physostigmine was administered in small (0.4–0.5 mg) aliquots, every 10 to 15 min at a median time post admission of 3.5 h (IQR: 1.3–12.6 h, *n* = 43), to a median total dose of 2.4 mg (IQR: 1.2–4 mg, *n* = 43) prior to rivastigmine administration. Fifteen patients required parenteral sedation most commonly with droperidol (*n* = 12) and/or benzodiazepines (*n* = 10). One patient who presented following an ingestion of quetiapine 24 g and ethanol, had three brief seizures prior to administration of any physostigmine or rivastigmine. Physostigmine and rivastigmine were administered later in the presentation for anticholinergic delirium, the patient had no further seizures.

### Rivastigmine administration

Rivastigmine was administered either as a transdermal patch or oral capsule in 22 and 28 patients, respectively (Table 1).

**Table 1.** Clinical characteristics and outcomes of 50 patients with anticholinergic delirium, who were treated by transdermal or oral rivastigmine.

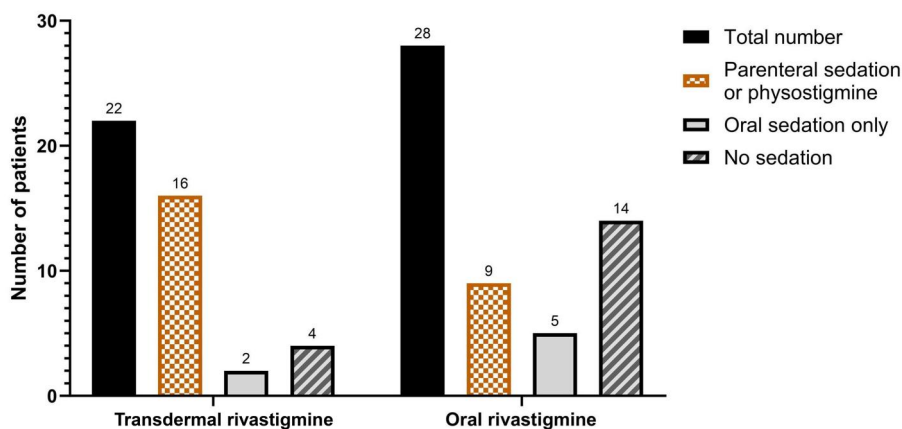
	All patients (n = 50)	Rivastigmine transdermal (n = 22)	Rivastigmine oral (n = 28)	95% confidence interval of the difference between medians (topical vs oral)	(P value)*
Median age (years) [interquartile range]	36 [25–49]	40 [26–51]	35 [22–47]	–4–13	0.218
Male	23 (46%)	11 (50%)	12 (43%)		0.776
Ingested >1 anticholinergic agent	7 (14%)	3 (14%)	4 (14%)		> 0.999
Co-ingested ethanol and/or sedating agent	27 (54%)	13 (59%)	14 (50%)		0.577
Tachycardia (heart rate > 100 beats per minute)	45 (90%)	19 (86%)	26 (93%)		> 0.999
Median maximum heart rate (beats per minute) [interquartile range]	121 [109–131]	120 [110–130]	122 [108–132]	–11–9	> 0.999
Median maximum temperature (°C) [interquartile range]	37.1 [36.9–37.9]	37.6 [36.9–38.2]	37.1 [36.8–37.8]	–0.3–0.7	0.342
Median lowest Glasgow Coma Scale score [interquartile range]	12 [8–13]	11 [8–12]	12 [8–14]	–3–0	0.093
Urinary retention requiring an indwelling catheter	40 (80%)	20 (91%)	20 (71%)		0.154
Mydriasis	23 (46%)	10 (45%)	13 (46%)		> 0.999
<b>Management prior to rivastigmine administration</b>					
Number administered parenteral sedation and/or physostigmine	44 (88%)	21 (95%)	23 (82%)		0.211
Number administered parenteral sedation	15 (50%)	8 (36%)	7 (25%)		0.536
Number administered physostigmine	43 (86%)	21 (95%)	22 (79%)		0.536
Median dose of physostigmine (mg) prior to rivastigmine [interquartile range]	2.4 [1.2–4]	3.6 [1.8–6]	1.8 [0.8–2.9]	0.4–2.8	0.009
Number physically restrained	14 (28%)	8 (36%)	6 (21%)		0.344
<b>Rivastigmine administration</b>					
Time post-ingestion [interquartile range]	22.5 [12.8–28.7, n = 36]	23.8 [12.2–33.3, n = 17]	16.3 [13.0–29.7, n = 19]	–6.1–10.8	0.655
Time post-admission [interquartile range]	11.2 [3.9–16.9]	12.0 [3.9–20.3, n = 22]	10.1 [3.7–15.4, n = 28]	–3.0–7.4	0.494
Time post physostigmine [interquartile range]	2.0 [0.5–9.9, n = 43]	3.8 [0.8–12.3, n = 21]	0.9 [0.2–9.3, n = 22]	–4.5–0.3	0.108
<b>Management post rivastigmine administration</b>					
Number administered parenteral sedation and/or physostigmine	25 (50%)	16 (73%)	9 (32%)		0.010
Number administered parenteral sedation	14 (28%)	10 (45%)	4 (14%)		0.025
Number administered physostigmine	19 (38%)	13 (59%)	6 (21%)		0.009
Median dose (mg) of physostigmine administered post rivastigmine [interquartile range]	2 [1.2–4.4]	3.6 [1.2–5.8]	1.4 [1.0–2.1]	–0.4–4.4	0.121

\*Mann–Whitney for continuous data and Fisher's exact test for categorical data.

**Table 2.** Anticholinergic agents ingested.

Drug ingested with anticholinergic effect	Number of patients* (n = 50)	Rivastigmine transdermal <sup>^</sup> (n = 22)	Rivastigmine oral <sup>#</sup> (n = 28)
Quetiapine	17 (Extended release:11, immediate release:6)	7 (Extended release:4, immediate release:3)	10 (Extended release:7, immediate release:3)
Olanzapine	9	6	3
Promethazine	9	3	6
Benzatropine	6	3	3
Amitriptyline	5	3	2
Oxybutynin	3	1	2
Trihexyphenidyl	1	1	
Clozapine	1	1	
Dimenhydrinate	1		1
Doxylamine	1		1
Datura	1		1
Hyoscine	1		1

\*Seven patients ingested more than one anticholinergic agent, <sup>^</sup>three patients ingested more than one anticholinergic agent, <sup>#</sup>four patients ingested more than one anticholinergic agent.

**Figure 1.** Sedation requirements in 50 patients after transdermal or oral rivastigmine administration for anticholinergic delirium.

Rivastigmine was given at a median time of 11.2 hours (3.9–16.9 hours) post hospital presentation. The rivastigmine transdermal patch was administered at a dose of 9.5 mg/24 h or 9.2 mg/24 h (two 4.6 mg/24 h transdermal patches) in 18 and four patients, respectively. All those who received oral rivastigmine received a dose of 6 mg, with six patients receiving further doses every 8 h for 1 to 7 days. Prior to the administration of rivastigmine, the clinical characteristics and sedation requirements were comparable between individuals receiving oral and transdermal rivastigmine (Table 1). However, those treated with transdermal rivastigmine received a greater median dose of physostigmine (Table 1). The median time to rivastigmine, post physostigmine was 3.8 h versus 0.9 h transdermal versus oral rivastigmine, respectively (95% CI of the difference:  $-4.5$ – $0.3$  h,  $P = 0.108$ ).

### Management post rivastigmine administration (primary and secondary outcomes)

Post rivastigmine 32 patients (64%) received further sedation (intravenous, intramuscular, or oral) and/or further physostigmine (Figure 1). Those receiving oral rivastigmine required less ongoing additional treatment for delirium compared to transdermal rivastigmine administration (Table 1, Figure 1).

No patients treated with either rivastigmine preparation developed bradycardia or gastrointestinal symptoms post

rivastigmine administration. One patient with a history of epilepsy who had taken oxybutynin 500 mg and ethanol had a seizure, 1.5 h post physostigmine administration and 7 h post transdermal rivastigmine. Following the seizure, the patient received further physostigmine for ongoing delirium with no further seizures.

### Discussion

In our case series focusing on the management of anticholinergic delirium with rivastigmine, it was observed that the transdermal patch formulation of rivastigmine seemed to be less effective than oral rivastigmine. This was reflected in more ongoing treatment for delirium with sedation and/or physostigmine. Notably, adverse effects were uncommon following the use of either oral or transdermal rivastigmine, indicating its apparent safety in treating anticholinergic delirium.

Our findings were similar to a recently published case series by Greene [6] of 22 patients managed with transdermal rivastigmine patch (9.5 mg/24 h or 13.3 mg/24 h) only ( $n = 7$ ) or transdermal patch and oral rivastigmine capsule ( $n = 15$ ) (oral dose varied from 3–12 mg). In Greene's case series [6] the majority of patients received a 13.3 mg rivastigmine transdermal patch and oral rivastigmine capsule 6 mg. Patients were reassessed every 15–30 min until symptoms

**Table 3.** Pharmacokinetic and pharmacokinetic properties of physostigmine and rivastigmine.

	Physostigmine (IV)	Rivastigmine transdermal	Rivastigmine oral
Time to peak plasma concentration	3–8 min	8.0 h	0.8–1.4 h
Half-life	15–40 min	Continuous patch	1.3–1.9 h
Time to peak acetylcholinesterase inhibition	5–30* min	8–16 h (decreases with increasing dose)	2–6 h
Duration of acetylcholinesterase inhibition	40–90* min	Sustained over patch application. Once removed: 3.4 h	Up to 8.5 h

\* = animal (rat) data [1,3,16–22]

resolved. The authors noted that those patients who were also administered oral rivastigmine had more rapid resolution in symptoms compared to the transdermal rivastigmine alone, with a median time of resolution of delirium of 2 h versus 5 h, respectively.

The difference between oral versus transdermal rivastigmine findings may be explained by the pharmacokinetic and pharmacodynamic profiles of these preparations (Table 3). The transdermal patches have a lower maximum concentration and longer time to reach this peak compared to the oral preparation [20]. Hence, oral rivastigmine has a shorter time to maximal acetylcholinesterase inhibition which will allow for faster resolution in anticholinergic delirium than the transdermal patch and hence less need for ongoing sedation.

The degree of acetylcholinesterase inhibition required to improve anticholinergic delirium is unclear. Failure of lower doses of rivastigmine to improve anticholinergic delirium may be due to insufficient acetylcholinesterase inhibition. The degree of acetylcholinesterase inhibition has been studied in both healthy volunteers and patients with Alzheimer dementia [13,16,20]. The studies of Alzheimer dementia patients show a dose-dependent correlation between plasma drug and metabolite concentrations and cerebrospinal fluid acetylcholinesterase inhibition [21]. A clinical study in healthy male volunteers showed that a single oral dose of rivastigmine 3 mg produced a maximum cerebrospinal fluid acetylcholinesterase inhibition of 38.9% at 2.4 hours post-ingestion [16]. A study in patients with Alzheimer disease treated with oral rivastigmine 6 mg twice daily, found the earliest time point at which significant acetylcholinesterase inhibition was observed was 1.2 h post-dose. Maximum acetylcholinesterase inhibition occurred at 5.6 h post-dose with 62% inhibition [21]. In studies of the transdermal patch, time to maximum acetylcholinesterase inhibition varies with dose, occurring at approximately 16, 12, and 8 h after application of the 4.6, 9.5 and 13.3 mg patches, respectively [22]. In comparison physostigmine in animal models achieves quicker acetylcholinesterase inhibition than rivastigmine with inhibition evident at 5 min (Table 2). Physostigmine has a ceiling effect of inhibition ~ 75%, with a reduction of this inhibition by 50% at 40 min post administration [1,3]. Hence, these pharmacokinetic properties explain the delay in clinical effect of rivastigmine to improve delirium. If used together, rivastigmine should ideally be administered soon after the administration of physostigmine which provides both diagnostic and therapeutic effects.

Hence, from the pharmacokinetic and pharmacodynamic data of oral and transdermal rivastigmine, oral rivastigmine

administration should result in faster control of delirium than the transdermal patch as demonstrated by Greene [6], with less need for ongoing sedation. For the management of anticholinergic delirium, we suggest starting with physostigmine administration (if available) as it allows faster resolution of delirium and facilitates the subsequent administration of oral rivastigmine. We recommend an initial dose of oral rivastigmine of at least 6 mg based on its pharmacokinetic and pharmacodynamic properties (Table 3), and as this dosage in our case series appeared to be safe. In severe cases of delirium, in which the patient is unable or unwilling to take oral medication and/or physostigmine is not available the transdermal rivastigmine patch 9.5 mg/24 h may be used. Even greater initial doses of oral rivastigmine of 9 to 12 mg or 13.3 mg/24 h transdermal patch may produce more rapid resolution of delirium, but requires further research [6]. Following an oral dose of rivastigmine either a repeat oral dose every 8 h or a transdermal patch will maintain rivastigmine concentrations. A prospective trial is required to help determine the optimum dose and dosing strategy and its efficacy compared to sedatives.

### Limitations

There are many limitations to this study. Firstly, this was a retrospective review and the abstractors were also not blinded to the outcomes which may have introduced bias to the results. However, the primary outcome examined was the use of ongoing parenteral treatment of delirium, which is an objective and clearly documented variable, so any bias would be expected to be minimal. Furthermore, the transdermal patch and oral rivastigmine capsule groups differed somewhat in respect to anticholinergic agents ingested with more patients in the transdermal group ingesting longer acting agents like olanzapine and amitriptyline. This may have exaggerated the effectiveness of oral rivastigmine. However, the overall numbers are small, and we suspect this effect would be limited. Secondly, there was no protocol for rivastigmine administration, with a wide variety of doses and time to administration between sites and over time. Initially the transdermal patches were predominately used as there was no access to the oral rivastigmine capsules, these patches were often placed many hours post physostigmine administration (Table 1). Also, those receiving oral rivastigmine may have had less severe delirium evidenced by their ability or willingness to cooperate with oral treatment and administration of a lower median dose of physostigmine prior to rivastigmine. However, there was no difference between the groups in terms of the number of patients

receiving parenteral sedation or physostigmine prior to rivastigmine. Another limitation was the administration of physostigmine was not standardised and physostigmine was not always available.

## Conclusion

Due to the lack of availability of physostigmine, rivastigmine has been increasingly used for the management of anticholinergic delirium. In our series the oral formulation of rivastigmine appeared more effective than the transdermal formulation. Further studies on the ideal dose of oral rivastigmine are required.

## Author contribution

AC, KI, BC, AH: drafted and edited the manuscript, AC, KI, AH: collated the patient data. All authors approved the final version of this manuscript.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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