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GUEST EDITORIAL

Cholinesterase inhibitors for delirium: what is the evidence?

Introduction

The current therapeutic agents advocated for the treatment of delirium (Meagher, 2001) have not been developed from an understanding of the underlying pathophysiology of this condition. Rather, they have emerged from "off label" clinical practice which has sought to reduce the distress experienced by both patients and clinicians. Accordingly, their use has not developed from a strong, specific evidence base, and nor is it now supported by large, well-designed clinical trials. It is also the case that these drug treatments will address the management (usually by sedation) of patients with florid, psychotic or "positive" delirium whilst quiet or "negative" delirium remains under-diagnosed and is poorly managed despite the distress it causes patients.

Recent pathophysiological evidence linking delirium to dysfunction of cholinergic neurotransmission, as well as the availability of well-tolerated drugs which principally improve cholinergic function, mean that we need to examine carefully whether these drugs should be recommended for the symptomatic treatment or prevention of all delirium types.

A delirium, or an acute confusional state, is defined in ICD-10 (World Health Organization, 1992) as a transient and fluctuating syndrome characterized by concurrent disturbance in several higher cognitive functions, including attention, perception, emotion, recent memory, psychomotor activity and the sleep-wake cycle. The DSM-IV (American Psychiatric Association, 1994) criteria further specify that clinical findings should indicate an underlying medical condition as the cause.

The prevalence of delirium varies according to the setting in which studies are conducted, but can be as high as 40% in acute hospital wards. The risk of delirium is greatly increased by age (Schor *et al.*, 1992), male gender, presence of dementia, medical comorbidity, alcohol abuse, hearing and visual impairment (Elie *et al.*, 1998). It is frequently missed as a diagnosis, especially in patients with the hypoactive/hypoalert variant (Inouye, 1994). Delirium increases hospital costs, in-hospital mortality, the risk of subsequent nursing home placement and the risk of subsequent death in the year following discharge (Cole and Primeau, 1993; Inouye *et al.*, 1998). Moreover, the hypoactive form of delirium is associated with an increased duration of hospital stay, a greater risk of hospital-acquired infections and an increased risk of developing pressure sores (O'Keeffe, 1999). The complicating effects of delirium are proportional to the severity of the delirium with the prognosis worsening if delirium remains undetected (Rockwood *et al.*, 1994). Although delirium (compared with dementia) is noted

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as an acute condition, symptoms can persist beyond the acute phase and for up to a year in approximately 15% of patients without comorbid dementia and in almost 50% of patients with pre-existing dementia (McCusker *et al.*, 2003). Apart from the overall risks associated with this condition, further problems can arise in the management of patients with delirium due to the occurrence of agitation and purposeless behaviors such as wandering, which confers an increased risk of falls (O'Keeffe, 1999).

Treating delirium or preventing its onset may lead to shorter in-patient hospital stays, as well as reducing patient distress. In addition to reducing the risks associated with delirium directly, complications (particularly hospital-acquired infections) that increase in incidence as a consequence of longer hospital stays could also be reduced.

Management of delirium at present involves the identification and treatment of the underlying medical cause, provision of an appropriate environment and good nursing care. However, a recent meta-analysis (Cole *et al.*, 1996) showed that these non-pharmacological interventions reduced the overall risks associated with delirium by only 13%. Pharmacological treatments such as typical and atypical antipsychotic agents have been used in delirium, particularly if patients are severely disturbed or distressed and pose a risk to themselves or others. The increased risk of extra-pyramidal side effects makes the use of typical antipsychotics a less favored option, but recent concern regarding the risk of cerebrovascular accidents in elderly patients treated with atypical antipsychotics (Schneider *et al.*, 2005) suggests these may not be ideal either. However, this finding has recently been challenged (Schneider *et al.*, 2006) and may be limited to patients with pre-existing cerebrovascular risk factors that had not been taken into account in earlier studies examining the risks of prescribing neuroleptics (Suh and Shah, 2005).

Benzodiazepines can be useful in delirium due to alcohol or benzodiazepine withdrawal or to treat severe agitation in those patients who may not be able to tolerate antipsychotics. Their primary action is one of sedation and, like antipsychotics, their use can make ongoing mental state assessment more difficult, impair the patient's comprehension abilities and increase the risk of falls. Moreover, paradoxical agitation has been reported following the administration of benzodiazepines (Paton, 2002).

In order to target pharmacological treatments of delirium, we require an understanding of the biological basis of delirium. It is well known that there are many different etiological factors for delirium, but as the phenotype is reasonably consistent with a deficiency principally of attention – it is plausible that, independent of the etiology of delirium, the genesis of delirium symptoms may have a common pathological or biochemical final step. In this regard, particular interest has been focused on cholinergic neurotransmission.

There are several observations that underpin this current focus and these will be explored in detail below. In summary though, cognitive deficits (e.g. attention), which are abnormal in delirium, are neuropsychological functions normally associated with cholinergic neurotransmission. Secondly, several factors that are associated with an increased risk of developing delirium also have a demonstrable effect on central cholinergic function. Finally, improvement

of cholinergic transmission pharmacologically is proving useful as a treatment paradigm worthy of more conclusive investigation.

Normal cholinergic function: how the symptoms of delirium may arise from dysfunction of this system

Analysis of the symptomatology of delirium supports a role for cholinergic dysfunction in its genesis. A recent study (Meagher *et al.*, 2007) of patients with delirium confirmed that attention deficits are the predominant cognitive feature of delirium. Acetylcholine plays a critical role in attention processing, and blocking its action through administering scopolamine (a potent antagonist at muscarinic receptors) has been shown to cause deficits in attention, learning and memory (Dunne and Hartley, 1986; Warburton and Rusted, 1993). Conversely, cholinergic agonists such as nicotine, are known to improve performance on attentional tasks e.g. (Mansvelder *et al.*, 2005).

Electroencephalogram (Reischies *et al.*, 2005) and imaging (Doyle and Warden, 1996) studies have also shown disruption of the localized attentional processing system in the posterior parietal cortex in delirium. Animal studies have demonstrated that acetylcholine improves the discrimination of and responsiveness to incoming stimuli, thereby enhancing attentional processes (Muir, 1996).

Another common symptom in delirium is a disturbance of the level of consciousness and general arousal. General cortical arousal is a cholinergic function mediated through receptors in the thalamus and most of the brainstem projections to the thalamus are cholinergic, indicating the centrality of cholinergic neurotransmission to conscious awareness (Perry *et al.*, 1999; Ballard *et al.*, 2002).

Memory deficits occur in almost 90% of patients with delirium (Meagher *et al.*, 2007). The nucleus basalis of Meynert in the basal forebrain provides cholinergic innervation to the neocortex, amygdala, cingulate cortex and hippocampus which are involved in learning and memory. Animal models have demonstrated deficits in learning and memory following lesions of the cholinergic pathways to the hippocampus (Hagan *et al.*, 1988) and in Alzheimer's disease (AD), where impairment of episodic memory is a common feature (Muir, 1997), degeneration of the basal cholinergic system is evident (Perry *et al.*, 1978). A phenomenologically indistinguishable amnesia can be induced in young people (Drachman and Leavitt, 1974) and in older patients with AD (Koller *et al.*, 2003) through administration of scopolamine, a muscarinic antagonist. As disruption of cholinergic neurotransmission both clinically and experimentally results in amnesia, it therefore follows that the amnesia in acute confusional states is likely to be due to cholinergic dysfunction.

Perceptual disturbances and delusions are also common in delirium. In psychotic illnesses these are widely believed to be due to a functional excess of dopamine and are therefore treated with dopamine antagonists. The dopaminergic and cholinergic systems are reciprocal, therefore the excess of dopamine in psychotic states is accompanied by a functional deficit in

acetylcholine. A hypocholinergic state therefore occurs in psychotic states and could underlie the psychotic symptoms seen in delirium. The improvement in delirium symptoms with antipsychotics could therefore be attributed to the relative increase in acetylcholine on dopamine blockade rather than a decrease in dopamine per se. The cholinergic etiology is further supported by the fact that hallucinations can be induced by muscarinic antagonists (Perry and Perry, 1995) as well as commonly prescribed anticholinergic medication, e.g. procyclidine (Mintzer and Burns, 2000). Also, the dopaminergic and cholinergic systems interact with glutamatergic, GABA and serotonergic systems (Gaudreau and Gagnon, 2005) with consistent evidence that the cholinergic system acts as a final common pathway following alterations in other neurotransmitter systems.

The fluctuating course, sleep-wake cycle abnormalities, delusions and hallucinations found in dementia with Lewy bodies (DLB) resemble the core features of delirium, and this disorder has also been attributed to disruption of the cholinergic system.

In summary, acetylcholine is central to normal cognitive processes such as attention, arousal and memory, and disruption of cholinergic neurotransmission has been linked to many of the key neuropsychiatric symptoms of delirium, such as decreased attention, impaired memory and hallucinations. These findings provide the etiological rationale for targeting acetylcholine in treatment of delirium and this is further supported by the associations which have been uncovered between factors which disrupt cholinergic neurotransmission and delirium.

Pathologies associated with central cholinergic impairment and their association with delirium

Cholinergic impairment is a cardinal feature of both AD (Perry *et al.*, 1978) and DLB (Perry *et al.*, 1994). Accordingly, this association with delirium therapeutically, symptomatically and epidemiologically is worth expanding upon. Therapeutically, AD symptoms can be improved with cholinesterase inhibitors (Ritchie *et al.*, 2004) as can symptoms of DLB (McKeith *et al.*, 2000). Moreover, symptoms of the later stages of AD can resemble delirium (Trzepacz *et al.*, 1998) with the distinction between chronic deterioration and acute exacerbations being often quite hard. Symptoms of DLB throughout its natural history are also very similar to delirium, not least the prominence of visual hallucinations, the fluctuating time course over the space of hours and a predominant deficit in attention as opposed to memory. Epidemiologically, there appears to be a reciprocal relationship between delirium and dementia, as there is an increased risk of delirium in patients with dementia (Elie *et al.*, 1998; Rockwood *et al.*, 1999) and an increased risk of dementia in those who develop delirium (Rockwood *et al.*, 1999), suggesting a shared underlying deficit. These observations hint at a shared biological basis between certain subtypes of dementia and delirium.

Drugs with pronounced anticholinergic effects are also associated with delirium. Predisposing factors interact with various precipitating factors such

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as infection, alcohol withdrawal, dehydration and general anesthetics to result in delirium. It is thought that about a third of delirium cases are caused by prescribed medication (Tune *et al.*, 1992), especially those with anticholinergic properties, which reiterates the potential importance of cholinergic system disruption in causing delirium. A direct measure of a person's anticholinergic burden has been available in the form of a radio receptor assay since the early 1980s (Tune and Coyle, 1980; Tune *et al.*, 1981). This test, serum anticholinergic activity (SAA), has been shown to correlate with the anticholinergic activity of specific drugs (Tune and Egeli, 1999) with both being associated with cognitive impairment (Mintzer and Burns, 2000) and the development of delirium in older people (Rovner *et al.*, 1988; Tune *et al.*, 1991).

Management of delirium

Improving cholinergic neurotransmission in different clinical conditions leads to improvement in symptoms which often occur in delirium. One example is the reduction of hallucinations in those prescribed antipsychotics that are known to cause a functional increase in acetylcholine. In addition, there have been many case reports (Noyan *et al.*, 2003; Slatkin and Rhiner, 2004) which have shown often dramatic improvement in patients with delirium who were given cholinesterase inhibitors. An open label study of rivastigmine in vascular dementia (Naughton *et al.*, 2005) demonstrated a reduced risk of developing delirium compared with those given aspirin.

As this is a new area of research interest mediated by the advent of well-tolerated acetylcholinesterase inhibitors, there are only a limited number of exploratory and more conclusive trials in this field. A randomized, double-blind placebo-controlled trial of donepezil hydrochloride given pre-operatively to reduce the incidence of post operative delirium was recently published (Liptzin *et al.*, 2005). In this study, over 1000 patients who were scheduled for elective knee or hip arthroplasty were screened, though fewer than 8% enrolled in the study. Moreover, adherence to study medication was reportedly poor in both groups and there was a high drop-out rate. The study demonstrated no significant difference in the incidence of postoperative delirium between the donepezil and placebo groups but it is important to note that the numbers eventually completing the trial were not sufficient to provide enough statistical power. Also, the patients selected were relatively young, with a mean age of 67 and were cognitively intact so the incidence rate of delirium in the placebo group may have been too low to allow a treatment effect to be observed.

A more recent trial of donepezil for post-operative delirium has also been reported (Sampson *et al.*, 2007). Again, this was a randomized, double-blind, placebo-controlled pilot study of donepezil in which 33 patients undergoing elective total hip replacement received either 5 mg of donepezil or placebo immediately after surgery and every day thereafter for three days. Donepezil was well tolerated, with no significant difference in adverse events noted between the two groups. Risk and severity of delirium was lower in the donepezil group, as was the length of hospital stay but these results did not reach statistical significance.

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This was most likely due to a type II error, and the group of patients selected would have had a relatively low baseline risk of delirium. This Phase 2a pilot study has suggested that donepezil would be useful in preventing postoperative delirium and it generated data to enable power calculations for a more definitive, randomized controlled trial of donepezil in 300 patients undergoing elective orthopedic surgery, which is currently underway in the U.K. led by the same group.

All of the above suggests an important relationship between central cholinergic dysfunction and the onset of delirium. However, an observed association does not equal causality. Working against the involvement of cholinergic disturbance and delirium are both physiological and clinical observations.

The EEG in delirium shows abnormal diffuse slowing of background activity in 80–90% of cases (Jacobson and Jerrier, 2000) suggesting a wide range of neurotransmitter abnormalities. Cholinergic neurotransmission may be the final common pathway for many neurotransmitter systems but if the primary abnormality in delirium lies elsewhere it would be more parsimonious to treat this upstream disturbance rather than treat a downstream consequence of the problem.

Also, up to 40% of delirium cases are due to a metabolic disturbance. It is unclear by what mechanism a range of metabolic disturbances could lead to a disruption in cholinergic neurotransmission. Inflammatory cytokines in the blood can lead to production of cytokines in the brain and, although these cytokines are associated with reduced acetylcholine activity in animal models (Seto *et al.*, 2002), once again, cholinergic dysfunction is not the primary abnormality.

Another common symptom of delirium is alteration in alertness level and changes in the sleep-wake cycle. Sleep is controlled largely by nuclei in the lower brain stem. Serotonin, produced by some of these cells, is associated with sleep onset (Zajicek *et al.*, 1997) and with the regulation of slow wave sleep. Other neurones produce noradrenaline, which regulates REM sleep and facilitates arousal (Shepherd, 1994). Noradrenaline is further implicated in delirium as the autonomic overactivity in delirium tremens is specifically attributed to the unmasking of chronic increased noradrenergic tone once the depressogenic effects of alcohol start to recede. These observations would support the argument in favor of exploring and therapeutically targeting these neurotransmitters rather than acetylcholine in managing delirium.

Although inattention has been attributed to cholinergic deficits, in conditions such as hyperkinetic disorder, where inattention is one of the key features, noradrenaline and dopamine have been strongly implicated. The treatment involves prescribing stimulants which increase both dopaminergic and noradrenergic neurotransmission.

Finally, we cannot ignore the fact that the two reported randomized controlled trials of a cholinesterase inhibitor did not demonstrate statistically significant benefit, although they probably lacked the power to demonstrate an effect had it existed. In addition, open label studies are of course prone to bias and case reports on their own cannot make a strong enough case for prescribing these drugs routinely to patients with delirium or prophylactically to those populations at high risk of developing this condition.

Conclusions

The etiology and clinical presentation of delirium are complex but there is a growing body of evidence to suggest that cholinergic deficits underlie most of the symptoms exhibited and may be the common final step in the convergence of numerous, apparently distinct etiologies and neurotransmitter pathways. The final proof of an association will arise through the observation of either prevention of incidence cases or improvement in symptoms of prevalent cases with treatments that directly and specifically improve cholinergic function. Case reports have shown promising results in the use of cholinesterase inhibitors in treating delirium. A large, randomized controlled trial and a Cochrane review are currently in progress and these will add further to and integrate the accumulated but patchy evidence.

The small amount of high quality research in such a prevalent and distressing condition is truly disappointing. A clearer understanding of subtypes of delirium phenomenologically and mapping these onto biological etiologies is long overdue. The evidence that does exist certainly supports an association between many of the symptoms of delirium and cholinergic dysfunction. This association is supported by both biological plausibility and epidemiological evidence. In addition, the evidence base supporting the use of acetyl cholinesterase inhibitors is much more robust than that supporting the use of sedatives and antipsychotics.

In theory, and hopefully one day in practice, cholinesterase inhibitors will represent a more rational choice for the treatment of delirium aimed at correcting the underlying cause of symptoms rather than gaining temporary symptom control through sedation. A definitive symptomatic treatment for delirium would improve detection of this common presentation and improve outcomes for patients significantly.

This review argues for a large increase in research investigating the biology of delirium, its epidemiology and ultimately optimal therapeutic interventions for the range of presentations. Currently, improving cholinergic function would appear overwhelmingly to be the most rational approach.

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