GUEST EDITORIAL

Low dose, high dose, or no dose: better prescribing of cholinesterase inhibitors for Alzheimer's disease

Background

We are approaching the 20th anniversary of tacrine's Food and Drug Administration (FDA) approval for Alzheimer's dementia which took place in 1993. Since then, three other cholinesterase inhibitors have been licensed, namely donepezil, rivastigmine, and galanthamine – all with remarkably similar clinical efficacy (Ritchie *et al.*, 2004). Little else has happened in terms of specific new treatments for Alzheimer's dementia since the early 1990s despite much effort and billions of dollars of investment in new drug discovery. New targets are proving elusive, with recently reported later phase trial successes tending to be with drugs that have a direct effect on central cholinergic activity (Prickaerts *et al.*, 2012) as opposed to novel symptomatic or disease modifying profiles.

In an attempt to keep energy in the prescribing system for Alzheimer's dementia, the manufacturers of the most commonly used drugs have developed new formulations of the same drug, for example patches (rivastigmine), extended release (galanthamine), and dispersible (donepezil and galanthamine) formulations as well higher doses (rivastigmine and donepezil) with all the standard preparations of these drugs now being available in generic preparations.

Over the last 10–20 years, clinical experience, post-licensing clinical trials, and a greater understanding of these drugs pharmacodynamics has meant that we can now meaningfully reflect on how best to use these drugs in our patients.

We can adapt the standard use of these drugs by answering four questions: (1) When should we start prescribing? (2) When should we dose escalate? (3) What should be the maximum dose we prescribe? And (4) at what point should we stop prescribing?

This editorial will provide a commentary to try and give some insights with regard to each of these four questions.

What do cholinesterase inhibitors do?

Since the introduction of the acetylcholinesterase inhibitor in early 1990s, this group of medications has been proved to be effective pharmacological interventions and widely used across the world for nearly two decades for in particular mild-to-moderate Alzheimer's dementia. Whilst they each have slightly different pharmacological profiles (Farlow, 2002; Birks, 2006) beyond their principal effect of inhibiting the enzyme acetylcholinesterase, efficacies on core cognitive and functional symptoms of Alzheimer's dementia are remarkably similar (Ritchie *et al.*, 2004).

The cholinergic deficits which these drugs target are associated with cognitive as well as neuro-psychiatric symptoms of Alzheimer's disease (Cummings and Back, 1998; Minger *et al.*, 2000), providing a neurobiological basis for the use of cholinesterase inhibitors in the management of the Alzheimer's dementia syndrome. The principal action of each of the cholinesterase inhibitors is the reversible inhibition of acetylcholinesterase. This membrane-bound, catalytic enzyme breaks acetylcholine released from the pre-synaptic neurone into acetyl and choline. As a result of the cholinergic neurones susceptibility to the pathological consequences of Alzheimer's disease in the brain mediated through the direct receptor toxicity of oligomeric $A\beta_{42}$ on the crucial α7nicotinic receptor (Nagele *et al.*, 2002), there is a marked reduction in cholinergic activity. This is compounded by the reduced synthesis of acetylcholine (as indexed by reduced choline acetyl transferase activity) in Alzheimer's dementia. Therefore, reducing the activity of acetylcholinesterase has proved a very worthwhile therapeutic target for manifest symptomatic benefit.

There have been numerous recent publications of late suggesting that the pathological processes associated with Alzheimer's dementia commence up to two decades before the dementia syndrome is diagnosed (e.g. Trojanowski *et al.*, 2010). Once diagnosed, patients with Alzheimer's dementia survive on average for about seven years, meaning that cholinesterase inhibitors could be prescribed for about ten years if initiated at the pre-dementia mild cognitive impairment (MCI) phase of the illness. During this period, there is an inexorable progression of Alzheimer's disease that may in itself affect the activity of acetylcholinesterase.

What are the consequences of such potential long-term acetylcholinesterase inhibition and disease progression on cholinesterase production

and activity? Recently, Parnetti and colleagues demonstrated a significant increase in acetyl but not butyl cholinesterase activity in the cerebrospinal fluid (CSF) of patients with Alzheimer's dementia who had been taking donepezil or other cholinesterase inhibitors (Parnetti *et al.*, 2011). There may be several factors that explain this rise in acetylcholinesterase levels. It has been recently demonstrated in animal studies that inflammation (de Oliveira *et al.*, 2012) and oxidative stress (Bond *et al.*, 2006) can lead to an increase in acetylcholinesterase production, both conditions clearly linked with Alzheimer's disease and its progression. Moreover, exposure of mice under stressful conditions (hypothesized to compromise the integrity of the blood–brain barrier) to pyridostigmine (a potent acetyl cholinesterase inhibitor) leads to an upregulation of central cholinesterase synthesis, an effect also observed specifically with donepezil (García-Ayllón *et al.*, 2007) and tacrine but not rivastigmine (Darreh-Shori *et al.*, 2004). Therefore, the CSF evidence presented by the European group is supported by a variety of basic science observations suggesting that Alzheimer's disease pathology may mediate increased acetylcholinesterase activity and (more speculatively) that long-term exposure to acetylcholinesterase inhibitors may in the long term promote acetylcholinesterase production and activity – which we could refer to as the "cholinesterase activation hypothesis."

Do clinical trial observations support the proposition that progressing Alzheimer's disease and treatment with acetylcholinesterase inhibitors leads to increasing levels of acetylcholinesterase? If this were to be the case, then the following would be observed: (1) a lack of efficacy of cholinesterase inhibitors over time; (2) withdrawal effects where patients deteriorate rapidly upon withdrawal of cholinesterase inhibition; (3) increased or maintained benefit with increased levels of cholinesterase inhibition achieved through administration of escalating doses of cholinesterase inhibitors; and (4) cognitive toxicity mediated by a reduction in cholinergic activity in people on long-term cholinesterase inhibitors in the absence of a disease which has reduced central cholinergic function.

Clinical trial evidence

Lack of efficacy over time

All clinical trials to date with any of the licensed cholinesterase inhibitors have shown two clear phases: an initial improvement over placebo and then a paralleling of decline. No published study has lasted longer than 12 months under double-blind, placebo-controlled conditions – hence, it is impossible to comment upon whether this paralleling continues *ad infinitum* or approached the placebo change over time.

Withdrawal effects where patients deteriorate rapidly upon withdrawal of cholinesterase inhibition

In the earlier studies of cholinesterase inhibitors, post-study follow-up visit were often undertaken under blinded conditions. Most notably in early donepezil studies, when participants were exposed to donepezil for 24 weeks, at a visit six weeks after active treatment was discontinued, the participants deteriorated rapidly to show decline from baseline similar to that of participants who had originally been randomized to placebo (Rogers *et al.*, 1998b), though this effect was not observed after 12 weeks of treatment (Rogers *et al.*, 1998a). One interpretation of this in light of the cholinesterase activation hypothesis proposed here is that exposures of 12 weeks are insufficient to increase the cholinesterase activity referred to above. More recently, the DOMINO (donepezil and memantine for moderate-to-severe Alzheimer's disease) study demonstrated conclusive evidence that patients on donepezil (in the majority of cases for over two years) who had reached an Mini Mental State Examination (MMSE) of just over nine went on to decline rapidly (almost five points on the MMSE within 12 months) when switched to placebo with the patients maintained on donepezil doing best either alone or in combination with memantine (Howard *et al.*, 2012).

Increased or maintained benefit with higher levels of cholinesterase inhibition

There was initial reluctance in clinical practice and in industry-sponsored trials to explore doses of cholinesterase inhibitors beyond those that were considered the most effective in pivotal trials. However, perhaps mediated by a combination of the observations outlined in this paper and the approaching loss of patents, new high dose preparations have been developed and tested of both donepezil and the rivastigmine patch. Patient selection in these trials did lead to some safety problems, whereas if patients had been excluded who upon initiation of the original cholinesterase had demonstrated tolerability issues (even if these abated over time), then the risk/benefit ratio would have been improved. To date, however (and despite this) – both in commercial (Farlow *et al.*, 2010; Cummings *et al.*, 2012) and non-commercial (Doody *et al.*, 2008) studies, the additional clinical benefit of high dose cholinesterase inhibitors has

been demonstrated in patients established on standard doses of cholinesterase inhibitors.

Cognitive toxicity in people on long-term cholinesterase inhibitors in the absence of a disease that reduces central cholinergic function

This is the hardest part of our cholinesterase activation hypothesis to find empirical evidence to support as giving cholinesterase inhibitors to people without a cholinergic illness has not been subject to prospective, long-term clinical trials. However, there have been trials in amnestic MCI (aMCI) with cholinesterase inhibitors. Although there is a presumption that patients with aMCI are at high risk of developing Alzheimer's dementia and therefore having Alzheimer's disease mediating their cognitive symptoms, a sizeable proportion of people with aMCI never develop Alzheimer's dementia and therefore are unlikely to have substantial central cholinergic neuronal pathology. Administering cholinesterase inhibitors to this group would therefore risk mediating an increase in cholinesterase activity leading to not only a lack of efficacy during the study (as they had a pre-existing healthy central cholinergic system) but also the risk of cognitive toxicity after the study was concluded when an unchecked increase in cholinesterase activity mediated by the cholinesterase inhibitor would lead in effect to central hypocholinergic function. The trials of cholinesterase inhibitors in aMCI were uniformly disappointing: failing to meet their pre-specified treatment goals (e.g. Winblad *et al.*, 2008; Doody *et al.*, 2009), with most commentators agreeing that this was due to the heterogeneity of the study samples. No post-trial follow-up data are available to determine whether some patients had accelerated cognitive decline after the study completed nor was there any sub-analysis presented of cognitive outcomes in those trial participants who did not progress to Alzheimer's dementia. Recent evidence from the Australian Imaging, Biomarker and Lifestyle (AIBL) study suggesting that patients with MCI exposed early to cholinesterase drugs had a worse prognosis would give some support to our proposition (Sona *et al.*, 2012). There are however several other reasons for the AIBL observation articulated in that paper's accompanying editorial (Schneider, 2012).

Summary and proposals

Better prescribing of cholinesterase inhibitors can be summarized in three domains: timing, balance, and selection.

On the basis of the observations outlined in this editorial, we would propose that initiation of cholinesterase inhibitors for patients with uncertainty regarding the presence or degree of cognitive decline due to Alzheimer's disease-mediated cholinergic dysfunction is to be avoided. In effect, the lack of empirical evidence of success and with the risk of precipitating longer term cognitive toxicity, cholinesterase inhibitors should not be used in aMCI or prodromal dementia. If a specific biomarker for cognitive decline secondary to central cholinergic dysfunction were available, then this could be used for patient selection; to date, no such biomarker exists. Additionally, if a standard single dose is to be used for the duration of the patient's illness, then early initiation in mild dementia may also lead to long-term detriment in cognitive function. When initiation does take place, it should be of the lowest effective dose rather than the current policy of incrementing over the course of weeks to the highest licensed dose. There is evidence of dose effects with rivastigmine and donepezil, but lower doses in trials remain effective (Ritchie *et al.*, 2004). Lower doses may be less likely to drive an increase in cholinesterase production and increments can be left in reserve if and when they are needed when the patient clinically deteriorates. The availability of generic cholinesterase inhibitors will increase access to them and this may increase injudicious prescribing of them in earlier disease and even in the absence of disease. We would argue that despite the price reduction, the pharmacological management of dementia and cognitive impairment remains complex and initiation, incrementation, and general review of interventions should remain a specialist's remit.

Increasing the doses of patients established safely on a cholinesterase inhibitor is backed up by clinical trial data and pre-clinical and clinical pharmacodynamic research. However, to achieve the optimal benefit to risk ratio, patients need to be carefully selected. First, they should only be selected if they have shown benefit when the drug was started originally and there were no observable side effects. This benefit can be assessed through objective cognitive or functional testing or through observations the patient has made about their own abilities or carers or family members have made about them.

When increments are made, then close safety monitoring is recommended – in particular undertaking pre- and post-increment Electrocardiograms (ECGs).

Once patients are stabilized on cholinesterase inhibitors – they should not be stopped as there is a significant risk of a rapid decline in function and cognition. In conclusion and referring back to the original four questions posed:

1. *When should we start prescribing?* Only when we are reasonably certain that patients have a central cholinergic deficiency leading to dementia symptoms.
2. *When should we dose escalate?* When there is clinical judgment that the patient is either not responding as we would anticipate or there is evidence of deterioration after initial efficacy on a lower dose. Going beyond standard doses may be reserved for patients who showed evidence of a beneficial effect at these doses and had little or no tolerability/safety issues.
3. *What should be our maximum dose?* Dose ceilings should be set by safety and tolerability, not efficacy. Doses double the standards have been subject to double-blind, randomized trials and this would appear a reasonable upper dose limit at this stage.
4. *When should we stop prescribing?* When there is evidence of safety concerns otherwise, once stabilized, a patient should not discontinue their cholinesterase inhibitor. However, cessation of a cholinesterase inhibitor should be considered as part of end of life management in very severe dementia.

Future research directions

Many of the observations and proposals made here would benefit from further empirical evidence. Prospective, double-blind Randomised Controlled Trials (RCTs) of different prescribing patterns with regard to both dose and increment patterns from initiation to mid and then high doses would be important. The development of a biomarker or panel of biomarkers in concert with a clinical signature for cholinergic mediated cognitive decline would also be welcome to help select patients most likely to benefit from this intervention type. We would also argue that all future trials of drugs affecting the cholinergic system should include a blinded review of participants after discontinuation of study medication.

Although it is almost 20 years since we started using cholinesterase inhibitors for patients with Alzheimer's dementia, the way we use these important drugs has changed little. We remain in the dark around timing of initiation, incrementation and discontinuation, patient selection, and dose levels. As we await new treatments for the symptoms of dementia and to address disease progression, there should be a move for more clinical trials like DOMINO (Howard *et al.*, 2012), which sought to answer critical clinical questions. It may be some time before we get new drugs for Alzheimer's disease and dementia so, in this hiatus, we must learn how to use the ones we do have better.

Conflict of interest

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