

EDITORIAL

Antioxidants and Alzheimer's disease: time to stop feeding vitamin E to dementia patients?

In 1974 one of us attended a lecture on aging by the Nobel prize winning immunologist, Sir Macfarlane Burnet. Burnet indicated that oxidative stress was central to the aging process, and that interventions to ameliorate this process should prolong the human lifespan and diminish the incidence of age-related diseases, one of the most important of which is, of course, Alzheimer's disease (AD). A decade after this lecture was given, Burnet died of rectal carcinoma – a typical age-related disease. Thirty three years on, has the field advanced at all?

Why might giving antioxidants to people with or at risk of Alzheimer's disease be a good idea?

The free radical hypothesis of aging dates back to 1956 (Harman, 1956), and proposes that free radical reactions, which damage cells, are the primary mechanism by which aging occurs. Surrogate markers of free radical injury are present in patients with AD (Grunblatt *et al.*, 2005) and the location of signs of oxidative damage near plaque and tangle sites, together with the presence of such changes in pre-AD states, such as Mild Cognitive Impairment (MCI) (Ames *et al.*, 2006), suggest that the oxidative changes may be implicated in the causation of AD, rather than being a mere epiphenomenon. Indeed, recent evidence points to the initial elevation of amyloid β as a physiological reaction to oxidative stress, as this protein has antioxidant properties (Nunomura *et al.*, 2006). The original sources of oxidative stress are many, but research now points to an important role for mitochondrial dysfunction (Reddy and Beal, 2005).

As well as the biological plausibility of antioxidant strategies being useful in treating or preventing AD, findings from epidemiological studies also support such an approach. Aging cohort studies which have used questionnaires to monitor the intake of the antioxidant vitamins C and E suggest the possibility of a mild beneficial effect of antioxidant intake upon the risk of developing AD, though the studies are far from unanimous in their conclusions (Stein and Sano, 2007). Most recently, polyphenols present in certain fruit and vegetable juices that have potent antioxidant activity have been reported to reduce the incidence of AD over a 10-year period (Dai *et al.*, 2006). So it makes sense to ask whether

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prospective administration of antioxidants to people affected by, or at high risk of, AD could be helpful.

Studies of antioxidants given to patients with manifest Alzheimer's disease

Vitamin E (α tocopherol)

Only one double-blind placebo controlled trial assessing the efficacy of vitamin E in the treatment of established AD has been conducted (Sano *et al.*, 1997). This trial compared the efficacy of 2000 IU/day of vitamin E, 10 mg/day of the inhibitor of monamine oxidase B, selegiline, both vitamin E and selegiline taken together, and placebo, in retarding progression of dementia in 341 individuals with moderately severe AD as rated by the Clinical Dementia Rating scale (CDR) (Morris, 1993) over two years. The primary outcome was the time to deterioration as measured by death, loss of the independent ability to perform any two of three basic activities of daily living (ADLs) (these were eating, grooming and using the lavatory), entry to institutional care, or progression from moderate dementia (CDR level 2) to severe dementia (CDR level 3). Secondary outcome measures included standard measures of cognition (the Mini-mental State Examination (MMSE) (Folstein *et al.*, 1975) and the Alzheimer's Disease Assessment scale cognitive subscale (ADAS-Cog) (Rosen *et al.*, 1984)), as well as measures of behavior, function and the presence of extra-pyramidal signs.

Unadjusted comparisons between the groups showed no significant difference in outcome on any of the primary or secondary outcome measures. However, when baseline cognitive function measured by the MMSE was included as a covariate (the placebo group turned out to have higher MMSE scores than the other groups and the baseline MMSE score was a strong predictor of final primary outcome) treated individuals had longer survival to primary endpoint than patients on placebo (230 days for vitamin E alone, 215 days for selegiline alone and 145 days for those on combined treatment) and all the findings attained statistical significance (risk ratios were 0.47, $p = 0.001$ for vitamin E, 0.57, $p = 0.012$ for selegiline, and 0.69, $p = 0.049$ for combined therapy).

Although these results suggest that both vitamin E and selegiline may retard deterioration in patients with moderate AD, there are a number of reasons why that conclusion can be at best tentative and at worst open to serious doubt (Drachman and Leber, 1997). First, the four endpoints are not strictly comparable (is being dead the same as being unable to eat or groom oneself independently?). Second, none of the cognitive measures showed evidence of response to drug treatments and this is inconsistent with the adjusted primary outcome results. Third, there is considerable disagreement among statisticians as to whether the *post hoc* transformation of the data by controlling for MMSE

score was appropriate or justifiable. When the statistical significance of a study is determined by the choice of analytic technique that interpretation is confounded. Fourth, the trial included a relatively small number of individuals (fewer than 100 in each treatment arm). Fifth, drug level monitoring indicated that not all patients allocated to specific therapies had evidence of those treatments in their urine or plasma and that some patients in the placebo group were nevertheless excreting metabolites of selegiline (13%) or had vitamin E in their serum (12%)! Sixth, if each of these treatments is helpful why did combined therapy produce an apparently smaller effect than either therapy alone? Last, the CDR is a blunt instrument and a change of a whole grade can be determined by a small decline in one of the domains for an individual close to the transition point to severe dementia, or may require quite large declines on more than one parameter for an individual who was until recently only mildly demented. If patients in different groups were closer to or further away from the CDR level 3 endpoint than patients in other groups then the groups could not fairly be compared.

The study by Sano and colleagues (1997) represents a worthwhile and unusual attempt to investigate the efficacy of a therapy which lacks patent protection, but in the absence of further studies showing vitamin E to be efficacious in the treatment of AD, we believe that it provides a manifestly insufficient basis to justify the prescription of vitamin E to people who have AD.

Inhibitors of monoamine oxidase B

Inhibitors of monoamine oxidase B may act as antioxidants. In addition, they increase catecholamine levels and such adrenergic stimulation may ameliorate the cognitive deficits seen in AD (Schneider *et al.*, 2005). These drugs include selegiline, lazabemide and rasagiline. A number of open label studies have suggested possible efficacy for selegiline in AD (it is licensed for the treatment of Parkinson's disease), but, as noted in the previous subsection, the largest double-blind placebo controlled trial in AD produced equivocal results (Sano *et al.*, 1997). A Cochrane review of selegiline treatment for AD (Birks and Flicker, 2003) included 17 trials in which between 8 and 87 patients were treated with selegiline for between 4 and 156 weeks. There were few significant treatment effects, though all favored selegiline, and there was little evidence of adverse effects. The review concluded that there was no evidence of a clinically meaningful treatment effect for people with AD treated with selegiline, irrespective of the outcome measures employed, and recommended against both its use for the treatment of AD and the conduct of future efficacy studies.

The Roche drug lazabemide (Sramek and Cutler, 1999) has been tested in at least four phase III double-blind placebo controlled trials, none of which

has been reported in the peer-reviewed literature. Conference presentations and abstracts have indicated that it was not wholly without efficacy in the treatment of mild to moderate AD, but concerns over safety and a failure consistently to produce beneficial effects on both cognitive function and global measures of change have led to the apparent abandonment of its development as a treatment for AD. However, interest in inhibitors of monoamine oxidase B as potential treatments for AD is not yet dead, as the agent rasagiline is now the subject of current clinical trials in patients with mild to moderate AD.

Idebenone

Idebenone is a benzoquinone derivative that protects cell membranes against lipid peroxidation and may improve brain metabolism (Gutzmann *et al.*, 1996). The drug has been assessed in two randomized trials of 6 and 12 months' duration respectively (Gutzmann *et al.*, 1996; Gutzmann and Hadler, 1998). The first trial randomized 300 AD patients, the second 450, and in both trials two-thirds of those randomized received various doses of active drug and one-third were treated with placebo. The second study also incorporated a 12-month extension in which all patients received idebenone (Gutzmann and Hadler, 1998). Both trials showed a robust, statistically significant dose-dependent beneficial effect of the drug on both standard measures of cognition and clinical global impression of change. Idebenone was reported to be well tolerated with no significant disadvantage over placebo in terms of reported adverse events. The drug's beneficial effects continued into a second year of treatment (Gutzmann and Hadler, 1998). It is therefore disappointing and mysterious that further reports of clinical development of idebenone to treat AD over the past eight years are lacking.

Ginkgo biloba

Among the many putative actions of ginkgo is its potential to act as a free radical scavenger (Schneider *et al.*, 2005). Some equivocal evidence of slight beneficial effects upon cognitive function has been seen in trials in people with AD, but its efficacy is considerably less than that of cholinesterase inhibitors, which have been attacked by some for their modest treatment efficacy (AD2000 Collaborative Group, 2004; Schneider *et al.*, 2005).

Clioquinol

Clioquinol affects the redox interaction between metal ions (in particular copper and zinc) and amyloid β (Bush, 2002), reducing hydrogen peroxide production. As well as other potentially therapeutic targets in AD, clioquinol is an antioxidant with potential as a treatment for AD. In a small single-centre study conducted in Melbourne, Australia, clioquinol showed cognitive benefits greater

than placebo in patients with more severe cognitive impairment (Ritchie *et al.*, 2003). Although development of clioquinol has ceased, a sister drug (PBT2) has demonstrated cognitive benefit in transgenic mice and is about to enter phase 2 testing in human subjects.

Trial of vitamin E in people with Mild Cognitive Impairment (MCI)

If vitamin E has the potential to treat established AD, in which substantial tissue damage has occurred by the time symptoms of cognitive decline are clearly apparent, one might hope that it could be more effective at an earlier stage of the pathological process, as represented by the diagnostic entity of Mild Cognitive Impairment (MCI). One study has compared the efficacy of vitamin E (2000 IU/day), donepezil (10 mg/day) and placebo in preventing the development of AD in 769 subjects with MCI over a three-year period (Petersen *et al.*, 2005). In all, 212/769 subjects developed possible or probable AD as defined by the McKhann criteria (McKhann *et al.*, 1984) over the three years of the study. There was a non-significant tendency for individuals treated with donepezil to be less likely to “convert” to clinical AD, but no such signal was seen in the vitamin E treated subjects whose hazard ratio for conversion to AD compared to placebo treated subjects was 1.02 (95% CI = 0.74–1.41, $p = 0.91$).

Long-term safety of high doses of vitamin E

Although the efficacy of vitamin E in the management of AD and related disorders has been unclear on the basis of available evidence, until recently individuals prescribing such treatment were consoled by the lack of any clear evidence of adverse effects in trials – the intervention seemed to be safe. However, vitamin E trials were powered to detect efficacy rather than to determine the rate of (possibly rare) adverse effects of the vitamin. In order to assess safety in more detail it was necessary to integrate the results of a large number of studies assessing use of the vitamin for a variety of indications, and this has now been done (Miller *et al.*, 2005). Miller and colleagues reviewed 19 trials in which 135,967 participants took vitamin E either alone or in combination with other vitamins and minerals at doses between 16.5 and 2000 IU/day for a diverse range of putative indications. High-dosage vitamin E was defined as doses above or equal to 400 IU/day. The pooled all-cause mortality risk difference for 11 high-dose trials (nine of which showed an increased risk for all-cause mortality) was 39/10,000 persons, though confidence limits were wide (95% CI = 3 to 74 per 10,000 persons, $p = 0.035$). This situation was reversed for low-dosage trials in which the difference was $-16/10,000$ (CI = -41 to $+10/10,000$ persons

$p < 0.02$). When dose-response analysis was performed a statistically significant relationship between vitamin E dose and all-cause mortality emerged, which was apparent for dosages above 150 IU/day. Possible mechanisms driving the slight increase in mortality at high doses include anti-coagulant effects (some trials reported increased rates of cerebral hemorrhage in participants taking vitamin E), paradoxical pro-oxidant effects at high doses, displacement of other antioxidants and inhibition of enzymes, which detoxify drugs and endogenous toxins.

Conclusions

There is some theoretical biological and epidemiological evidence to suggest that antioxidants might retard the emergence and perhaps the progression of AD. Trial evidence for vitamin E, the most widely advocated antioxidant therapy, is inadequate for firm conclusions to be drawn, but so far indicates dubious efficacy for the treatment of AD and absolutely no efficacy in the prevention of conversion from MCI to symptomatic AD, despite the fact that one would expect it to be of greater use at an early rather than late stage of the illness before profound tissue damage has already occurred. There appears to be a slight increase in all-cause mortality among individuals taking high-dose vitamin E, and given the lack of evidence that it is helpful, and some suggestion that it may do harm, it would therefore seem unwise to advocate its use by individuals at risk of or affected by AD. Inhibitors of monoamine oxidase B have a rather disappointing track record but at least one is still under development for the treatment of AD. Idebenone and clioquinol and related compounds appear to show clinical promise, but further trials are needed to determine whether or not they have any place in the treatment of AD. The lack of further publications over the past eight years may indicate that development of idebenone has been abandoned for some reason. As with so many other promising therapeutic possibilities for the treatment of AD, theory and epidemiology have promised much in relation to antioxidant interventions, but clinical trials have failed conspicuously to deliver the knockout punch to AD that we seek.

Conflict of interest declaration

Both authors have acted as consultants for, and have undertaken research sponsored by Prana, the company which pioneered the use of clioquinol for the treatment of AD and is now evaluating its sister compound PBT2 for the same indication. David Ames has acted as an investigator in two trials of

lazabemide for the treatment of AD and one of rasagaline used for the same indication.

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