Therapeutic Possibilities in Patients with Senile Dementia

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This article looks at the present therapeutic possibilities for slowing or reversing the mental impairment in patients with senile dementia. Space will not allow discussion of the management of acute confusional states or of the vital necessity of excluding treatable causes of chronic confusion by clinical and laboratory investigations. Furthermore, equally important topics such as the control of incontinence, insomnia and wandering will not be covered, even though they are frequently the cause of a caring person withdrawing help and are now redeemable.

There is clear evidence of a cholinergic dysfunction in age-related memory disturbances. First, significant changes in cholinergic markers occur in brains of aged animals and man. Second, these changes can be related to the loss of cholinergic function at the neuronal level. Third, relationships can be established between these changes in the cholinergic system and the loss of memory that occurs with ageing. Fourth, artificial disruption of the cholinergic mechanisms in young subjects impairs memory tasks in ways strikingly similar to those that occur naturally in old age and dementia, and last, a narrow range of doses of certain cholinominetics can significantly decrease the memory impairment in aged subjects[1]. It is self-evident, therefore, that the major therapeutic thrust should involve cholinergic pathways. This is not to dismiss other neurotransmitter systems which may prove later to be equally or more important[2], but with present knowledge it seems important to ask whether clinically useful improvements can be made in chronically confused patients by manipulating the cholinergic neurotransmitter system and whether currently marketed drugs affect that system.

Acetylcholine Neurotransmitter System

Effect of Altering Diet

(a) On Brain Acetylcholine Concentrations. Choline is present in egg yolk, meat, fish and cereals and absent in fruits and soft vegetables. Increasing choline or lecithin (a normal dietary source of choline) in the diet increases acetylcholine concentration in the plasma and in the brain[3-5]. Conversely, decreasing choline in the diet decreases the acetylcholine content of the brain in rats. Thus pharmacological or pathological changes in choline availability influence synthesis of the neurotransmitter acetylcholine, and even fluctuations in dietary choline such as would occur in a non-fad eater cause parallel changes in acetylcholine concentrations, especially within the caudate nucleus.

(b) On Alzheimer Patients. Despite such evidence, demented patients disappointingly do not seem to improve on choline or lecithin diets[1]. Although some studies used an inadequate study period, e.g. one day[6], or patients who were clearly very severely impaired, the effects of precursor loading are far from impressive even in well-controlled double-blind studies[1]; homeostatic processes in the brain may reverse any acute increase in acetylcholine concentrations following dietary alteration[7].

Effect of Cholinergic and Anticholinergic Drugs

Physostigmine has been somewhat more successful in improving long-term memory in normal, old and young subjects[8,9] but is attended by adverse effects, a short half-life and a narrow effective dose range. It does, however, reverse the memory dysfunction caused by scopolamine whereas amphetamine does not. Scopolamine significantly impaired cognitive function in a group of normal subjects[10], a result mirrored by hyoscine[11] and also shown in Parkinsonian patients given benzhexol[12,13]. Although results are so far not therapeutically outstanding, they must stimulate more studies and research for drugs similar to physostigmine but with fewer disadvantages.

Utilisation of the Increased Concentration of Acetylcholine

In vitro work on brain biopsies from normal and Alzheimer brains shows that glucose oxidation is not impaired in Alzheimer neurones whether resting or stimulated by potassium[14]. However, Alzheimer tissue is less able to produce acetylcholine in the presence of excess choline even though there is still a response to potassium stimulation. Similar methods were used to demonstrate the effects in rats on the flux of glucose into acetylcholine of drugs marketed for the treatment of dementia. Pipradol, piracetam and hydrgine had no effect on glucose oxidation or acetylcholine synthesis; nafldrofuryl increased glucose oxidation, which has been shown before[15,16], but caused a reduction in acetylcholine synthesis[17]. Meflofenoxide enhanced acetylcholine synthesis but had less effect on glucose oxidation[17].
Dietary manipulation of the acetylcholine neurotransmitter may be unsuccessful because the brain has to enjoy neuronal stimulation to increase acetylcholine synthesis in demented patients when extra precursor is available[1]. Clinical impressions support the view that some demented patients improve functionally when removed from an isolated situation to one of increased stimulation such as a younger household or a hospital where their diet is presumably also better. Bartus and co-workers[4] showed that aged rats performed no better in a passive avoidance task when given choline than when given placebo, despite markedly increased brain choline concentrations, but did significantly better when given piracetam in addition to choline, although piracetam abolished the rise in choline levels. One possibility is that the choline had been utilised.

A preliminary study of piracetam and choline in man produced mildly encouraging results along the same lines. Three out of ten patients with senile dementia improved clinically and objectively up to 70 per cent in some tests when given a combination of piracetam and choline[19]. However, there is still no convincing evidence to support the hypothesis that an additional factor is necessary in demented brains to allow the cholinergic neurones to use the excess or increased choline concentrations that can be easily produced by diet. It is, however, an area of intense interest and research at present, when the most promising mixture is that of choline and meclofenoxate; unfortunately, that drug has been withdrawn from the market.

Drugs Currently Marketed for the Treatment of Senile Dementia of the Alzheimer Type

Despite the vast experimental work in the biochemical field on dementia, the practising physician remains justifiably sceptical about whether any such drugs produce clinically effective improvement in demented patients. The reasons are twofold: first, many of the drugs have been around for 20 or more years, so detailed pharmacokinetic studies have never been done, and second, the clinical studies proving effect are largely wanting. A more detailed look at two market leaders, co-dergocrine mesylate and naftidrofuryl oxalate, will elaborate these points.

Pharmacokinetics

Unless a drug or its active metabolite arrive in adequate concentrations at the receptor site it will have no demonstrable effect. Table 1 outlines the known kinetics of co-dergocrine mesylate and naftidrofuryl, but note that the data come almost entirely from a single report in each case[19-21].

| Co-dergocrine mesylate [19] | Nafldrofuryl [20, 21] |
|-----------------------------|-----------------------|
| Absorption from gastrointestinal tract | about 25% | 50-100% |
| Bioavailability | 5-12.5% | approx. 24% |
| Volume of distribution (litre/kg) | 9.9-20.5 | 0.37 |
| Plasma half-life | 13.9 (9.5-18.4) h | 40.5 (32.5-46.6) min |

There are large gaps in our knowledge of the kinetic characteristics of both drugs. In particular there is no good agreement on the correct dose of co-dergocrine for man, and we do not know whether chronic dosing affects the kinetics, or how much of the drugs penetrate the CNS in normal individuals and in those with dementia.

Co-dergocrine Mesylate. This drug is a collection of dehydrogenated ergot peptide derivatives in the methanesulphonate form (mesylates). All are large, many ringed, quaternary ammonium compounds, so the application of basic pharmacological principles would predict incomplete and unreliable absorption from the gastrointestinal tract, and difficulty in crossing the blood-brain barrier[22]. Published kinetic evidence supports the view that co-dergocrine mesylate crosses the gut membrane poorly. Kleimola et al.[23] were unable to detect by radioimmunoassay any drug in plasma during 24 hours following 3 mg doses to man and 5 mg to dogs. Only 0.41 per cent of a 3 mg dose was excreted in 32 hours in man even though tablets were taken under optimum conditions for absorption. The problem is not one of formation since no greater amount is absorbed even if the drug is taken in solution[24]. Xanthine improves absorption byComplexing with the drug[19] but an average of 25 per cent of an oral dose is absorbed under normal conditions[19,23]. There is a marked `first-pass' effect so the absolute bioavailability is between 5.3 per cent and 12.4 per cent after a single dose[19]. The apparent volume of distribution of dihydroergotoxine is relatively large (9.9-20.5 litre/kg) and the mean half-life of the beta-elimination phase is 13.9 (range 9.5-18.4). Hepatic metabolism is the main route of elimination[19].

Naftidrofuryl. There is good (up to 100 per cent) but variable absorption of naftidrofuryl after oral administration but the drug undergoes extensive `first-pass' metabolism so that about 24 per cent is bioavailable. The apparent volume of distribution is small (mean 0.37 litre/kg), suggesting high protein-binding[20]. Pseudo-cholinesterase in the blood rapidly metabolises the drug, which has a beta-elimination half-life of about 40 min[21]. The metabolites, which may be active, appear in the bile and undergo enterohepatic circulation, but none of the original compound is found in urine or faeces. There is some evidence that the drug penetrates into the CNS[26].

Pharmacodynamics

Co-dergocrine Mesylate. Ermini and Markstein[29] found that co-dergocrine acted in a regulatory manner at dopaminergic and serotoninergic sites. It appeared to act both as a partial agonist and a blocker, depending on the level of endogenous neurotransmitter. It also blocks alpha 1 and 2 receptors and decreases the cyclic AMP response to noradrenaline.
There is consistent evidence that co-drgocine has a beneficial effect in demented patients. Yesavage et al.[28] reviewed the literature in 1979 and found 32 clinical studies on hydergine, of which 22 met the criteria for controlled studies. All showed improvement, which in 18 was judged to be of practical importance. McDonald[29] enlarged the number of studies reviewed to 38 in 1982. He agreed that in almost all the studies co-drgocine showed varying degrees of success compared with other substances (mostly placebo) in clinical rating scales. Of the studies 50 per cent showed a positive improvement in symptoms, the best being in depression, confusion and disorientation, and the drug was generally agreed to be safe and well tolerated at a dose of 3-4.5 mg a day. Hindmarch[30] showed that 12 mg per day significantly increased critical flicker fusion levels and the speed of cognitive processing tasks in normal young volunteers. Psychostimulants and some antidepressants also produce similar responses[30] but, unlike co-drgocine, such effects do not persist for two weeks after withdrawal of medication. Kugler et al.[31] found similar results in a study involving a large number of demented patients, 50 per cent of whom improved on co-drgocine compared to 37 per cent on placebo, whereas 36.7 per cent on co-drgocine and 57.5 per cent on placebo became worse. However, analysis of this deterioration showed that functional loss on the drug was half that on placebo.

A large body of evidence thus apparently supports the claims that co-drgocine is beneficial to demented patients. It is difficult, therefore, unless a more detailed analysis of the studies is made, to understand why many doctors, especially in the UK, remain sceptical about its beneficial effects[32]. An analysis reveals that for example, five of the 38 studies published by McDonald[29] were merely proceedings of medical meetings and nine were published in journals which receive a fee for publication from authors. A further study was published in a journal that commissions articles and pays a fee. The prime tool chosen to evaluate efficacy in almost every study was clinical observer rating scales which limit the observer’s sphere of reference to the immediate situation, require patient co-operation, may not allow direct observation of social behaviour and performance in daily activities and may miss episodic behaviour. There are also problems of measurement such as leniency error, translating behaviour to a rating scale and often translating a third party’s impression of the patient into a rating score, i.e. scoring someone else’s impression of the patient’s performance. Although there was ample statistical evidence of the superiority of co-drgocine over the comparison substance, especially in the areas of mental alertness and depression of mood, there was a shortage of objective evidence that the drug increased cognitive functioning in ageing and demented patients. The drug did not improve practical management or decrease hostile behaviour[33]. Hughes et al.[34] carried out a critical review of 12 clinical trials of co-drgocine used in the treatment of dementia, six of which were published in the Journal of the American Geriatric Society, one in the Johns Hopkins Medical Journal and five in Current Medical Research and Opinion or Current Therapeutic Research.

Again the reviewers found consistent statistically significant improvements in 13 symptoms associated with dementia. However, further analysis showed that large numbers of patients improved a very small amount, and that evidence for a sustained improvement was scant. They concluded that the drug had a minor place in the treatment of dementia.

Other Drugs for Senile Dementia. The criticism of studies of co-drgocine can be levelled at those involving other drugs marketed for the treatment of dementia, such as nalfidrofuryl, piracetam and meclofenoxate. Indeed, the evidence is very much less in favour of a beneficial effect than with co-drgocine. For example, McDonald[29] reviewed 13 clinical double-blind studies in which piracetam was compared with placebo in 881 patients with mild to moderate dementia. Eight studies found the drug no better than placebo, any significant positive effects being sporadic. Overall there was no support for the use of piracetam in patients with senile dementia. Two studies involving nalfidrofuryl involved very small numbers of patients with several diagnoses and although the studies showed beneficial effects it is difficult to be sure that those with senile dementia benefited from the drug[35,36]. Although meclofenoxate acts favourably on the cholinergic neurotransmitter system (see above) the clinical evidence of any beneficial effect is scant[37].

In summary, there are few hard clinical data to support a worthwhile beneficial effect of any of the drugs marketed for patients with senile dementia. It would seem, therefore, that medical scepticism about the benefits of such medication is justified and healthy.

Selection of Patients

The problems of conducting clinical drug studies in patients with senile dementia are enormous. Many studies suffer from inadequate numbers, use unacceptable physiological tests and run into the difficulties of evaluating confused patients[38]. However, any beneficial effect from a drug depends not only on adequate concentrations at the right receptor site but also on the ability of the lesion to respond. A major criticism of clinical trials is the lack of an attempt to define the type of dementia. Many studies must have included patients who were unable to respond under any circumstances[39]. Future studies must make a concerted effort to categorise patients clinically[40] and by special investigations such as measurement of cerebral blood flow and CAT scan. The latter has only a minor role in patient selection but can at least rule out patients with marked atrophy, though dementia may occur in patients with apparently normal brains and not in patients showing marked atrophy on CAT scan. It would seem reasonable to suspect that the disease would be more likely to respond to drugs if the CAT scan was normal than if it showed marked atrophy of the brain.

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