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Letter to the Editor

REAL and CALM: What Have We Learned?

In early 2002, I questioned the merits and feasibility of functional imaging neuroprotection studies in Parkinson's disease.[1] I speculated that the trials in progress at that time might fail and suggested that it might be time to call a temporary halt to such trials. The final results of the CALM-PD [^{123}I] β-CIT SPECT study and REAL-PET study are now available,[2,3] and it is time to appraise that view. The arguments around the value of imaging endpoints in progression studies have already been made[1] and will not be discussed again. Instead, this letter concentrates on the methods and interpretation of the completed studies.

The imaging arm of CALM-PD was presented in April 2002,[2] and concludes that "patients initially treated with pramipexole demonstrated a significant reduction in loss of striatal [^{123}I] β-CIT uptake, a marker of dopamine neurone degeneration, compared with those initially treated with levodopa." REALPET, presented in abstract form[3] and awaiting full publication, concludes that those patients taking L-dopa showed a significantly greater reduction in putamen [^{18}F]-dopa uptake than did those patients taking ropinirole and "supports the early use of ropinirole in preference to L-dopa in PD."

Under scrutiny, neither conclusion is justifiable. The key to the failure of the CALM-PD study lies in the concept of sensitivity of imaging measurement to clinical deterioration.[4] Some years ago, Vingerhoets and I published data from essentially similar [^{18}F]-dopa PET progression studies[5,6] with hugely conflicting results (my estimate of annual rate of progression was 7% of the normal mean per year whilst Vingerhoets and colleagues estimated 7.8% per decade). To resolve this discrepancy, the method of PET analysis from each study was applied to one set of patients; the conclusion was that functional imaging methods vary in their sensitivity to clinical change.[4] The mechanism can be explained. When one looks at the putamen alone, ideally with small regions of interest, the area within the region sampled is the area in which change in dopaminergic function underlies change in clinical severity.[7] When a larger area is included, and areas of tissue are included in which there is less or no change with clinical progression, the effect of change in the putamen is diluted, and the method is, as a consequence, less sensitive to clinical progression. Like the PET method used by Vingerhoets and colleagues,[6] the [^{123}I] β-CIT SPECT measurement used by CALM-PD lacks sensitivity to clinical change. From a previous publication by this group,[8] one can estimate that striatal ratio might change by a maximum of 8–10% of the normal mean with each 10-point change in total UPDRS (striatal ratio is likely to be less sensitive to clinical change than putamen ratio[4]).

In the CALM-PD study, both subgroups changed clinically by an average of 4 total UPDRS points over the 4 years of the study. Despite the vehement denial,[9] this clinical rate of progression is very slow when compared with comparable studies of de novo Parkinson's disease with assessment of UPDRS, as in this trial, *off* medication.[5,10,11] We can, however, leave aside this point. With knowledge of the sensitivity of the technique to clinical progression, it can be estimated that striatal ratio might have been expected to change by a maximum of 4–5% of the normal mean (or 8–10% of baseline) for the 4-point change in UPDRS in each arm of the study. Instead, in CALM-PD, the striatal ratio changes by 16% of baseline in one arm and 25.5% in the other. It can be seen that such enormous changes in SPECT measurement with such a small change measured clinically (when using an imaging method that lacks sensitivity to clinical change) cannot possibly be the result of disease progression. One way to illustrate the problem is to note that if striatal ratio changes by around 20% with a change in total UPDRS of 4 points, then over the typical 50- to 100-point change in total UPDRS in the entire course of the illness, it might be expected to change by as much as 250 to 500%. To argue that clinical measurement and SPECT measurement need not be closely related is to argue that SPECT has little or no relationship to the clinical state, and thus becomes of little value. It has been pointed out that the difference in the two arms of the trial might be a consequence of different effects of the drugs on the dopamine receptor.[9] This may be the case, but we should also not underestimate the influence of chance and error.

REAL-PET is, in many ways, a more satisfactory study. It is much larger, the patients have progressed at a clinical rate that is more typical, the technique used has greater sensitivity to clinical change, the methodology has ensured blinding of analysis, and patients were scanned on medication at both the start and finish of the study. However, it, too, has a problem. When the entire cohort was assessed, although there was a trend in favour of the agonist, the difference between the subgroups did not reach statistical significance. A decision was made to exclude from the analysis 11% of patients in the trial on the grounds that the result of their initial PET scan was within the normal range. This decision is questionable. It has been known since 1995 that there is an overlap between the normal and early PD range in putamen Ki, and some PD patients will have "normal" scans.[12] It must be assumed that all patients taking part and completing REAL-PET were believed, by clinical assessment, to have PD; if this were not the case, it would have been unethical to keep them in the trial, treat them with medication as having PD, and expose them to radiation twice. If there is any neuroprotective or neurotoxic effect of either medication, the sample size in this study has been too small to detect it. It should also be noted that clinically there was no significant difference in the rate of progression between the two groups, again casting doubt on the validity of the functional imaging result.

A further point that arises both from these data and from a third trial (ELLDOPA[13]) that uses [^{123}I] β-CIT SPECT imaging is the discriminatory power of the techniques. In each trial, a significant number of patients with clinically definite PD have had scan results within the normal range. It is perhaps time to end the conceit[14,15] that either method (even with 3-D PET) at this time can reliably separate recent onset PD from normality. It is to be expected that the normal-scan subgroups of patients will prove to be relatively slow in progression. In my study of 32 de novo patients,[4] 5 had normal first scans; clinically they behaved as typical PD and their mean rate of progression was not significantly different from that of the other 27 (the subgroup was too small to expect otherwise). One argument is that this group may not have PD at all, implying that the scans are better in diagnosis than the experienced clinician. Time will tell but I am confident that the majority of these patients, having been diagnosed as having PD by experienced clinicians (and fulfilling diagnostic criteria), will indeed prove to behave as typical PD.

The failure of the above studies reinforces my view that it is time to call a halt until the techniques are refined further.

There is a final concern. Both REAL-PET and CALM-PD have received substantial financial support from the pharmaceutical industry and both trials have been interpreted as supporting the use of the sponsor's product. It might have been safer in each case to analyse and report the findings more neutrally, pending broader discussion of their validity in the scientific community.

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