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Editorials

Long term oxygen therapy in moderate hypoxaemia

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When the MRC[1] and NOTT[2] trials of long term oxygen therapy (LTOT) in chronic obstructive pulmonary disease (COPD) showed that LTOT improved survival in patients with stable arterial Po_2 of less than 8.0 kPa (60 mmHg), it seemed logical to extend their results by assessing LTOT in patients with less severe hypoxaemia. More than 15 years have passed without this extension, probably because of the expense involved in mounting a trial that would very likely yield less dramatic results than the first two. The paper by Górecka *et al*[3] in this issue of *Thorax* seeks to fill this gap.

The study they describe is a randomised controlled clinical trial of LTOT in patients with COPD with moderately severe hypoxaemia – that is, with an arterial Po_2 of 7.4–8.7 kPa (56–65 mmHg), the mean value being 8.0 kPa (60 mmHg). In patients given LTOT there was no survival advantage over controls during a follow up period that was at least 36 months in survivors. Mortality was so closely similar in the two groups that it is very difficult to argue that the outcome would have differed if more of the same kind of patients had been studied or if the follow up period had been longer. There does not seem to be a positive result lurking in these data.

What are we to make of this? Is this a definitive study and how does it relate to the other definitive studies of LTOT – the MRC and NOTT trials? Beyond the fact that it studied patients with less hypoxaemia, the Polish trial differed from its predecessors in a number of ways, some of which may have been important. Patient characterisation and follow up was considerably less intense in the Polish study; there were no cardiac catheterisations or psychometric tests, and no follow up lung function data are presented. This is reasonable. The previous trials had established death as the best end point, and Górecka *et al* sensibly avoided the effort and expense of examining other less important outcomes. There was a statistically significant difference between the groups in mean baseline Po_2 but the absolute difference was very small (0.3 kPa (1.8 mmHg)). Significance was, as the authors indicate, at least partially an artefact. The range of baseline Po_2 was restricted so the standard deviation of the mean Po_2 was reduced to the point that small differences attained statistical significance. Furthermore, the authors were unable to show that, within their limits, baseline Po_2 influenced mortality. These arguments are convincing. Of greater concern was their oxygen prescription. They aimed for 17 hours a day of LTOT but do not specify the extent of oxygen administration during sleep. They apparently did not increase oxygen dosage during sleep and exercise, as was done in the NOTT study. Finally, their patients averaged 13.5 hours of LTOT per day. While this may have been comparable with that achieved in the MRC study, it is considerably less than the "continuous" LTOT in the NOTT trial which we consider the gold standard. We are puzzled that the Polish investigators did not try to give oxygen for more hours per day and apparently did not emphasise nocturnal use, since most patients experience their most severe hypoxaemia during sleep. It could be argued that more oxygen should have been used; the fact that it was delivered via concentrators would have minimised extra costs. The authors tried and failed to show that mortality was influenced by oxygen use, but this cannot be regarded as definitive since the interpretation of such post hoc analysis is extremely difficult. Should this study be repeated it would be helpful to give oxygen for a greater fraction of the day with emphasis on the nocturnal hours. It remains to be seen if patients with moderately severe hypoxaemia will comply with instructions to use oxygen more extensively.

Do the results of the study by Górecka *et al* raise questions regarding the interpretation of the NOTT and MRC trials? We think not. Although there was overlap between the patient populations of the Polish study and its predecessors, patients in the MRC and NOTT trials were more sick. In particular, they were more hypoxaemic with a mean arterial Po_2 some 1.3 kPa (9 mmHg) less than that of the patients in the study by Górecka *et al*. Not entirely by accident, the MRC and NOTT trials complemented each other and their results were mutually supportive. In patients with severe hypoxaemia some oxygen was better than no oxygen and the more continuous the therapy, the better the effect. This seems unassailable on the basis of the present evidence. Concerns have been voiced about the MRC trial failing to show a treatment-related difference in mortality for its first 18 months. We believe that, given its relatively small sample size (less than 100 patients), the trial needed a longer follow up period to draw any conclusions and that, when this was available, true differences became apparent. The Polish trial is larger than that of the MRC, and has a follow up period that is at least as long.

Other than its main outcome, the results of the Polish trial fit well with careful longitudinal studies of COPD. As in other series, the main determinants of mortality were age, forced expiratory volume in one second (FEV_1), and body mass index, although an inverse relation to FEV_1 also had an independent influence on survival. The overall mortality in the patients in the study by Górecka *et al* was 11–12% per year, close to that of patients on continuous oxygen therapy in the NOTT trial.

Finally, how should the results of Górecka *et al* influence the practice of prescribing LTOT? The MRC and NOTT trials indicated that, in stable patients with an arterial Po_2

of less than 8 kPa (60 mmHg), LTOT improved survival. Górecka *et al* have shown that LTOT as they prescribed it did not improve survival in stable patients with an average arterial Po_2 of slightly more than 8 kPa. It seems reasonable to continue to use the NOTT/MRC guidelines for oxygen prescription and to regard the Polish data as evidence that justifies withholding LTOT from patients with less severe hypoxaemia.

It must be noted that this does not refer to the prescription of home oxygen for episodic hypoxaemia, whether the episode occurs during sleep or exercise. Unfortunately we do not appear to have advanced in our knowledge of the effects of oxygen in these situations over the past 15 years, and in this context we must still operate on the basis of clinical impressions.

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