Epoprostenol use in a National Pulmonary Hypertension Centre from 1997 to 2007

The cost-effectiveness of prostanoids in pulmonary arterial hypertension (PAH) has recently been called into question by the National Institute for Health and Clinical Excellence (NICE), and the possibility exists that this treatment would not be recommended by this body. This would be the first time that a treatment already in routine clinical practice would be withdrawn as a result of NICE recommendations. Guidelines published by the UK, European and US authorities still advocate prostanoid use in certain patient groups. Of the disease-targeted therapy available for PAH, only epoprostenol has been shown to improve patient survival in the context of a randomised controlled trial. To assess the impact that withdrawal of intravenous epoprostenol in 1997 would have had, its use was retrospectively reviewed in a well-defined population of patients with PAH. This analysis includes eras before and after the licensing of oral agents in 2002.

All patients treated with intravenous epoprostenol by the Scottish Pulmonary Vascular Unit from 1997 to 2007 were identified. Case notes of this cohort were reviewed to determine (1) the reason for initiation of epoprostenol, (2) the outcome after 12 months of treatment as assessed by changes in conventional outcome measures and survival, and (3) the outcome in those patients whose treatment with epoprostenol commenced after licensing of oral disease-targeted therapy in 2002. Patient improvement was defined as either an improvement in functional class or an improvement in the 6-minute walk distance (6MWD) 3 months after initiation of treatment. Patients were then divided into the following groups: (1) improvement and survived >12 months; (2) stabilised (ie, no improvement but survived >12 months); (3) died within 12 months; or (4) intolerant of treatment. Where available, N-terminal pro-B-type natriuretic peptide (NT-proBNP) and quality of life (QOL) measurements were also analysed.

Fifty (20%) of 252 patients with PAH were identified as having received epoprostenol during this period. Of this group, 30 (60%) either improved or stabilised for >12 months. Data on the improvements in 6MWD, QOL, functional class and NT-proBNP are included in the online supplement. Figure 1 shows the survival advantage for patients whose functional class or 6MWD improved with intravenous epoprostenol.

For the subset of patients following the introduction of oral disease-targeted therapy agents in 2002, 30 (15%) out of 199 required epoprostenol; 17 (57%) improved, 9 (30%) died before 12 months, 3 (10%) stabilised and 1 was intolerant of the agent. Included in this group were 12 patients who required epoprostenol after deterioration on oral agents; 7 improved, 3 died, 1 stabilised and 1 was intolerant. Data on the improvements in 6MWD, QOL, functional class and NT-proBNP in this group of patients are also shown in the online supplement.

REFERENCE


Do all occupational respiratory sensitisers follow the united airways disease model?

Point prevalence data (see online supplement) still demonstrated an ongoing need for epoprostenol in the current era of oral agents.

This study suggests that, had intravenous epoprostenol not been available over the last decade as a treatment for PAH, a significant number of patients in Scotland would have been denied an effective treatment. Where data are available in the subjects, there were improvements in all outcome measures (functional class, 6MWD, NT-proBNP, QOL). More compelling, however, is the survival analysis of the entire cohort which demonstrated a large survival advantage in those patients in whom functional class or 6MWD improved. This situation remains true in the era of oral treatments. This should have implications for future NICE review of the role of epoprostenol in PAH.

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model does apply to occupational causation overall. However, as they readily acknowledge, an attempt to stratify this relationship according to whether the causative agent is of high molecular weight (HMW) or low molecular weight (LMW) is limited by the small size of the study population. An epidemiological approach offers a means of complementing the observations from this type of clinical study in order to better characterise how the frequency of rhinitis varies with type of exposure.

National reporting schemes for occupational diseases such as The Health and Occupation Reporting (THOR) network² in the UK provide data on the causative agents for a large number of cases of OR and OA reported by networks of respiratory and occupational physicians. In a preliminary study we have determined the number of cases of rhinitis (with or without asthma) as a proportion of the total number of cases of rhinitis and/or asthma for the 15 respiratory sensitisers most frequently reported to THOR during the decade 1997–2006.³

The data suggest significant differences in the rhinitis:asthma ratio between the various causative agents. Few, if any, of the cases of OR reported to THOR would have been confirmed by acoustic rhinometry, and their diagnosis is probably based on a history of nasal symptoms, sometimes accompanied by rhinoscopy, which can have poor specificity. This, together with potential reporting biases, limits conclusions that can be drawn from these provisional THOR data. They do, however, raise the possibility that respiratory sensitisers differ in the extent to which they cause rhinitis compared with asthma. This is particularly evident when the rhinitis:asthma ratio is compared for the two most frequently reported respiratory sensitisers—laboratory animals and isocyanates—with a much higher proportion of rhinitis associated with the former.

A number of toxicokinetic factors, such as particle size or solubility, could determine the relative distribution of a sensitizer in the upper and lower airways. Toxicodynamic factors might relate to molecular weight, with the suggestion from the data that higher molecular weight agents might be preferentially associated with rhinitis. The THOR data are consistent with the hypothesis that OR (when in conjunction with OA) is more likely to be caused by sensitisers that cause disease through IgE-mediated mechanisms. On the other hand, LMW agents such as diisocyanates, which may cause OA by non-IgE mechanisms, do not associate strongly with OR. Morphine, which had the highest rhinitis:asthma ratio in our study, may act through direct mast cell degranulation.⁴ Further clinical and epidemiological research could help to substantiate such mechanistic hypotheses. Castano and colleagues have shown that the united airways disease can apply to occupational causation, but this might not be consistent across the diverse range of respiratory sensitisers.

**REFERENCES**