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EDITORIAL

Is nedocromil sodium effective treatment for asthma?

*P.M. O'Byrne, D. Cook

In the past decade, the treatment of asthma has changed. This evolution occurred with the realization that prevention of regular asthma symptoms is preferable to treatment of asthmatic symptoms when they develop. This understanding is reflected in the consensus reports on asthma management, which have recently been published in several countries [1–4]. These reports agree that the main aim of management is to keep asthmatic patients functioning as close to normal, for as much of the time, as possible. With this in mind, the currently available drugs to treat asthma, for practical purposes, fall into two classes: those which are most useful to treat symptoms when they develop (such as β_2-agonists or theophylline), and those which are most useful in preventing regular symptoms and exacerbations of asthma from occuring (such as inhaled corticosteroids or crom-oglycate). Whilst this division is somewhat artificial, (for example, inhaled β_2-agonists are very useful for preventing exercise-induced bronchoconstriction), the distinction between these classes of drugs has practical importance, as inhaled corticosteroids or crom-oglycate are now recommended as the most appropriate regular maintenance treatment for asthmatic patients with anything other than infrequent symptoms [1–4].

A recent addition to the physicians therapeutic armament for asthma treatment is nedocromil sodium, which was originally developed as an agent which would inhibit the release of mediators from inflammatory cells present in the airways of all (even mild, stable) asthmatics. The drug was developed as an extension of cromolyn, which was thought at the time to have similar pharmacological properties. It was hoped that nedocromil would have significant therapeutic advantages, but would retain the low side-effect profile of cromolyn.

Nedocromil has been extensively studied in asthma, and the results of all known published and unpublished, placebo-controlled, double-blind, randomized clinical trials have been incorporated into a meta-analysis by EDWARDS and STEVENS [5]. These authors are associated with the company which has developed and marketed nedocromil and, thereby, have access to all available clinical trials, including unpublished data, which affords them with a unique opportunity to fully evaluate the efficacy of this drug.

Scientific overviews, which include a comprehensive search for relevant literature, an unbiased assessment of the validity of the primary research, and an examination of the reasons for differences in study results, can provide important insights into both beneficial and adverse treatment effects [6]. Meta-analysis is a type of scientific overview, which applies statistical principles to the quantitative results of study outcomes. This approach is used to combine the results of relevant trials, to increase statistical power and to provide a more precise and robust estimate of the treatment effect.

The initial step in reading an analysis of the type provided by EDWARDS and STEVENS [5] is an assessment of whether or not the questions and methods were clearly stated. This requires explicit identification of the population of interest (asthmatic patients), the intervention/exposure (inhaled nedocromil) and the outcomes (physiological and functional assessment of asthma control). The second step is an evaluation of the comprehensiveness of search methods used to locate relevant studies. EDWARDS and STEVENS [5] raised the concern that readers should have about publication bias: the extent to which positive results are more likely to be published (and therefore included in an overview) than negative studies [7]. The more selective a meta-analyst's search, the more likely it is that there will be a bias in the conclusions. An analysis conducted by individuals affiliated with the therapy, as in this instance, may be more likely to include completed unpublished studies; on the other hand, they may be more likely to avoid the identification of studies that are unfavourable. EDWARDS and STEVENS [5] have included all published and unpublished material in their analysis (excluding trials that contributed less than nine patients per treatment group), and report on 4,723 patients enrolled in 127 centres. However, it would have been interesting to know how many studies were represented, how many were published and unpublished, and whether the overview results changed with inclusion and exclusion of the unpublished material. Another potential problem with this approach is that the lack of availability of the unpublished results makes it impossible for other investigators to reproduce the conclusions of the analysis.

After the search for relevant articles is described, the

* The Asthma Research Group and the Dept of Medicine, McMaster University, Hamilton, Ontario, Canada.

reader should then look for the description of how articles were chosen for inclusion in the analysis, and how the methodological quality of the primary studies was assessed. Such descriptions should be as detailed as possible, framing the criteria according to study design, population, intervention and outcome. In analysing articles on therapy, the reader is interested in the strength of the study design, such as whether subjects were randomized to different therapies, whether subjects and investigators were blind to treatment allocation, and the completeness of follow-up. This analysis of EDWARDS and STEVENS [5] included only studies which were double-blind, placebo-controlled, randomized clinical trials. However, the length of follow-up for each study is not reported, nor is the proportion of patients who completed the studies. Assessment of the primary studies in a scientific overview should ideally be reproducible and free from bias. Unfortunately, expert assessment of primary research is characterized by considerable potential for bias and disagreement [8]. Nevertheless, problems can be minimized by making the selection criteria as explicit as possible.

Before accepting the results of an overview, the reader should consider whether the results of the primary studies have been combined appropriately. This is to avoid the problems of combining "apples and oranges" *i.e.* pooling the results of fundamentally different studies. The strength of a methodologically rigorous meta-analysis is that it critically appraises all relevant literature addressing a question of clinical relevance, and statistically aggregates the results to yield the most unbiased and precise estimate of the treatment effect. In this context, a group of nonsignificant randomized trials may, when aggregated, yield a statistically significant benefit in favour of treatment (largely due to the increase in power afforded by pooling data).

After going through this exercise [9, 10], the reader of a meta-analysis can step back and evaluate whether the reviewer's conclusions are supported by the data cited. EDWARDS and STEVENS [5] have concluded that nedocromil is more effective than placebo in treating asthma, and may be of most benefit to patients who continue to be symptomatic while receiving bronchodilators alone. They also suggest that nedocromil is of less benefit to patients already treated with inhaled corticosteroids. These conclusions appear to be supported by the information provided by the analysis. The authors also conclude that nedocromil is useful as a first line maintenance treatment in patients with mild to moderately severe asthma. However, this conclusion critically depends on the comparator therapy. This meta-analysis does not provide any information about relative efficacy and tolerability, when compared to the therapies currently suggested as first line maintenance treatment in patients with mild to moderate asthma, cromoglycate or low doses of inhaled corticosteroids [1–4]. Such information is very scant for nedocromil, and without it, it is very difficult to decide the appropriate use of nedocromil in the treatment of asthma.

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