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Meeting Report

Symposium: controversies in asthma therapy

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An important reason for the Fisons pharmaceutical company to organize this symposium was the appearance of the International Consensus Report on the Diagnosis and Treatment of Asthma in March of this year. The report came after a long period during which controversies have arisen with respect to both the efficacy and the safety of some medications widely used in this condition, controversies which (at least with respect to safety) have sometimes seemed insoluble.

An opening section provided a clear background to the current situation, when Dr R. Beasley (Southampton, United Kingdom) reviewed the developments with respect to the possible risks of the β_2 -antagonists in asthma. Various series of epidemiological findings played an essential role in the debate, and marked international differences in the mortality rate were prominent. In New Zealand, patient 5–34 years of age showed a much higher mortality, than did populations in, for example, Sweden and The Netherlands; in particular there were two peaks of mortality in New Zealand during the sixties and the seventies. In the sixties, it soon became clear that the peak was not due to a higher prevalence of asthma (or of severe asthma), nor to environmental factors and that it might be linked to the treatment itself. After careful study it was concluded that the use of isoprenaline could be regarded as the major cause. When therefore the second peak occurred in the following decade, the search for the cause was centred on the treatment. This time circumstantial evidence pointed to the use of fenoterol. A case control study was then undertaken, particular care being taken to ensure that the severity of the asthma was similar among fenoterol takers and controls, primarily by using as one of the inclusion criteria a stay in the hospital. This study showed clearly that fenoterol was related to an increase in mortality. In-depth studies using different designs supported these results. An important question is then to what extent the problem is limited to fenoterol or could be a class effect of all β_2 -agonists. The New Zealand data suggest it is not a class effect, but a study in Saskatchewan (Canada), published in the *New England Journal of Medicine* in 1987, came to the conclusion that it might very well be a class phenomenon. Dr Beasley pointed out that the Saskatchewan study had not a very well matched control group, i.e. it was not limited to people admitted to hospital; the severity of the asthma might therefore well have differed between fenoterol users and the comparison groups.

Moreover, when comparing fenoterol and salbutamol use by the oral route, the salbutamol group was too small to allow firm conclusions.

Quite apart from the peaks in mortality in the sixties and seventies, a steady increase in morbidity, mortality and severity of asthma could be seen. In the light of published evidence, Dr Beasley illustrated the development of the concept that β_2 -agonists have a long-term detrimental effect involving a reduction of lung function. Since regularly scheduled use of inhaled β_2 -agonists (as opposed to administration as required) has been associated with diminished control of asthma, it is now thought that an explanation may lie in continuous exposure, but the understanding of long-term effects is still far from clear. Moreover, the role of inflammation in asthma has become more prominent. Airway inflammation is present in virtually all patients, and the control of this inflammatory process has now become a central element in treatment.

The International Consensus Report, presented by Prof. R. Pauwels of Gent (Belgium) who was a member of the team which produced it, stresses the importance of the central goal of the treatment: improvement of quality of life by controlling the symptoms of asthma. One will be seeking to attain the lowest possible level of chronic symptoms (including nocturnal attacks), minimal exacerbations, a minimal need for β_2 -agonists, no limitations on activity, a circadian variation in the PEF of less than 20%, and a near normal average PEF throughout the 24 h; naturally one will also be seeking to reduce or avoid adverse reactions from the drugs used. The Consensus Report chooses a stepwise approach, stepping up the intensity of treatment when needed and stepping down when possible. Step 1, appropriate to the treatment of mild asthma, uses short acting β_2 -agonists as needed but not more than $3 \times$ a week, adding a short acting β_2 -agonist or cromolyn before exercise or exposure to antigen. If this is not enough (and the criteria for inadequate response are described in the consensus), the treatment should be moved up to step 2. This comprises the use of anti-inflammatory drugs, choosing either inhaled corticosteroid (200–500 mg) or cromolyn, if necessary proceeding to inhaled corticosteroid 400–750 mg, and adding a short acting β_2 -agonist, but not using the latter more than 3–4 times a day. If step 2 proves successful over a reasonable period of time (3 months) stepping down should be considered. Step 3 consists of increasing the dose of inhaled corticosteroids to 800–1000 mg and supplementing these with sustained-release theophylline, oral β_2 -agonists or long acting inhaled β_2 -agonists and use of a short acting inhaled β_2 -agonist, again given not more than 3–4 times a day. In step 4 oral corticosteroids are added. In this stepwise regimen, the frequency with which it is necessary to give β_2 -agonists is regarded as a measure of the degree to which the asthma is under control. The report provides specific recommendations with respect to children.

An interesting aspect of the consensus report is the development of a so-called asthma management zone system has been developed for patients. The zone system helps the patient to understand the chronic and variable nature of asthma, to help to monitor the disease, to identify signs of deterioration and to act quickly to gain control. The green zone indicates that the asthma is under control; the yellow zone

that asthma symptoms are recurring and need to be taken care of, while red is the alarm zone in which one must inhale β_2 -agonists and contact the physician. The report also provides a long list of proposals for research.

In discussing the presentation of the International Consensus report, the Brussels meeting paid particular attention to a notable discrepancy between its recommendations and those of a Dutch General Practice Standard for the treatment of asthma which has been published only a few days before the meeting. One striking difference relates to the choice of initial treatment; in the Dutch standard this is regular use of a short acting bronchodilator as opposed to the short-acting β -antagonist proposed in the international document. One explanation may lie in a difference of indication, since the Dutch report relates to chronic obstructive pulmonary disease; moreover, the emphasis may have been more on the treatment of the elderly than in the consensus.

The afternoon session at Brussels opened with a presentation by Prof. M.N.G. Dukes (Groningen, The Netherlands), who provided an overview of the history of side effects of drugs in general and how society has dealt with them, not always in a realistic and balanced manner. In the field of asthma there has been a long history of adverse reaction problems, beginning with the traditional 'asthma cigarette' containing plant material rich in atropine-like compounds but sometimes also tobacco. The arrival of cromolyn put the perspicacity of drug regulators to the test, for it was a compound of unusual structure having an unknown mechanism of action and administered in an unorthodox manner; what is more, there had been certain changes in toxicological studies in monkeys, which were difficult to interpret. Recognizing the drug's unique value, the Canadian authorities registered it rapidly. Norway followed, thanks to the provisions in its law which enabled a new drug to be released progressively rather than made generally available at once. The American FDA provided a demonstration of extreme regulatory hesitance; not only was there a delay of years, but the drug was ultimately approved only with a series of obscure warnings in the data sheet which no physician could be expected to understand. For a drug almost without adverse effects, the U.S.A. data sheet of the 1980s was an astonishing catalogue of supposed problems.

Dr P.L. Padfield (Edinburgh, Scotland) led the Brussels meeting through the problems posed by the endocrine effects of corticosteroids. There is evidence that, even when given in normal (low) dose, systemic effects are seen on glucose homeostasis, on bone formation and in terms of a short-term reduction of growth in children; however, no effect on lipids has been found. Dr O. Zetterstrom (Stockholm, Sweden) contributed from the floor evidence that even the new corticosteroids can lead to hoarseness and changes in the voice. By stopping the medication the problem can be much diminished, but the risk of residual symptoms remains.

Prof. P. König (Columbia, USA) also reviewed the risks and benefits of various forms of corticosteroid treatment, involving what he called choosing between shades of grey. Inhaled corticosteroids are clearly effective in mild to moderate asthma, yet he too stressed that suppression of the adrenal cortex and effects on bone formation are important side effects to be taken into account. In the case of

children, his own view was that the effect on the growth rate is still unclear; older studies show no relationship, newer studies apparently do so; this may be because more sensitive tests are now used (as in the work earlier adduced by Padfield), but it may also be because the more recent studies look more at the milder forms of asthma. The question is further complicated by the fact that severe asthma may in itself have an effect on growth suppression, which can be positively influenced by effective therapy. All in all inhaled corticosteroids are important for mild to moderate asthma attacks. Non-corticosteroid anti-inflammatory drugs are cromolyn and more recently nedocromil; the evidence shows that both drugs can improve bronchial hyperreactivity and that the inflammation is indeed improved clinically. Königs concluded that in mild asthmatics such non-steroidal anti-inflammatory drugs are satisfactory as a first step, but that in severe asthmatics the inhaled corticosteroids have an acceptable risk-benefit profile, in particular because of their stronger effect. Prof. Koëter (Groningen, The Netherlands), like other speakers, stressed the fact that inflammation is already present even in mild asthma and that its treatment is therefore essential. The evidence today is that nedocromil is effective both in allergic and non-allergic young adults. The very limited data available comparing nedocromil with cromglycate point to a higher potency of the former, but no firm conclusions can be drawn. In comparison to corticosteroids the effect of nedocromil in reducing complaints, improving lung function and diminishing diurnal variation and the general level of bronchial hyperreactivity are similar, but the effect on exacerbations and the decline in FEV1 is unclear.

In vitro nedocromil appears to be effective on all relevant cells. Koëter concluded that there is certainly a place for nedocromil in the treatment of mild to moderate asthma and the conclusion was also voiced by the panel discussion which closed the day.

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