Combination medications with bronchodilators in the treatment of COPD

A considerable number of new drugs for the treatment of COPD have appeared on the market in recent years. The Geneesmiddelenbulletin’s New Drugs section has reported that these new drugs offered no added value as monotherapies. This article discusses studies into the efficacy and side-effects of fixed-combination preparations of long-acting bronchodilators. Since these studies used different primary outcome measures, and not all of them compared their efficacy with that of placebo, the various outcomes cannot be compared. Another interesting conclusion is that in a number of cases, the reported differences with long-acting parasympathicolytics as monotherapy are statistically non-significant, although the differences with long-acting β₂-sympathomimetics were all statistically significant. None of the studies found differences of more than 100 mL between the combination and the drugs as monotherapy, making them clinically irrelevant even in terms of the less stringent requirements for clinical relevance. None of the combination preparations was found to have a synergistic effect. Since not all of the studies were placebo-controlled, it is impossible to determine whether there was an additive effect, but the differences found between the combination preparations and the individual drugs suggest that the combination is less effective than might be expected from the results obtained with the individual drugs. Since the number of exacerbations is a better indicator of the burden of disease in COPD, it is important to know that most of the combinations were not (or not primarily) tested to see whether they reduced the number of exacerbations or improved the prognosis. The only study discussed here that examined exacerbations in the relevant target group (i.e. patients with the more severe forms of COPD) found a clinically relevant reduction in the number of exacerbations, but this difference was largely due to a reduction in exacerbations not requiring treatment. The results of questionnaire studies showed statistically significant differences between the combinations and the individual drugs, but these differences were not clinically relevant. The conclusion must therefore be that the introduction of the various combination preparations has not resulted in any therapeutic progress relative to monotherapy.

The results were obtained in study populations largely composed of patients with milder forms of COPD, a target group that does not correspond to the group of patients for whom these drugs are intended according to the Dutch guidelines (i.e. patients with severe to very severe COPD being treated in secondary care). Since the elasticity of the airways is less strongly reduced in the group of patients with milder forms of COPD, the results are probably more favourable than they would have been in the intended target group. Since the various combination preparations have not been compared with each other, it is impossible to decide whether one of them is to be preferred over the others. It remains unclear whether the use of long-acting anticholinergics increases the risk of cardiovascular side-effects. Independent research continues to yield indications of increased risk, whereas industry-sponsored trials regularly come to different conclusions, viz. that there is no evidence for problems. It is advisable not to treat patients with cardiovascular disorders with these drugs, especially as alternatives are available.

Although manufacturers’ advertisements in medical and pharmaceutical journals claim advantages of combinations such as ease of use and improved compliance, these have not been assessed in methodologically well-designed and executed studies. The single application of combination preparations has not only advantages but also disadvantages, as an incorrectly inhaled dose results in a reduced effect of two drugs at once. The conclusion must be that these preparations offer no added value compared to existing treatment and hence have no place in the treatment of the more severe forms of COPD.

References*
22. KNMP Kennisbank, via: KNMP Kennisbank online.


*The literature refers to the Dutch text*