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EDITORIAL

High doses of sympathomimetics in severe bronchial asthma

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In a short but excellent review published in a previous issue of the Journal, NOSEDA and YERNAULT [1] present a thorough and updated analysis, and new concepts on the treatment of acute severe asthma by beta-agonists. The route of administration of the drugs, as well as the doses and procedure are carefully presented and discussed.

To anyone in the nineteen sixties, the administration of high doses of beta-agonists to severe asthmatics who had already emptied their inhaler without result, would have come as a surprise, if not seen as heresy. Indeed, at that time, the increase in the mortality of asthmatics in England and Wales [2], was attributed, although not proved, to an excessive use of beta-agonists, especially isoproterenol. Why administer again the same drug, which had previously been shown to be ineffective?

Several studies have demonstrated, that most patients with acute severe asthma, who had previously (or not) used (or abused) beta-agonists without results, do respond to a higher concentration of the same drug, administered by nebulizer [3–6] or as recently shown, by an inhaler provided with a spacer [7, 8]. The response is clinically manifest and can be demonstrated by spirometric tests. Whatever the explanation, the clinical and functional improvement is dose-related. As emphasized by NOSEDA and YERNAULT [1], the dose delivered by the inhaler is 10–20 times higher than that delivered by the nebulizer.

A minority of asthmatics will not respond even to large doses of beta-agonists within a couple of hours, and will improve only if cortisone and theophylline are given [9]. Finally, a subset of severe asthmatics will require assisted ventilation.

What is the explanation for the failure of low doses of beta-agonists and the success of higher ones? The authors of this review favour an inadequate mode of administration in some patients, and severe inflammation of the airway in others [1]. Even if we accept that a large proportion of asthmatic patients do not use inhalers correctly, it is hard to dismiss others, who have certainly learned how to use these devices. In a recent review on the control of asthma by aerosols, NEWHOUSE and DOLOVITCH [10] wrote that "not surprisingly larger doses of aerosol must be administered during episodes of severe asthma to achieve the maximal effect, since high inspiratory frequencies and flow rates, low tidal volumes and pathologically narrowed airways all conspire to reduce the delivered dose and the peripheral distribution of inhaled medication". Furthermore, they wrote that "in patients with marked airflow obstruction, there is decreased penetration and deposition of aerosols in peripheral airways, where the largest number of beta-receptors are located". In some way this explanation is related to another one, often invoked in the past: some lung regions, in severe asthma, may be closed by mucous plugging of the airways, thus preventing the penetration of aerosols. In this case, one would expect, that parenteral administration of beta-agonists would yield a better result than aerosolized drugs. As recently shown, this is not the case, indeed both methods of administration provide a similar result [11]. Part of the drug, administered as aerosol, may reach the bloodstream by absorption through the mucosa of the mouth and upper airways. However, delivery of beta-agonist aerosols to the mouth has shown only limited, though significant, improvement in lung function [12].

Finally, several authors have suggested that lack of response to beta-agonists in severe asthma may be an expression of down regulation of beta-receptors. The development of a decreased sensitivity to beta-agonists is well recognized [13, 14]. A high concentration of beta-agonists induces the uncoupling of the receptors from the intracellular effector mechanisms [15]. The receptors are regulated or destroyed by a feedback control mechanism which is thought to prevent excessive agonist stimulation of the cells. However, despite controversy, receptor down regulation is not considered to be a relevant mechanism in clinical practice for most asthmatics [16].

Although the explanation of the benefit of high doses of beta-agonists in severe asthma appears to be elusive, the clinical results are rewarding. Theoretically, an inhaler with a 10–20 times higher concentration of beta-agonists than the present inhalers, might be as effective as the nebulization of these drugs. The *a priori* advantage of such a "super inhaler" would be the shorter duration of administration of beta-agonists. Indeed, repeated nebulization of beta-agonists is time-consuming, a deleterious factor for these exhausted patients.

The concept of administration of high doses of beta-agonists in severe asthma is not the result of fundamental discoveries, or indentification of new drugs. It was developed from the analysis of good data, using good statistics.

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