EDITORIAL

Should we banish morphine from the treatment of acute pulmonary oedema?

¿Debemos desterrar la morfina en el tratamiento del edema agudo de pulmón?

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Acute pulmonary edema (APE) is one of the most serious manifestations in patients with acute heart failure (AHF) and is a common reason for emergency department attention.[1] For its treatment diuretic drugs have classically been used. Mainly loop diuretics such as furosemide, vasodilator drugs, intravenous nitrates, and support with supplemental oxygen or mechanical ventilation depending on the clinical severity.[2] Intravenous opioids have also been included in the usual therapeutic management, including intravenous morphine, which relieves dyspnea and anxiety and produces a bradycardic and venous vasodilator effect that decreases preload, thus reducing myocardial oxygen demand.[3]

However, several retrospective studies have suggested that morphine in this setting is associated with worse outcomes at the expense of increased mortality, need for intensive care, prolonged hospitalization or increased need for mechanical ventilation.[4,5] Thus, in the latest clinical practice guidelines of the European Society of Cardiology on heart failure, the routine use of opioids in AHF is not recommended except in selected patients.[6] More recently, the results of the MIMO study (Midazolam versus morphine in acute cardiogenic pulmonary oedema), a prospective, randomized, open-label, prospective, open-label, prospective, open-label, randomized, open-label study, have been published. More recently, the results of the MIMO study (Midazolam versus morphine in acute cardiogenic pulmonary oedema), a prospective, randomized, open-label, multicenter study comparing the efficacy and safety of midazolam versus morphine in patients with APE seen in the emergency department, have been published.[7]

This study was stopped after an interim analysis, after randomization of 111 patients (56 treated with morphine and 55 with midazolam). The results showed no significant differences in in-hospital mortality, but a significant increase in serious adverse events (SAEs) at 30-day follow-up in those patients assigned to morphine treatment.[7]

In the present issue of EMERGENCIAS, we publish the results of a subanalysis of the MIMO study,[8] in which Domínguez-Rodríguez *et al.* evaluated the efficacy and safety of both treatments according to the presence or absence of left ventricular systolic dysfunction [left ventricular ejection fraction (LVEF) ≥ 50% or < 50%]. Specifically, the authors examined the effect of the intervention on the risk of occurrence of the first or combined event of death at 30 days or SAE. Most patients (75.7%) had preserved LVEF. The results of this substudy showed no heterogeneity based on LVEF. Therefore, there is no evidence of a differential protective effect of midazolam vs morphine in terms of the endpoints considered here based on the presence or absence of left ventricular systolic dysfunction.[8]

The present study is a post hoc analysis of a clinical trial of great relevance, since it addresses important issues for daily clinical practice, providing certainty on the management of APE. We have other studies and registries that reflect the current situation of AHF treatment in Spain;[9,10] however, the MIMO study provides very valuable information on the specific management of APE, a clinical form of AHF where a large part of the therapeutic recommendations are empirical or of low level of evidence.[6] Similarly, we commend the great difficulty required to carry out an independent clinical trial in patients with severe acute pathology and where the interventions evaluated here lack commercial interest.

With respect to the results of the present substudy, it is worth noting the low prevalence of patients with LVEF < 50%, a fact that increases the possibility of type II error and makes it difficult to draw definitive conclusions regarding the objective set out here. In this same sense, the limited power prevents us from knowing the effect of the comparison of morphine vs midazolam according to the three LVEF categories (≤ 40%, 41- 49% and ≥ 50%) currently supported by international recommendations.[6]

Another aspect to discuss is the percentage of about 18% of patients treated with vasopressors or inotropic drugs despite the high blood pressure of most

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of the patients included here. In this regard, there are two potential subgroups where a priori we could glimpse some degree of heterogeneity in the results. These could be those subjects with previous chronic obstructive pulmonary disease and subjects with lower blood pressure figures, situations in which excessive respiratory depression and a reduction in preload attributable to morphine could show even more deleterious results. Future substudies in this regard would certainly be most welcome. Finally, the evaluation of a dose-response effect is a point still pending.

In short, this subanalysis shows that there is no heterogeneous effect of LVEF on the differences in safety and efficacy of midazolam over morphine in patients with APE. More quality studies like this one are needed to determine whether we should completely banish morphine from treatment in the entire spectrum of APE patients.

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