Editorial

Safety of opioids and benzodiazepines in patients with breathlessness and respiratory failure associated with Chronic Obstructive Pulmonary Disease

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Dyspnea, defined by the 1999 ATS nsity"[1], is a highly distressful symptom, experienced by 94% of severe chronic lung disease and 78% of advanced lung cancer patients during the final year of their life[2]. Furthermore, pain and anxiety are cardinal symptoms highly prevalent in both diseases[3].

Provided that treatment of the underlying condition has already been optimised, benzodiazepines and opioids are pharmacological options considered by physicians for the management of refractory dyspnea. While there is not enough evidence in the literature supporting a beneficial effect of benzodiazepines on breathlessness[4], oral and parenteral opioids have been shown to have a statistically significant effect in managing refractory dyspnea[5,6]. On the other hand, not enough data support the use of nebulized opioids[5,7]. The possible mechanisms by which opioid seem to alleviate dyspnea include reductions in the central perception of dyspnea (similar to the central perception of pain), dyspnea-associated anxiety, total ventilation, oxygen consumption, sensitivity to hypoxemia and hypercapnia, as well as an improvement in cardiovascular function and an increase in ventilator efficacy with exercise[5,8].

However, concerns mainly about respiratory depression and overdosing often make clinicians reluctant to treat refractory dyspnea using these pharmacological agents[9,10].

Results are conflicting. In a systematic review by Simon et al, benzodiazepines seem to cause more drowsiness than placebo, yet less than morphine[4]. Nevertheless, Chan et al found no association between use of benzodiazepines and opioids and time from ventilator withdrawal to death[11], while in a systematic review by Jennings et al, only one out of eleven studies demonstrated a significant reduction of oxygenation due to opioid use. In only one of four studies, measuring arterial blood gases as part of their protocol, was a significant increase in pCO_2 found, yet it did not exceed 40mm Hg[12]. Confusion, constipation, nausea and vomiting, psychosis and hallucinations are additional adverse effects linked with opioid use[9].

Given the apparent need for further clarification of the safety of benzo-

diazepines and opioids administration in severe dyspnea, Ekström et al., recently conducted a population based longitudinal consecutive cohort study investigating the issue[13]. 2249 patients who started long term oxygen therapy for COPD were included in the study. 24% of the patients were using benzodiazepines, 23% were using opioids and 9% were taking both categories of drugs. No association between treatment with benzodiazepines or opioids and increased risk of hospital admission was demonstrated (hazard ratio 0.98 for both drugs). Concurrent treatment with those two agents was associated with a lower admission rate. This effect, though, was interestingly limited to WHO performance statuses 3 and 4, presumably due to more intense health care, including concurrent treatment with opioids and benzodiazepines, provided to these patients, thus obviating hospital admission. Additionally, the presence of hypercapnia, anxiety or depression, injury and drug naïvety did not influence drug effects.

Concerning mortality, treatment with benzodiazepines was found to be associated with a higher adjusted mortality. A trend of a dose relation with mortality was noted for both opioids and benzodiazepines. Nevertheless, low opioid dosage, defined as ≤30 mg oral morphine equivalents/day, was not associated with increased mortality. The same applies to concurrent treatment with low dose opioids and benzodiazepines, while high dose concurrent treatment significantly increased mortality. Hypercapnia, previous injury, being naïve to the drugs, concurrent use, anxiety/depression were not found to alter drug effects.

This large scale prospective study supports the use of low dose opioids in managing very severe respiratory disease, as no increase in mortality or hospital admission was found. On the other hand, the role of benzodiazepines in the same setting appears less clear, as its use was associated with a moderate increase in mortality, with a trend towards a dose relation.

The results of this study provide further evidence that supports the safety of opioids in treating refractory dyspnea, given the reluctance of many physicians in prescribing them, mainly because of concerns regarding possible adverse effects[15]. This observation is in accordance with previous data not demonstrating any significant effects on arterial blood gases or oxygen saturation[5], hospital admission due to respiratory depression[16], or death related to low dose opioids[17]. As for benzodiazepines, data associating their use with increased mortality are less consistent[16].

In conclusion, this study further prompts clinicians to use low dose opioids for breathlessness in patients with respiratory failure associated with COPD, in concordance with the guidelines on the management of refractory dyspnea[9,18,19], cautiously titrating dosage in order to achieve a careful balance between benefits and possible adverse effects.

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