The Endless Question of Opioid Doses for Breakthrough Pain

I read with interest the comments [1] on a paper describing the differences of breakthrough pain (BTP) between patients with cancer receiving lower and higher doses of opioids for background pain [2]. I thank the colleagues because they allow me to express my thoughts better on the opioid doses to be used for BTP. They pointed out three different questions, which are of paramount importance in the still-open debate regarding the use of BTP medications.

The first is based on the proportional dose of opioids to be given for BTP in relation to the background analgesic regimen. For decades, after years of experience with intravenous morphine, we have been testing a dose of one-fifth of the background opioid doses. The choice was based on the fact that to control a rapid increase in pain of high intensity, one needs to provide a sufficient amount of drug, which should be calibrated to the level of tolerance. Thus, minimal doses would not be effective in patients receiving high doses of opioids. In other words, with the level of tolerance, we already have a clue to the doses to be used without starting with the lower dose available (which is?) to be titrated against the effect, while providing an as effective as safe intervention. We learned from pioneer experience that even doubling patients' fourth hourly dose nightly does not cause them to experience great problems [3]. For example, in patients receiving 60 mg of oral morphine equivalents, an intravenous dose of 4 mg (considering an intravenous/oral ratio of 1:3, oral should be 12 mg) was given in large exploratory studies, with thousands of patients and episodes treated successfully and safely [4–6]. The concept can be extrapolated for fentanyl preparations, which are characterized by a short onset of action.

The second point is even more important, as with this approach, the request of additional doses is very limited, as most episodes will be covered for intensity and duration. Pragmatic studies have shown a high level of effectiveness and safety [7]. Only "difficult patients" may have a new episode. We do not use specific lock-out. However, when requests are frequent throughout the day or the episode reappears after 1–2 hours, it is obvious that we have to reserve our attention to the background pain. When episodes become frequent, patients express poor basal pain control. There are many alternatives to improve background pain that fall outside this discussion [8]. The third point is strictly connected to the second one. Patients who recur to three or more BTP medications per day should be better re-evaluated. For instance, in a noninterventional study, the

majority of clinicians have been using BTP opioid doses proportional to basal opioid doses successfully and safely [9].

Currow et al. recently performed an interesting study, the first one to the best of my knowledge, assessing oral morphine for the management of BTP in different dose ranges proportional to the background opioid dose [10]. Oral morphine is the first-line drug recommended by National Institute for Health and Care Excellence guidelines, despite no study ever having assessed the effectiveness of oral morphine in the management of BTP [11]. They showed that oral morphine at any dose was ineffective, as no dose provided at least a 2-point difference or a 33% decrease in pain intensity. I notice that a trend in favor of the one-sixth dose is evident in table 2, with the same side effects, although not significantly, possibly for the low number of patients. According to these results, instead of recommending using the lower doses (1/12), I would say to not use oral morphine at all. Why should we give any substance, however cheap, if patients do not have a clinical benefit from this administration? Rather, pain relief could be the consequence of a spontaneous disappearance of BTP event (expected to last less than 1 hour, on average), whereas the causes of further requests may express the ineffectiveness of oral morphine. A recent paper reported that the vast majority of patients had a good response to oral opioids for BTP, given as 10% of background opioid dose, although only the judgment of patients regarding effectiveness on a 7-point Likert scale, and not the changes in pain intensity, were assessed [12].

I strongly agree that standardizing dose proportion in future cohort studies by using similar methods with all the available pharmacological alternatives will allow for optimization of the use of BTP medications.

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Disclosures

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