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Letter to the Editor

Stop and go strategy for opioid switching requires flexibility

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To the Editor:

I read with interest the paper published by Moksnes et al.[1] This is the first controlled trial regarding opioid switching and authors should be complimented for giving such evidence-based information. On the basis of the data they collected, they conclude that stop and go strategy (SAG) for switching from oxycodone or morphine to methadone produced more pain, more drop-out and adverse effects, suggesting that a switch performed in three days (3DS) works better than SAG. There are some considerations that could help in making clear some points, regardless of data reported with the strict protocol dictated by the rules of a randomized controlled study.

The rationale of 3DS was based on concerns about the safety of switching to methadone, due to poor information about conversion ratios existing at that time. From their retrospective data, the same authors also proposed to use a conversion ratio dependent on the previous opioid dosage, the highest dose requiring the highest ratio, that means a lower dose of methadone.[2,3] The authors of the original work (Edmonton group) no longer use this approach. In fact the SAG strategy argues that an unfavourable clinical condition associated with a drug, can be optimally changed, stopping the offending drug and providing a new one. This approach may take time, ranging from 3 to 11 days, which is inconvenient in circumstances of uncontrolled symptoms.

A rapid substitution of morphine with methadone using a fixed ratio 5:1 was used to circumvent these problems. The aim was to provide a priming and to accelerate the achievement of a steady state of methadone plasma concentration, then changing the dose day by day according to the clinical situation. Of interest, the starting morphine-methadone ratio, relatively higher in comparison with previous approaches, did not change, approximately maintaining the initial 5:1 conversion ratio, although patients on relatively high doses of morphine had to reduce one-third the doses of methadone.[4] The SAG strategy has never been reported to be superior to 3DS, but it gained popularity for the obvious pharmacokinetic advantages, producing rapid changes of plasma concentration of the two opioids, and consequently of the clinical effects produced by them, rather than facing the effects of two drugs together. While providing a more rapid effect, it requires expertise and flexibility in the subsequent days in managing methadone doses according to the clinical picture, especially when the switching is started with high doses and switching requires careful monitoring in a protected environment. In my opinion, SAG cannot provide the best performance with a protocol which does not allow any change in doses for 5 days.

Indeed, they report that SAG group reported more adverse effects and drop-outs. Apart from the low num-

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ber of patients (most patients dropped out for different reasons, not necessarily adverse effects), pain relief in the SAG group seems to be lower (significantly?) at day 3. This is unexplainable, whether one takes into account that more adverse effects should also correspond to better analgesia if methadone concentrations are presumed to be higher in the SAG approach. Looking at the protocol, practically the only difference between groups resides in the first two days as the entire methadone dosage becomes similar at the third day. This period seems to be covered by more rescue doses per day in the 3DS group, so it is likely that patients are receiving a similar treatment when they are assessed, whether they use methadone as a rescue drug (this data is lacking).

The differences found in pain intensity at day 14 cannot be explained as at that time patients in both groups are receiving the same treatment for more than 10 days. At the end, 10 SAG patients completed the study and were compared with 18 3DS patients, with obvious statistical implications.

Globally, data reported are not surprising, as SAG strategy requires flexibility in dosing, rather than maintaining the doses for 5 days consecutively, as per protocol. While it is important to perform controlled studies in the field of opioid switching, some points should be carefully taken into consideration. The rationale of 3DS seems to be already overcome, as there is no advantage in reducing the doses of a drug which is ineffective/toxic. Rather, a more flexible use of SAG methadone and strict clinical observation to change doses according to the clinical response may provide the optimal treatment in patients receiving high doses of morphine or oxycodone. The low number of patients, the logistics of the study and the lack of flexibility in methadone doses, particularly in the SAG group, does not allow to draw the conclusion that 3DS works better than SAG.

Conflict of interest statement

None declared.

References

1. Moksnes K, Dale O, Rosland JH, et al. How to switch from morphine or oxycodone to methadone in cancer patients? A randomized clinical phase II trial. *Eur J Cancer* 2011;**47**:2463–70.
2. Bruera E, Pereira J, Watanabe S, et al. Opioid rotation in patients with cancer pain. A retrospective comparison of dose ratios between methadone, hydromorphone, and morphine. *Cancer* 1996;**78**:852–7.
3. Lawlor P, Turner K, Hanson J, Bruera E. Dose ratio between morphine and methadone in patients with cancer pain. A retrospective study. *Cancer* 1998;**82**:1167–73.
4. Mercadante S, Casuccio A, Calderone L. Rapid switching from morphine to metadone in cancer patients with poor response to morphine. *J Clin Oncol* 1999;**17**:3307–12.