Opioid Rotation: What Is the Rush?

There are no two people in pain management that I can think of who have saved more lives than Drs. Webster and Fine. In their piece suggesting a new paradigm for opioid rotation [1], they add a distinctly useful clinical approach to what heretofore has been their empirical, political, and advisory efforts in this domain. Dr. Webster has worked tirelessly with his Lifetree foundation and with the Utah Department of Health to attempt to reduce overdose deaths through his empirical studies, root cause analyses and educational websites such as his zero unintended deaths website. Dr. Fine has made multiple contributions to this area, but few may know that he recently had to fight with a third party payor to get them to rescind a dose conversion table they had printed up for use as they urged physicians in their plans to switch patients to methadone to cut costs; this table contained a conversion to methadone from other opioids, which if widely employed in the plan, would likely have led to many, many deaths. With their present contribution, they are attempting to simplify and render safer a process that is poorly understood and practiced in tremendously divergent ways.

As I read their article, I am tempted to put it into a bit of historical context. I was at the Memorial Sloan Kettering Cancer Center (MSKCC) back when Nathan Cherney [2] published his famous article in which he outlined how common the need to rotate opioids was in patients cared for by the MSKCC palliative care team. Indeed, the average patient underwent several changes of drug and/or route during their care (average number of changes was 4). Like so many concepts that guide opioid therapy, the roots of opioid rotation are found in the cancer pain management experience and literature. And like so many such concepts, over time some have required modification in the way in which they are applied to chronic noncancer pain scenarios [3].

In cancer, opioid rotation often occurs in the context of an emergent pain crisis. For example, a patient develops new, painful, metastatic disease. While new palliative oncology treatment may be planned and eventually brings the pain under control, there is often a period wherein opioid dosages are rapidly escalated to accommodate the new pain. Sometimes this is well tolerated and sometimes it is not. When it is not, it is often severe toxicity (hallucinations or delirium) that triggers a rotation of drug or route; but it is not a simple case of the need to reverse opioid toxicity because it is occurring in the context of a pain crescendo. Thus, conversions are made somewhat quickly in oncology and if it is in the setting of intense pain, it is often going to lead to a greater degree of tolerance for opioid-related side effects including respiratory depression than in a less dramatic setting. In chronic noncancer pain management, opioid rotation might be practiced because of less severe toxicity or to “unwind” the patient, or to capitalize on incomplete cross tolerance. In any case, the sense of urgency to make a change—likely something that should become a planned aspect of long-term opioid therapy in the future—is less and can be done much more slowly.

In Webster and Fine’s approach, I am reminded of the now well-known, and repeatedly demonstrated, finding from the rapid onset opioid (ROO) trials in which little to no relationship has been found to exist between a patient’s degree of opioid tolerance and the dose of a ROO it takes to relieve their breakthrough pain episodes [4]. This has been demonstrated for all of the fentanyl products in this category. Thus, the titration models that have developed for their use suggest that all patients start at the lowest dose of the product. More recently, the same lack of relationship between opioid tolerance and the dose of immediate-release oxycodone required to relieve a breakthrough pain episode has also been demonstrated [4]. These findings have called into question formulaic clinical conventions that suggest that breakthrough opioid doses should be a set percentage (i.e., 15% or so) of the patient’s daily opioid requirement. Given that our field has been enlightened by the work of Gavril Pasternak [5] on the genetic heterogeneity that underlies incomplete cross tolerance and the idiosyncrasies of opioid responding, it is small wonder that the formulaic approach in breakthrough pain has been undermined by careful clinical studies. Is it any less wonder that conversions to be used in opioid rotation are meeting a similar fate in the hands of Webster and Fine? It is almost as if they are recommending an approach to rotation that is the equivalent of starting all patients to be treated with ROOs for breakthrough pain on the lowest dose of the product and doing a slow, careful titration.

Our late, great colleague, Daniel Brookoff, an oncologist by background, was always highly critical of opioid conversion tables. He used to joke that if we approached our infectious disease colleagues and asked how much gentamycin equaled how much penicillin, they would think we are crazy as it has no meaning given what they understand about the molecular aspects of infectious disease. And in less of a joking fashion, he would remind audiences when he lectured about how so many such tables were developed in single dose, nontolerant patients in acute pain models on mainly young male subjects. That they should be viewed as providing little reliable guidance in the making of opioid conversions and rotations in chronically

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dosed, tolerant, chronic pain patients who might also be older women, seems obvious. It is no surprise that as we, too, have learned more about the molecular bases of the disease we treat, chronic pain, that the notion of equivalence is seemingly becoming more and more farfetched.

I hope that pain clinicians will read this article and try to incorporate the suggestions from these two highly experienced pain clinicians with an eye toward changing their practices. As one of the people who coined the four As and seen it get widely adapted, I realize how much busy clinicians value mnemonics and shortcuts and recipes. I also recognize that the flipside of this tendency is to resent something that suggests that a clinical situation may be more complex, painstaking, and time consuming than one initially learned it was. In this case, it is time well spent. I hope that it will move us closer to Lynn Webster’s ultimate goal of “zero unintended deaths.”

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