Fentanyl, Morphine, and Opioid-Induced Constipation in Patients with Cancer-Related Pain

Opioid drugs are known to inhibit gastric emptying and peristalsis in the gastrointestinal (GI) tract, which results in delayed absorption of medications and increased absorption of fluid. At the receptor level, in the GI tract, the mu and delta receptors predominate and are found in the myenteric and submucosal plexus. The opioid receptors stimulate the production of adenylate cyclase and inhibit the calcium channels, which, in turn, results in a decrease in neurotransmitter release. Tolerance to opioids not only develops pain but also the pharmacological effects on the GI tract.[1,2] The lack of fluid in the intestine leads to hardening of stool and constipation. Most patients with opioid-induced constipation complain of straining and incomplete emptying of the rectum during defecation. Opioids also increase the anal sphincter tone impairing the defecation reflex. Moreover, opioids have been found to decrease emptying of pancreatic juice and bile leading to delayed digestion.[3-5]

In the article "*A comparative study of transdermal fentanyl patch versus sustained release oral morphine in patients on palliative care with regard to bowel function discomfort,*" the authors found that patients converted from oral morphine to transdermal fentanyl reported a significant improvement in constipation. This comparison has been around in published literature for quite some time. Although the results of randomized trials are conflicting,[6-10] two systematic reviews of patients receiving opioids for cancer and noncancer pain concluded that there is less constipation with transdermal fentanyl than with oral sustained-release morphine.[11,12] There have been no direct comparisons of the constipating effects of these drugs, and in the absence of anecdotal reports of differential effects on the gut, the explanation for these observations has focused on the route of administration. The nonoral route presumably impacts opioid receptors less than the oral route and, for this reason, may be less constipating. Other proposed mechanisms include the reduction of first-pass metabolism, the difference between a 12-h and 72-h sustained-release delivery system, and/or a combination of all three.[6-8,13-19] Furthermore, in this context, we should also be aware of an alternative hypothesis proposed by Grunkemeier *et al.* regarding the opioid withdrawal syndrome.[20,21] According to the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition criteria, signs and symptoms of opioid withdrawal include lacrimation or rhinorrhea, piloerection "goose flesh," myalgia, diarrhea, nausea/vomiting, pupillary dilation and photophobia, insomnia, autonomic hyperactivity (tachypnea, hyperreflexia, tachycardia, sweating, hypertension, and hyperthermia), and yawning.[22] Davies *et al*. have suggested that opioid withdrawal syndrome can significantly bias the results in short-term studies (for example, the present one), and so, we should be aware of this entity while choosing between opioids in this matter.

The present study conducted at Palliative Care Center, R.K. Birla Cancer Center, SMS Hospital, Jaipur, compares two opioids, each in a different formulation – oral or transdermal. This is a welcome trial in a difficult area. The focus is which drug (or formulation) gives the fewest problems or is preferred by patients, at the same level of pain relief. Unfortunately, the design of the trial means that we must question the results. Rule one of drug trials that compare different formulations and use subjective outcomes such as patient preference is that the comparison should be done double-blind. This may be awkward, and it will be more expensive, but breaking the convention means that the conclusions may not be correct. Yet here, we are with a study which compared different formulations and used subjective outcomes and was not done double-blind. The problem we are left with is whether any difference between formulations is credible, and whether any credible difference is worthwhile given the marked price difference between the two products.[23] Given the high prevalence of cancer pain and its major impact on quality of life, it is time that we had a better grip on what works in clinical practice and when.

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To the authors of "A comparative study of transdermal fentanyl patch versus sustained-release oral morphine in patients on palliative care with regard to bowel function discomfort."

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