Fentanyl Preferred to Morphine for Treatment of Nonmalignant Pain

Allan L, Hays H, Jensen NH, et al. Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. BMJ 2001;322:1154–8.

Study Overview

Objective. To determine whether patients with chronic nonmalignant pain prefer long-acting oral morphine sulphate (LAM) or transdermal fentanyl (TF).

Design. Randomized open-label crossover trial.

Setting and participants. Subjects were recruited from 35 pain clinics in 7 countries. Patients were eligible if they were older than 18 years, had chronic nonmalignant pain requiring continuous treatment with potent opioids (not defined in the article) for 6 weeks preceding the trial, and had achieved moderate pain control with a stable dose of oral opioid 7 days before the trial. Various exclusion criteria were used, including pain not responding to opioids, history of allergy or hypersensitivity to opioids, life-threatening disease, concomitant psychiatric disorders, and history of substance abuse.

Intervention. Patients received a 4-week course of TF and of LAM without run-in or wash-out periods. Two study groups were formed, with roughly the same amount of patients, based on which drug was administered first. TF and LAM dosages were determined using information provided by manufacturers. Medications for breakthrough pain were allowed and not standardized.

Main outcome measures. The primary outcome measure was patient preference for either LAM or TF, which was assessed at the end of the trial or at the time patients withdrew from the study. Secondary outcomes included quality of life as measured by the SF-36, pain control as assessed by both investigator and patient using a global assessment tool (not described in the article), and adverse events including a bowel function questionnaire (not described in the article).

Main results. Of the 256 patients randomized, mean age was approximately 51 years, and slightly more than half were men. Half of study patients had nociceptive pain, one quarter had neuropathic pain, and one quarter had combined nociceptive/neuropathic pain. Forty percent of patients had low back pain, and similar proportions had pain of either musculoskeletal/connective tissue or nervous system origins. Three quarters had taken a morphine preparation before the trial began, with 1 in 8 stating that preparation efficacy was "bad" or "very bad."

Investigators assessed preferences in 212 patients, including 21 (not described in the article) out of 60 who withdrew from the study early. More patients withdrew while taking TF than while taking LAM (39 versus 21, *P* not reported), and more patients "preferred" or "very much preferred" TF (65% versus 28%, $P < 0.001$). Results were similar for subgroup analyses examining patients with nociceptive, neuropathic, or combined nociceptive/neuropathic pain and those who were not accustomed to either TF or LAM prior to the study ($n = 66$; *P* values not reported for any subgroup analyses). Pain control scores (scale, 0 to 100) were lower during TF treatment (57.8 [range, 33.1 to 82.5] versus 62.9 [41.2 to 84.6] during LAM treatment, $P < 0.001$), and more patients reported "good" or "very good" pain control with TF use (35% versus 23%, $P = 0.002$). However, patients took more breakthrough medications while receiving TF (29.4 mg/day versus 23.6 mg/day, $P < 0.001$). Patients scored higher on the total SF-36 and 4 of the subscales (statistical data not reported) while taking TF. The overall incidence of adverse effects was similar in both groups (about 72%); few serious adverse effects (about 3%) and no deaths occurred. More patients withdrew because of adverse effects while taking TF (11% versus 4%, *P* not reported). Fentanyl was associated with a higher incidence of nausea (26% versus 18%, *P* not reported) but less constipation (16% versus 22% by report and 29% versus 48% by the bowel function questionnaire, *P* not reported).

Conclusion. Patients preferred TF to LAM for chronic nonmalignant pain.

Commentary

Allan and colleagues should be congratulated on conducting a large international study focusing on patient treatment preference. Despite great advances in outcomes research, simply asking patients what they prefer is done too infrequently.

Although its unblinded design somewhat diminishes the scientific validity of its findings, the study provides important pragmatic information. A substantial concern mitigating these conclusions, however, is whether TF may have had an advantage because a majority of patients had been using LAM prior to the study. The authors note that an "incomplete cross-tolerance" may have resulted in more patients withdrawing due to adverse events during TF treatment while this difference disappeared in the subgroup naive to both treatments. This same effect may have given TF a physiologic advantage, particularly given the short study period. Moreover, considering that no more than 35% of patients reported good pain control at the end of the study, one can assume that few patients had maintained good pain control before entering the study. Anticipation of a new treatment—particularly one that may have seemed "high tech" because of a relatively unusual delivery mechanism—likely generated a placebo effect strongly favoring TF. Notably, this study was funded by the manufacturer of Duragesic, the TF preparation used as study treatment. Such studies should always be examined with a skeptical eye, especially when blinding and placebo control are not used.

Applications for Clinical Practice

Although it presents useful data on TF's effectiveness for chronic nonmalignant pain, this study does not provide evidence that TF should be the initial treatment of choice. Before such a conclusion can be reached, more data is needed on factors such as long-term effectiveness (ie, whether preferences extend past the first month of therapy) and relative cost-to-benefit ratios for the 2 treatments. It should also be noted that, although TF was clearly favored overall, over a quarter of study patients preferred LAM. Using the proportion of patients with "good" or "very good" pain control, the number of patients needed to be treated with TF to achieve at least good control is about 9. More careful attention must be paid to patients with chronic pain of any etiology. This study clearly demonstrates that options exist for pharmaceutical management of chronic pain; these options should be explored for patients who do not experience satisfactory relief.