Successful Dose-Finding With Sublingual Fentanyl (Abstral®): Combined Results From 2 Open-Label Titration Studies

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Purpose

Sublingual fentanyl (Abstral®) has been shown to be efficacious in the treatment of breakthrough pain (BTP) in patients with cancer, at a dose determined by individualized titration in each patient. The aim of this analysis was to use pooled clinical trial data to describe the likelihood of identifying an effective dose during initial dose-finding, and to describe the relationship between effective dose and the baseline opioid dose.

Method

Data were derived from two clinical trials (Clinical Trials.gov identifiers NCT00262678 [Study 1] and NCT00263575 [Study 2]) of sublingual fentanyl in patients with BTP associated with cancer. Both trials consisted of a 2-week titration phase followed by a 12-month maintenance phase. All patients started at a dose of 100 µg, and were titrated until reaching an effective dose between 100 and 800 µg. Effective dose was defined as the dose producing effective relief of all BTP episodes on 2 consecutive days; this was the first dose during the maintenance phase or last dose during the titration phase. Relationships between baseline patient characteristics and effective doses, and between baseline characteristics and titration success, were analyzed using a classification tree approach with recursive partitioning.

Results

A total of 131 patients in Study 1 and 139 patients in Study 2 entered the dose-titration phase. Mean (±SD) age of the patients was 55.0 ± 11.5 years in Study 1 and 57.0 ± 11.6 years in Study 2; 54% and 55% of patients, respectively, were female. Mean (± SD) BTP opioid dose at baseline was 16.9 ± 12.3 mg morphine equivalent, mean baseline around-the-clock (ATC) opioid dose was 192.3 ± 144.2 mg morphine equivalent, and mean baseline BTP/ATC ratio was 0.14 ± 0.14. In Study 1, a total of 78/131 patients (59.5%) completed the dose-titration phase; in Study 2, a total of 96/ 139 patients (69.1%) completed this phase. Thus, 174/270 patients (64.4%) across both studies were successfully titrated to an effective dose of sublingual fentanyl.

The mean effective maintenance dose of sublingual fentanyl was 498.2 ± 234.8 µg. There was no significant correlation between the effective dose and baseline pain severity or between the effective dose and baseline ATC opioid dose. The proportions of patients reaching effective pain relief were at the following doses of sublingual fentanyl: 100 µg (6.3%), 200 µg (8.6%), 300 µg (20.1%), 400 µg (14.4%), 600 µg (23.0%), and 800 µg (27.6%). Factors associated with successful titration were analyzed in 263 patients, 167 (64.7%) of whom achieved an effective dose. Success rates were higher in patients receiving ATC daily morphine equivalent doses <425 mg than in those receiving higher doses (69.3% vs 37.5%); early data analysis provided no evidence of a causal link or clinical association between these two factors.
Conclusions

Despite the stringent criteria defining effective maintenance dose in these trials, an effective dose of sublingual fentanyl was identified in 64.4% of patients, similar to results with other formulations of fentanyl for BTP using significantly less stringent criteria. Patients receiving baseline ATC morphine equivalent doses <425 mg were more likely to find an effective dose within the dose range studied. Results of this pooled analysis showed that there was no correlation between the effective dose of sublingual fentanyl and baseline ATC opioid dose.