

BEMA™ (BioErodible MucoAdhesive) Fentanyl Demonstrates a Favorable Pharmacokinetic Profile Compared to Oral Transmucosal Fentanyl Citrate (Actiq®) in Healthy Volunteers

Niraj Vasisht¹, PhD, Jeffrey Stark², PhD, and Andrew Finn¹, PharmD

(1) BioDelivery Sciences International, 801 Corporate Center Drive, Suite 210, Raleigh, NC 27607, USA;

(2) CEDRA Corporation, 8609 Cross Park Drive, Austin, TX 78754, USA

INTRODUCTION

Oral transmucosal delivery of fentanyl is a rapid and proven route of administration for treating breakthrough pain in cancer patients. However, variability in fentanyl pharmacokinetics has been observed with the use of oral transmucosal fentanyl citrate (Actiq®), which is attributed to several uncontrolled factors including patient mouth surface area, patient diligence in the application process, and the amount of swallowed fentanyl.

BEMA™ technology consists of a small patch that adheres to the oral mucosa and rapidly delivers fentanyl into the systemic circulation through a defined surface area. After 20-30 minutes the patch dissolves so that it has not to be removed after use.

The objectives of this study were:

- To evaluate the effect of system pH on the absorption of fentanyl from the BEMA™ delivery system.
- To compare the pharmacokinetics of fentanyl from the BEMA™ delivery system with that from Actiq®.

METHODS

Study Design

A total of 12 healthy volunteers (9 males, 3 females; mean age 32 years) received single 800µg doses of three BEMA™ fentanyl citrate formulations (pH 6.0, 7.25, 8.5) and Actiq® 800µg at 48-hour intervals in an open-label, four-period, Latin-square, crossover study. Serial blood samples for fentanyl analysis were collected over a 48 hours after each dose. All subjects received naltrexone throughout the study to block the respiratory depressive effects of fentanyl.

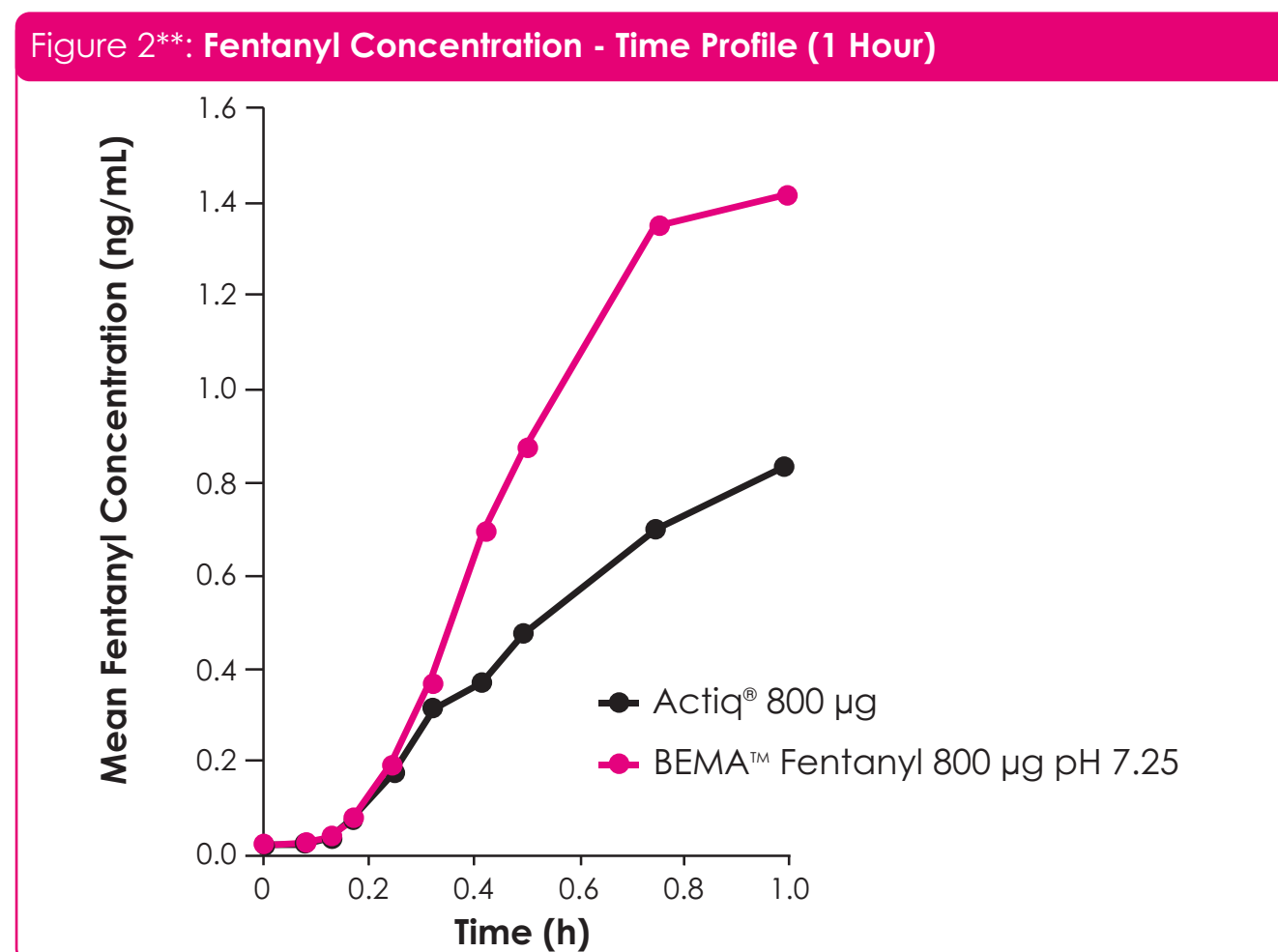
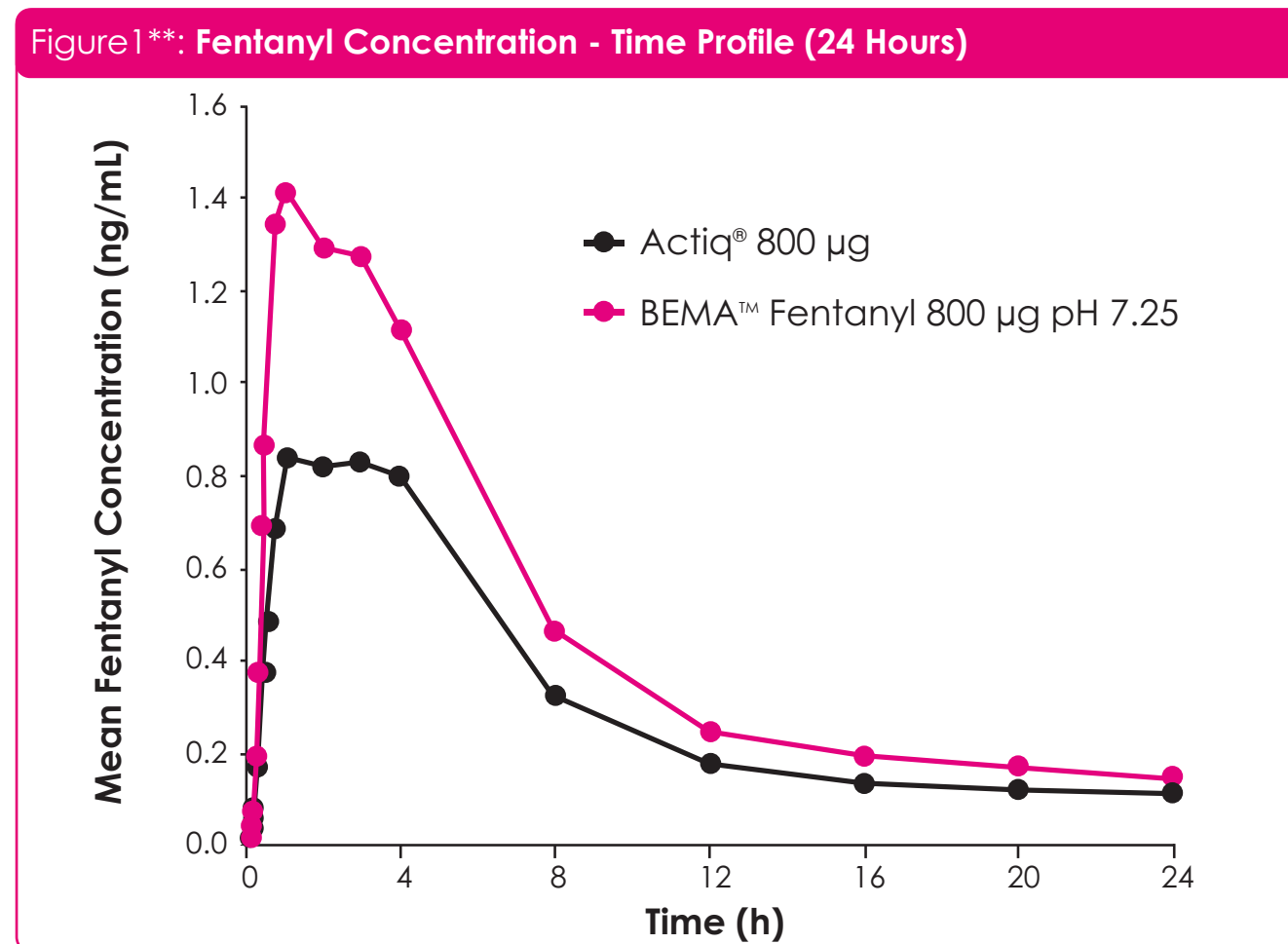
Statistics

Pharmacokinetic data were analyzed by noncompartmental methods using the WinNonlin software package (Pharsight, Inc.).

RESULTS

	T _{first} (min)	C _{max} (ng/mL)	AUC _{inf} (h•ng/mL)	T _{max} (h)
Actiq® 800 µg	13.2 ± 10.8	1.03 ± 0.248	10.30 ± 3.842	2.00
BEMA™ Fentanyl 800 µg pH 6	7.8 ± 1.8	1.40 ± 0.491	13.68 ± 4.546	2.00
BEMA™ Fentanyl 800 µg pH 7.25	9.0 ± 4.8	1.67 ± 0.754	14.46 ± 5.403	1.00
BEMA™ Fentanyl 800 µg pH 8.5	12.0 ± 6.0	1.39 ± 0.409	13.11 ± 4.773	2.00

Means ±SD, except for T_{max} (medians)



CONCLUSIONS

- All three BEMA™ Fentanyl formulations provided faster absorption, significantly higher maximum plasma concentrations, and greater systemic availability of fentanyl compared to Actiq®.
- The absorption with BEMA™ Fentanyl pH 7.25 was quicker than with Actiq® (T_{max} 1h vs. 2h).
- BEMA™ Fentanyl pH 7.25 provided peak plasma concentrations of fentanyl 62% higher than those observed with Actiq®.
- The systemic exposure to fentanyl was 40% greater with BEMA™ Fentanyl pH 7.25 compared to Actiq®.
- The more rapid absorption and increased systemic availability with BEMA™ Fentanyl pH 7.25 may provide clinical benefits.

Pharmacokinetics

* Table 1; ** Figures 1 and 2.

- BEMA™ Fentanyl pH 7.25 optimised fentanyl absorption compared with all the other formulations (highest mean C_{max} and AUC, shortest T_{first} and T_{max}).
- The mean fentanyl C_{max} achieved with 800 µg BEMA™ Fentanyl (pH 7.25) was 1.67 ng/mL, which was 62% higher than that observed with Actiq® at the same dose level.
- The mean fentanyl AUC_{inf} achieved with 800 µg BEMA™ Fentanyl (pH 7.25) was 14.46 hr•ng/mL, which was 40% greater than that observed with Actiq® at the same dose level.
- The median T_{max} for BEMA™ Fentanyl pH 7.25 half as that for Actiq® (1h vs. 2h).

Safety

- BEMA™ Fentanyl units adhered to the oral mucosa within 5 seconds of application and dissolved in less than 30 minutes without causing local irritation.
- There were no serious adverse events or deaths during this study.
- The most frequent adverse event was sedation (25% of subjects under Actiq® and 8% under each of the BEMA™ Fentanyl formulations).