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DETECTION OF NALTREXONE AND NALTREXOL IN PATIENTS PRESCRIBED EMBEDA®

To the editor:

EMBEDA® is a combination opioid agonist/opioid antagonist product indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Embeda capsules consist of pellets containing a 100:4 ratio of morphine sulfate (opioid receptor agonist) to naltrexone (opioid receptor antagonist), with the latter being sequestered inside an inert membrane at the core of each pellet. The naltrexone is added to improve patient safety and deter abuse. When taken orally as directed, the sequestered naltrexone is minimally absorbed by the GI tract, and is intended to have no clinical effect. However, if the medication is crushed, the naltrexone is released from sequestration. The released naltrexone acts to inhibit the physiological effects of the morphine by competitively binding at mu-opioid receptors.[1]

While trace concentrations of naltrexone and its major metabolite 6-β-naltrexol have been observed in plasma following controlled Embeda administration,[1] detection of these compounds in urine following use of Embeda has not been previously investigated and reported. Herein, we report that a retrospective review of quantitative LC-MS/MS urine drug test results for patients reported to be prescribed Embeda suggests that a significant percentage produce positive UDT results for naltrexone and/or 6-β-naltrexol.

A database of de-identified quantitative LC-MS/MS drug test results for urine samples submitted for testing between January and August 2016 was filtered to include only results for patients being prescribed Embeda. This sub-set was further filtered to exclude patients also being prescribed naltrexone. The resulting sub-set was then further filtered to include only results for patients for which morphine, naltrexone and 6-β-naltrexol were available. Finally, patients that tested negative for morphine (and therefore likely not taking Embeda) were removed from the data set. The cutoff concentrations for morphine, naltrexone and 6-β-naltrexol were 50, 10 and 10 ng/mL, respectively. The resulting data set consisted of 213 samples from patients who were prescribed Embeda, not prescribed naltrexone, and tested positive for morphine. The relevant UDT results from this dataset are presented in Table 1. This research was approved by the Aspire Independent Review Board, Santee, CA.

A total of 35 samples (16.4 percent) tested positive for naltrexone, 6-β-naltrexol or a combination thereof. As a control, results from a second data set for patients not being prescribed Embeda or naltrexone was reviewed. The positivity rate for naltrexone and/or 6-β-naltrexol in this second dataset was <1 percent, suggesting that the detection of 6-β-naltrexol and/or naltrexone in the first dataset is associated with Embeda use.

Table 1. Morphine, naltrexone and 6-β-naltrexol UDT results for patients prescribed Embeda (N = 213)

	Morphine (+) Naltrexone (-), Naltrexol (-)	**Morphine (+) Naltrexone (+), Naltrexol (-)**	**Morphine (+) Naltrexone (+), Naltrexol (+)**	**Morphine (+) Naltrexone (-), Naltrexol (+)**
Occurrences	178	3	6	26
Morphine Concentration (ng/mL)	64.4 - > 100,000 Median 16,007	12,259 - > 100,000 Median 39,868	17,878 - > 100,000 Median 91,710	834.1 - > 100,000 Median 60,122
Naltrexone Concentration (ng/mL	--	Range 623.5 – 1873 Median 1400	Range 10.6 – 73.3 Median 18.8	--
6-β-naltrexol Concentration (ng/mL)	--	--	Range 33.2 – 205.9 Median 43.6	Range 10.6 – 110.0 Median 26.9

Morphine concentrations for the 213 samples ranged from 64.4 to > 100,000 ng/mL with a median concentration of 19,194 ng/mL. The majority (80 percent) of the naltrexone/6-β-naltrexol positive samples were found in samples containing morphine above the median concentration. However, using an R^2 regression analysis, there was no correlation found between morphine concentrations and naltrexone/6-β-naltrexol positives, suggesting that regardless of morphine concentration produced in the urine, naltrexone/6-β-naltrexol may be found.

In conclusion, these observations suggest that an LC-MS/MS urine drug test used to monitor patients prescribed Embeda may result in a positive for the naltrexone component of the drug, and should be noted by clinicians as a possible expected result.

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REFERENCE

1. Embeda [package insert]. New York, NY: Pfizer Pharmaceuticals, Inc; 2016.

ERRATUM

It has come to our attention that in the article, Chen C, Bujanover S, Gupta A: Effect of dosing interval on pharmacokinetics of fentanyl pectin nasal spray from a crossover study. 2015; 11(2): 139-146, the protocols used in the research were at least partially developed by A.N. Fisher, PhD during his employment with the company that conducted the research. Unfortunately the authors of this paper did not credit A.N. Fisher, PhD for his work. As publishers, this oversight was out of our control. We do however regret that Dr. Fisher was not credited with his contributions to developing the protocols used in the research.