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A Science-based Approach for Recommendation of Antagonist Blockade in the Bioequivalence Studies of Opioid Drug Products

Christine Oh[1,2], Agm Mostofa[1], Karthika Natarajan[1], Wei-Jhe Sun[1], Heather J. Boyce[1], Myong-Jin Kim[1]

[1]Division of Therapeutic Performance II, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

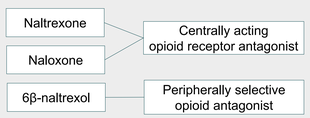
[2]Oak Ridge Institute for Science and Education

CONTACT INFORMATION: christine.oh@fda.hhs.gov

PURPOSE

Administration of an antagonist blockade during in vivo studies of opioid drug products can reduce the risk of opioid-related serious adverse events, drug liking, and addiction potential. There are different types of opioid antagonist (Figure 1). Antagonist blockade is not routinely recommended in the bioequivalence (BE) studies. Product-specific guidances (PSGs) aim to guide the generic drug industry to develop therapeutically equivalent generic drugs based on the current thinking and expectations of the agency.[1] A review of PSGs of opioid drug products was conducted to assist for antagonist blockade recommendation for future PSG development of opioid drug products.

Figure 1. Types of opioid antagonist[2,3]



Naltrexone
- High affinity and potency
- High oral bioavailability (BA)
- Long elimination half-life

OBJECTIVE

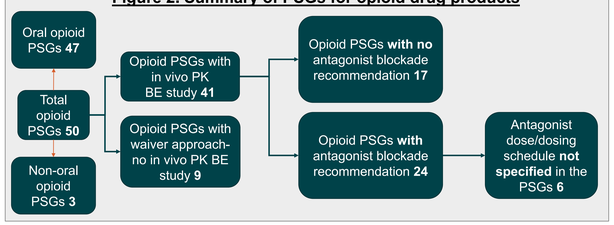
This study aims to identify a science-based approach to standardize the recommendation of antagonist blockade for in vivo pharmacokinetic (PK) BE studies of opioid drug products.

METHODS

The study was conducted using:
- Searched and found 50 opioid product PSGs (with 14 different opioid active pharmaceutical ingredient) from public PSG database[1] to determine opioid antagonist recommendation for all opioid products, including single and combined opioid products.
- Then oral opioids with published PSGs were categorized based on their potency relative to morphine and their pharmacological properties such as receptor binding affinity.
- A systematic review of literature, in-house new drug applications (NDAs) and abbreviated new drug applications (ANDAs) for BA/BE studies of opioid drug products.

RESULTS

Figure 2. Summary of PSGs for opioid drug products



RESULTS

- The summary of PSGs found in the PSG database[1] for opioid drug products is shown (Figure 2).
- 41 out of 50 total opioid PSGs recommend an in vivo PK BE study.
- 24 out of 41 opioid PSGs with in vivo PK BE study provide antagonist blockade recommendation but 6 of the 24 do not provide details on either dose or dosing schedule or both.
  - ➢ 4 out of 6 PSGs were published on or before 2010 and lack details on antagonist administration (dose, dosing schedule).

Table 1. Rank ordering of agonists with PSG based on the intrinsic potency[2,4,5]

Opioid Agonists	Relative binding affinity to various opioid receptors			Potency Relative to Morphine
	MOR*	KOR**	DOR***	
Fentanyl	++++	++	+	100X
Buprenorphine	++++	+++	+++	80-100X
Methadone	+++	++	++	5-10X
Levorphanol	+++	++	++	8X
Hydromorphone	+++	++	++	4-5X
Oxymorphone	+++	++	++	3X
Oxycodone	+++	+	+	1.5X
Morphine	+++	+	+	1X
Hydrocodone	+++	+	+	0.67X
Tapentadol	+++	+	+	0.33X
Tramadol	++	+	+	0.1X
Codeine	++	+	+	0.1X
Dihydrocodeine	++	+	+	0.1X
Propoxyphene	+	+	+	0.05X

*mu opioid receptor; **kappa opioid receptor; ***delta opioid receptor

Table 2. Identified oral intermediate and high potent opioids in consideration for antagonist blockade recommendation in the PSG with dose/dosing schedule based on intrinsic pharmacological properties and specific drug product-related factors

Current PSG recommendation for antagonist	Oral opioid product (dosage form, strength)	Other API	Antagonist blockade in the NDA studies	Antagonist blockade in the ANDA studies	Current PSG
No antagonist blockade in PSG	Tapentadol (IR Tablet, 100 mg)	N/A	Not used	Naltrexone; Dose: 50 mg Schedule: -12 h, 0 h, +12 h	No antagonist in PSG
	Hydrocodone (ER Capsule, 10 mg)	N/A		Differences among ANDA (used in 1 ANDA but not used in the other)	No antagonist in PSG
	Oxycodone (ER Tablet, 7.5 mg)	Acetaminophen		Naltrexone dose/dose schedule: slight differences	No antagonist in PSG; recommend plan for respiratory monitoring
	Hydromorphone (IR Tablet, 8 mg)	N/A		Naltrexone dose/dose schedule: slight differences	No antagonist in PSG; clear plan for continuous respiratory monitoring
No defined dose/dosing schedule of antagonist blockade in PSG	Morphine (IR Tablet, 30 mg)	N/A	Naltrexone; Dose: 50 mg Schedule: -12 h, 0 h, +12 h	Naltrexone dose/dose schedule: slight differences	Naltrexone; Consult physician
	Oxycodone (IR Tablet, 15 mg)	N/A			Naltrexone given prior to test/reference product administration
	Oxymorphone (IR Tablet, 10 mg)	N/A			Naltrexone; Consult physician
	Oxymorphone (ER Tablet, 40 mg)	N/A			Naltrexone; Consult physician

High Potent Opioids (Table 1: in Blue)

BA/BE studies in NDAs or ANDAs: Antagonist blockade is used in most BA/BE studies of high potent oral opioids (exception of hydromorphone).

PSG: Hydromorphone is the only high potent oral opioid that did not recommend an antagonist blockade in the PSG.

Intermediate Potent Opioids (Table 1: in Yellow)

BA/BE studies in NDAs or ANDAs : Antagonist blockade is used for higher strengths of intermediate potent opioids in BA/BE studies of hydrocodone and tapentadol.

PSG: Antagonist blockade is used for higher strengths of intermediate potent opioids:
1) Hydrocodone with drug content ≥20 mg (1 PSG) but not with drug content ≤10 mg (4 PSGs)
2) Tapentadol 250 mg (1 PSG) but not for 100 mg tapentadol (1 PSG)

Low Potent Opioids (Table 1: in Green)

BA/BE studies in NDAs or ANDAs : Antagonist blockade was consistently not used in the BA/BE studies in low potent opioids.

PSG: Low potent opioids consistently do not include recommendation for antagonist blockade in the PSGs.

- Antagonist blockade use in the studies submitted to NDAs and/or ANDAs are shown (Table 2). From the 17 PSGs with no antagonist blockade recommendation and the 6 PSGs with no specified dose/dosing schedule (Figure 2), some of the identified oral intermediate and high potent opioid products in consideration for antagonist blockade recommendation in the PSG based on intrinsic pharmacological properties and specific drug product-related factors are shown (Table 2).

CONCLUSIONS

The following should be considered when making antagonist recommendations for the opioid PSG development:

- Intrinsic pharmacological properties of the opioids (e.g., receptor binding affinity, potency)
- Specific drug product-related factors (e.g., drug load)

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DISCLAIMER

This poster reflects the views of the authors and should not be construed to reflect the FDA's views or policy.

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