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

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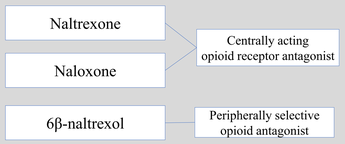
Background

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. Figure 1 shows the different types of opioid antagonist. A review of 50 product-specific guidances (PSGs) of opioid drug products revealed that use of antagonist blockade is not routinely recommended, including potent opioids.

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



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

Objective

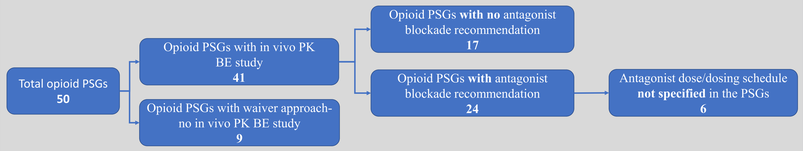
This study aims to identify a science-based approach to standardize the recommendation of antagonist blockade for in vivo pharmacokinetic (PK) bioequivalence (BE) studies of opioid drug products.

Methods

The study was conducted using:
- Search of opioid products PSGs from public PSG database[3] to determine opioid antagonist recommendation for all 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 and PK properties.
- 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.

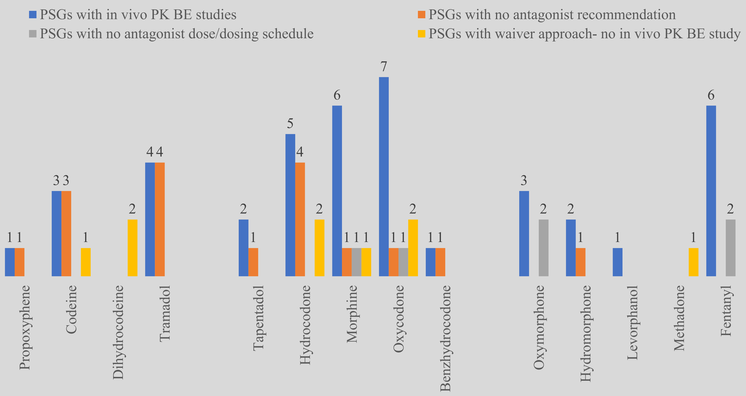
Results

Figure 2. Number of PSGs for opioid drug products



- Figure 2. shows the number of PSGs found in the PSG database[3] for opioid drug products.
- 41 out of 50 total opioid PSGs recommend 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 dose/dosing schedule.
  - ❑ 4 out of 6 PSGs were published on or before 2010 and lack details on antagonist administration (dose, dosing schedule).

Figure 3. Summary antagonist blockade recommendation in the PSGs of different opioid agonists



- Figure 3. is a detailed summary of antagonist blockade recommendation in the PSGs.
- 17 out of 41 opioid PSGs with in vivo PK BE study show no antagonist blockade recommendation.
  - ❑ Example: among the five PSGs of hydrocodone products, only one PSG recommends antagonist blockade.

Results

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

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, Dihydrocodeine	++	+	+	**0.1X**
Propoxyphene	+	+	+	**0.05X**

Table 2. Identified oral opioid drug products to recommend antagonist blockade with defined dose/dosing schedule in the PSGs

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)				Naltrexone given prior to test/reference product administration
	Oxymorphone (IR Tablet, 10 mg)	N/A			Naltrexone; Consult physician
	Oxymorphone (ER Tablet, 40 mg)				Naltrexone; Consult physician

High Potent Opioids (Table 1: in Blue)

BA/BE studies:
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:
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:
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 was not used in the BA/BE studies of 12.5% of immediate-release (IR) and 17.6% of extended-release (ER) intermediate and high potent oral opioid products.
  - ➢ Antagonist blockade appears to be more consistently used for the IR dosage form of oxycodone.
  - ➢ Oxycodone has three IR dosage form with antagonist use in NDA/ANDA studies and three out of four ER form with antagonist use in NDA studies. Furthermore, the one ER form without antagonist use does not have an antagonist recommendation in the PSG.
- Literature search suggests antagonist blockade does not have any significant impact on the PK profiles and/or reduces the frequency and severity of opioid-related adverse effect of certain opioids (morphine, oxycodone, hydromorphone).[6,7,8]
- Antagonist blockade use in the studies submitted to NDAs and ANDAs are shown in Table 2. From the 17 PSGs with no antagonist blockade recommendation and the 6 PSGs with no specified dose/dosing schedule (Figure 2), Table 2 shows 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.

Conclusions

The following should be considered when making antagonist recommendations for the opioid PSG:
- Intrinsic pharmacological properties of the opioids (e.g., receptor binding affinity, potency)
- Specific drug product-related factors (e.g., drug load, dosage form, PK characteristics, and adverse effects)

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Disclaimer

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

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