Drug Trial Designs: Designs, Endpoints, and Methodological Concerns

Bradford D. Harris, MD
Medical Officer
Division of Anesthesia, Analgesia, and Addiction Products
Center for Drug Evaluation and Research
FDA

May 03, 2012

Outline

- Approved sedatives
  - Highlights of two of the most recent approvals
- Methodological concerns

Drugs Approved for Sedation

Drug	Year of Approval
• Lorazepam	1980
• Midazolam	1984
• Propofol	1992
• Fospropofol	2008
• Dexmedetomidine	1999

Dexmedetomidine

- Indications
  - Intensive Care Unit Sedation
    - Precedex® is indicated for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. Precedex should be administered by continuous infusion not to exceed 24 hours.
    - Precedex has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and post-extubation. It is not necessary to discontinue Precedex prior to extubation.
  - Procedural Sedation
    - Precedex is indicated for sedation of non-intubated patients prior to and/or during surgical and other procedures.

Dexmedetomidine: ICU Sedation

- Trials
  - Two randomized, double-blind, parallel-group, placebo-controlled clinical trials 754 patients receiving mechanical ventilation
- Endpoints
  - Study 1 and 2: Amount of rescue medication required to achieve specified level of sedation
  - Study 1: Percentage of patients who achieved a sedation score without the use of additional rescue medication

Ramsay Sedation Scale

Level	Response
1	Awake and anxious, agitated, or restless
2	Awake, cooperative, accepting ventilation, oriented, tranquil
3	Awake; responds only to commands
4	Asleep; brisk response to light glabellar tap or loud noise
5	Asleep; sluggish response to light glabellar tap or loud noise stimulus but does not respond to painful stimulus
6	Asleep; no response to light glabellar tap or loud noise

Dexmedetomidine: Procedural Sedation

- Trials
  - Two randomized, double-blind, placebo-controlled multicenter clinical trials evaluated non-intubated patients prior to and/or during surgical and other procedures

Dexmedetomidine: Procedural Sedation

- Study 1 – elective surgeries/procedures performed under monitored anesthesia care.
  - Primary endpoint: the percent of patients <u>not requiring rescue midazolam</u> to achieve a specified level of sedation using the standardized Observer's Assessment of Alertness / Sedation Scale
- Study 2 – patients undergoing awake fiber optic intubation prior to a surgical or diagnostic procedure.
  - Primary endpoint: the percent of patients <u>requiring rescue midazolam</u> to achieve or maintain a specified level of sedation using the Ramsay Sedation Scale

Fospropofol

- Indication
  - Monitored anesthesia care sedation in adult patients undergoing diagnostic or therapeutic procedures.
- Trials
  - Study 1 – Randomized, blinded, dose-controlled study for sedation in patients undergoing colonoscopy.
  - Study 2 – Randomized, blinded, dose-controlled study for sedation in patients undergoing flexible bronchoscopy.

Fospropofol

- Endpoint: Rate of "sedation success," defined as proportion of patients, who:
  - Did not respond readily to their name spoken in normal tone of voice using the Modified Observer's Assessment of Alertness/ Sedation Scale score
  - Completed procedure without use of alternative sedative medication
  - Did not require manual or mechanical ventilation

Methodological Concerns

- Clinical meaningfulness of the endpoints
- Appropriate metrics
- Rescue medications
- Reproducibility of assessments
- Dose equivalency estimates
- Type of trial and analysis

Clinically Meaningful Outcomes

- Are the endpoints evaluating something that has clinical meaning for the patient?
  - Potential for the endpoints most closely related to the action of the drug (e.g., sedation scales) to be statistically significant, yet the treatment effect may not be clinically meaningful.
  - Selection of the targeted depth of sedation

Methodological Concerns

- Clinical meaningfulness of the endpoints
- Appropriate metrics
- Rescue medications
- Reproducibility of assessments
- Dose equivalency estimates
- Type of trial and analysis

Appropriate Metrics

- The scale should be used in setting or population for which it was developed and in which it has been validated

Methodological Concerns

- Clinical meaningfulness of the endpoints
- Appropriate metrics
- Rescue medications
- Reproducibility of assessments
- Dose equivalency estimates
- Type of trial and analysis

Rescue Medication

- Which rescue medication is best to use
  - May vary by clinical scenario
  - Different PK/PD properties of these medications
- Multiple rescue-type meds in same trial
  - Opioids for pain and other sedating drugs used as standard of care for multiple applications
- Concomitant rescue meds and dose-changes of test treatment

Methodological Concerns

- Clinical meaningfulness of the endpoints
- Appropriate metrics
- Rescue medications
- Reliability and reproducibility of assessments
- Dose equivalency estimates
- Type of trial and analysis

Reliability and Reproducibility of Assessments

- Little documentation is seen in submissions concerning the training of study staff
- Rater training can be used to lend some assurance that investigators are properly evaluating the patient and that the assessments are consistent within and between investigators

Methodological Concerns

- Clinical meaningfulness of the endpoints
- Appropriate metrics
- Rescue medications
- Reproducibility of assessments
- Dose equivalency estimates
- Type of trial and analysis

Dose Equivalency Estimates

- Appropriate selection of the active comparator
- Appropriate rescue medication
- Converting within a class
  - Commonly applied in opioids
  - Can it be done with sedative agents?
    - If so, on what would it be based?
- Converting between classes of agents
  - Benzodiazepines and Propofol
  - Benzodiazepines and Dexmedetomidine
  - Propofol and Dexmedetomidine
- How should metabolites be considered?

Methodological Concerns

- Clinical meaningfulness of the endpoints
- Appropriate metrics
- Rescue medications
- Reproducibility of assessments
- Dose equivalency estimates
- Type of trial and analysis

Type of trial and analysis

- Setting and patient populations
- Placebo vs Active Comparator
- Superiority vs. Non-inferiority

Background Slides

Approved Drugs for Sedation.1

Drug	Year of Approval	Indication
Dexmedetomidine	1999	**Intensive Care Unit Sedation** Precedex® is indicated for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. Precedex should be administered by continuous infusion not to exceed 24 hours. Precedex has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and post-extubation. It is not necessary to discontinue Precedex prior to extubation. **Procedural Sedation** Precedex is indicated for sedation of non-intubated patients prior to and/or during surgical and other procedures.
Fospropofol Disodium	2008	LUSEDRA(TM) (fospropofol disodium) injection is an intravenous sedative-hypnotic agent indicated for monitored anesthesia care (MAC) sedation in adult patients undergoing diagnostic or therapeutic procedures.
Propofol	1992	Initiation and maintenance of Monitored Anesthesia Care (MAC) sedation - Adults only Combined sedation and regional anesthesia - Adults only Intensive Care Unit (ICU) sedation of intubated, mechanically ventilated patients - Adults only

Approved Drugs for Sedation.2

Drug	Year of Approval	Indication
Lorazepam (Inj)	1980	ATIVAN Injection is indicated in adult patients for preanesthetic medication, producing sedation (sleepiness or drowsiness), relief of anxiety, and a decreased ability to recall events related to the day of surgery. It is most useful in those patients who are anxious about their surgical procedure and who would prefer to have diminished recall of the events of the day of surgery.
Midazolam	1984	• intramuscularly or intravenously for preoperative sedation / anxiolysis / amnesia; • intravenously as an agent for sedation/anxiolysis/amnesia prior to or during diagnostic, therapeutic or endoscopic procedures, such as bronchoscopy, gastroscopy, cystoscopy, coronary angiography, cardiac catheterization, oncology procedures, radiologic procedures, suture of lacerations and other procedures either alone or in combination with other CNS depressants; • continuous intravenous infusion for sedation of intubated and mechanically ventilated patients as a component of anesthesia or during treatment in a critical care setting.

Observer's Assessment of Alertness/Sedation Scale

Responsiveness	Speech	Facial expression	Eyes	Score
Responds readily to name spoken in normal tone	Normal	Normal	Clear, no ptosis	5
Lethargic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (< half of the eye)	4
Responds only after name is called loudly or repeatedly	Slurring or prominent slowing	Marked relaxation (slack jaw)	Glazed and marked ptosis (> half of eye)	3
Responds only after mild prodding or shaking	Few recognizable words	-	-	2
Does not respond to mild prodding or shaking	-	-	-	1

Modified Observer's Assessment of Alertness/Sedation Scale

Level	Response
6	Agitated
5	Responds readily to name spoken in normal tone (alert)
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Does not respond to mild prodding or shaking
0	Does not respond to deep stimulus