Introduction

• Morphine sulfate is a potent opioid analgesic used in the treatment of severe acute and chronic pain.
• Morphine achieves its effects primarily through interactions with the µ-opioid receptor in the brain and central nervous system.
• Extended-release oral formulations of morphine such as AVEK® offer the advantage of a longer interval (24 hrs) between dosing and a more continual pain relief profile, but do not allow for dose modulation to control drug induced side-effects.
• Common side-effects of extended-release morphine (incidence 10% or greater, 2006 FDA) include: nausea, vomiting, sedation, headaches, and constipation.
• While tolerance to repeated morphine dosing is a clinically well-recognized phenomenon, little data exists about the development of tolerance, including its time course and effect on common adverse events (AEs).

Methods

Study Design

Several morphine ER bioequivalence studies with similar methodologies were conducted at a large, phase I facility and provided comparative data.

• AVEK® 120mg or bioequivalent morphine ER 120mg was study administered in separate in-clinic, single-dose, two-period crossover bioequivalence studies of brand morphine 120mg ER (AveK®) versus bioequivalent generic versions, administered orally. Healthy, opiate-naïve volunteers (n = 90, ages 18-55) completed both periods, which were separated by 7 days.

Results

Out of all subjects, 20% (18/90) experienced one or more AE in the first period compared to 6.8% (6/90) in the second, which was a significant difference (p = 0.016). The incidence of all individual AEs (nausea, sedation and headache) was lower in the second dosing period compared to the first. Nausea was the most common AE. In addition, females experienced significantly more AEs over both periods than males (32.4% vs. 13.2%, p = 0.05). Most AEs (±70%) occurred within 4 hrs post-dose.

Conclusion

Overall, results demonstrate that tolerance to common initial AEs of opiates can develop even after a single exposure in opiate-naïve subjects. The potential influences of this finding, including the relationship between AE appearance and PK, subject expectations, and the therapeutic implications for initiating opioid therapy in naïve patients will be discussed.

Discussion

• There were significantly fewer subjects experiencing AEs in the second period (5) compared to the first period (10).
• The incidence of each AE by type was also reduced in the second period compared to the first period. This difference was significant for nausea. Sedation and headache were also reduced in the second period but the numbers were too small for statistical significance.
• All AEs occurred within the first 4 hrs. Nausea, vomiting, and headache were also reduced in the second period but the numbers were too small for statistical significance.
• All AEs occurred within the first period. AEs appeared immediately after either AE occurrence was significant for nausea.
• Sedation and headache were also reduced in the second period but the numbers were too small for statistical significance.

Conclusion

These findings demonstrate that tolerance to common initial AEs of opioids can develop even after a single exposure in opiate-naïve subjects.