Dosing Observations and Pharmacokinetics by Surgery Type across Four Randomized, Placebo-controlled Trials with the Sufentanil Sublingual Tablet

Albert Dahan, MD, PhD[1], Jean-Pierre Estebe, MD[2], Maurice Jove, MD[3]

[1]Leiden University Medical Center, Leiden, Netherlands; [2]Centre Hospitalier Universitaire Rennes, Rennes, France; [3]DeKalb Medical Center, Decatur, GA

Background

Inpatient and outpatient postsurgical complications related to inadequate pain management negatively affect patient welfare and hospital performance.[1-3] Poorly managed acute pain can lead to hypersensitization and within hours of onset, acute pain can provide physiological conditions that facilitate persistent pain syndrome or chronic pain.[4,5] Multimodal approaches have demonstrated value but opioids still remain the cornerstone of acute post-operative pain management.[6] The Sufentanil Sublingual Tablet System (SST 15 mcg; Zalviso®), a PCA device dispensing 15 mcg tablets, is approved in Europe for treatment of acute post-operative pain. A second sufentanil product, a 30 mcg tablet (SST 30 mcg) dispensed by a healthcare professional (HCP) in emergency medicine and short-stay surgery settings is also under review by the European Medicines Agency. Sublingual sufentanil has unique pharmacokinetic and pharmacodynamic properties and data evaluating two dosage formulations is now available across a broad range of orthopedic and abdominal surgery pain models.[7-9] The primary objective of this post-hoc analysis was to evaluate drug utilization and sufentanil plasma concentrations by surgery type across the SST 15 mcg and SST 30 mcg pivotal trials.

Figure 1. Sufentanil Sublingual Tablet System and SST 30 mcg




Methods

Study Design

- All studies were multicenter, randomized and placebo-controlled.
- Two were conducted with SST 15 mcg following open abdominal (ABD) surgery (IAP310) and knee (TKA) or hip (THA) replacement surgery (IAP311)
  - SST 15 mcg patients were allowed to dose every 20 minutes as needed via PCA device
- Two studies were conducted with SST 30 mcg following bunionectomy (SAP202) or abdominal surgery (ABD) including abdominoplasty, laparoscopic abdominal surgery or hernia repair (SAP301)
  - SST 30 mcg patients could receive a dose as needed throughout the study but not more frequently than hourly
- Before study staff could administer the first dose of study drug in any trial, patients must have reported a pain intensity (PI) score of 4 or higher on a validated, 11-point numerical rating scale (0-10).
  - Rescue medication was available for all patients upon request

Efficacy Assessments

- The primary efficacy variable in all studies was the time-weighted summed pain intensity difference (SPID) to baseline over the 48-hour (IAP310 and IAP311) or 12-hour (SAP202 and SAP301) study period
- Key secondary endpoints included PI over the first hour, total pain relief (TOTPAR) and early termination due to inadequate analgesia
- Detailed dosing data were collected and plasma sufentanil concentrations were derived from blood samples drawn at 12, 24 and/or 48-hours after the first dose.

Safety Assessments

- Safety assessments included adverse events (AEs), vital signs, including oxygen saturation, and the use of concomitant medications

Results

Sufentanil Dosing and Plasma Drug Levels (pg/mL)	IAP311 SST 15mcg		IAP310 SST 15mcg	SAP202 SST 30mcg	SAP301 SST 30 mcg
	TKA N=152	THA N=163	ABD N=114	BUN N=40	ABD N=107
Mean (median) # Doses, 0-12hrs	13(12)	11(10)	11(10)	5(5)	4(4)
Mean 12h Plasma Concentration	NA	NA	NA	50	39
Mean (med) # Doses, 0-24hrs	23(22)	21(20)	20(18)	NA	7(7)
Mean 24h Plasma Concentration	106	84	71	NA	44
Mean (med) # Doses, 0-48hrs	34(34)	34(32)	30(26)	NA	NA
Mean 48h Plasma Concentration	97	85	69	NA	NA

Baseline Demographics and Patient Disposition

- A total of 429 patients (152 TKA, 163 THA and 114 ABD) were randomized to SST 15 mcg; average age was 63 years, 64% were female
- A total of 147 patients (40 BUN and 109 ABD) were randomized to SST 30 mcg; average age was 42 years, 63% were female
- Baseline pain intensity scores were lowest among hernia patients (5.0/10) and highest among abdominoplasty patients (6.5/10).

Efficacy

- Each of the four pivotal studies with SST met its primary endpoint of statistically superior pain reduction compared to placebo ($p<0.001$ for studies IAP310, IAP311, SAP301 and $P=0.003$ for SAP202)
- Dosing results indicate that patients undergoing orthopedic procedures (TKA and BUN) required more doses of SST to manage their post-operative pain than did patients undergoing ABD surgery
- Sufentanil plasma concentrations at all time points were higher among orthopedic vs abdominal surgery patients, with the SST 15 mcg PCA cohort titrating to comfort between 70-100 pg/mL vs 40-50 pg/mL for SST 30 mcg patients that had shorter lengths of stay.

Safety

- **Table 2** includes AEs by surgery-type; nausea was the most common.

Table 2. Common Adverse Events by Surgery Type

Adverse Event %	IAP311 SST 15mcg		IAP310 SST 15mcg	SAP202 SST 30mcg	SAP301 SST 30 mcg
	TKA N=152	THA N=163	ABD N=114	BUN N=40	ABD N=109
Nausea	56	50	31	63	36
Pyrexia	18	20	15	0	0
Anemia	11	16	2	0	0
Vomiting	11	15	9	28	9
Headache	6	15	4	8	20
Pruritus	7	9	9	10	3
O_2 Sat Decr.	5	11	6	0	1
Dizziness	3	9	9	20	6

Conclusion

- **Sublingual sufentanil was effective for the treatment of post-operative pain across a variety of short and long-stay surgeries**
- **Patients undergoing painful orthopaedic procedures such as TKA and bunionectomy may require more frequent dosing**
- **Nausea was the most commonly reported AE across all studies**

References

1. Jakobsson J. Pain Management in Ambulatory Surgery-A Review. *Pharmaceuticals 2014;7:850-865*
2. Meissner, W. et al. Improving the management of post-operative acute pain: priorities for change, Current; Medical Research and Opinion, 2015; 31:11, 2131-2143
3. Awad and Chung, F. **Factors affecting recovery and discharge following ambulatory surgery. Canad J Anesthesia 2006; 858-872.**
4. Rathmell JP, et al. *Regional Anesthesia and Pain Medicine*. 2006;31(4 Suppl 1):1–42 Mather LE. Opioids: a pharmacologist's delight! *Clin Exp Pharmacol Physiol* 1995; 22:833-6.
5. Pergolizzi JV, Jr., et al. *Pain Manag Nurs*. 2014; 15(1):380-90
6. **Lovich-Sapola et al. Post-operative Pain Control Surg Clin North America; 2015;95: 301-318**
7. Mather LE. Opioids: a pharmacologist's delight! *Clin Exp Pharmacol Physiol* 1995; 22:833-6.
8. Lötsch J. Pharmacokinetic-pharmacodynamic modeling of opioids. *J Pain Symptom Manage* 2005; 29(5):S90-S103.
9. Scott JC, Cooke JE, Stanski DR. Electroencephalographic quantitation of opioid effect: comparative pharmacodynamics of fentanyl and sufentanil. *Anesthesiol* 1991; 74:34–42.

Poster presentation at Euroanaesthesia 2017, 03 June – 05 June; Geneva, Switzerland