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TITLE:
Optimizing a Drug for PCA Delivery: The Clinical Importance of $CST_{½}$ and $t_{½ke0}$

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AFFIRMATIONS:

Affirmations (Complete):
*: I agree to the above statements
*: Yes
*: No animal subjects were involved in the research
*: Yes, I have IRB or IACUC approval

SESSION CATEGORY:
7.3 DRUG DISPOSITION - Human Pharmacodynamics

QUESTIONNAIRE:

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Please select: No, do not consider my abstract for the ANESTHESIOLOGY Journal Symposium
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ABSTRACT:
INTRODUCTION
The ideal opioid for patient-controlled analgesia (PCA) administration should have a rapid onset, sufficient duration to avoid frequent redosing, rapid equilibration with the CNS, limited efflux transporter effects, no active metabolites, limited effect of hepatic or renal impairment on clearance, and tolerable side effects. Since opioids function at CNS receptors and not in plasma, traditional venous pharmacokinetic (PK) parameters can be misleading in determining opioid effects. The $t_{½ke0}$ (plasma/CNS equilibration half-life) is better than standard PK parameters in predicting onset of action. Additionally, the $CST_{½}$ (context sensitive half-time or time required from C_{max} to 50% of C_{max}) is a more appropriate reflection of duration/offset of action than the elimination half-life. Sufentanil has a high therapeutic index with minimal respiratory depressive effects relative to its analgesic effect, has no active metabolites, and minimal PK differences based on age or organ function. While these attributes could be ideal in a post-operative opioid analgesic, its rapid redistribution from plasma following IV administration ($CST_{½}$ of 8.4 min) results

in a short duration of action requiring excessive redosing. The Sufentanil NanoTab® PCA System (system) was designed to optimize drug delivery in the acute pain setting. We seek to compare sufentanil PK characteristics with different routes of delivery with morphine.

METHODS

The Sufentanil NanoTab® PCA System allows patients to self-administer sufentanil 15 mcg sublingual (SL) doses with a 20-minute lockout via a hand-held device. Using results from a single-dose crossover design (IV, PO, SL, buccal [BU] sufentanil 15 mcg) PK study[i] and a randomized repeat dose clinical efficacy, safety and PK study of SL sufentanil vs. IV PCA morphine,[ii] a comparison of PK and PD parameters of morphine PCA vs. SL sufentanil was made. A literature review of comparative values of opioid PK and PD was performed.

RESULTS

Compared to IV sufentanil, the slower absorption across the SL mucosa results in a $CST_{½}$ that was 18-fold longer (2.50 h vs. 0.14 h), thereby avoiding a limitation of IV sufentanil PCA delivery while producing a $CST_{½}$ that is longer than currently used IV PCA opioids (Table 1). IV morphine has instantaneous venous C_{max} compared to SL sufentanil's C_{max} of 50 min yet the $t_{½ke0}$ of morphine is 168 min vs. 6.2 min for sufentanil, suggesting a slower onset of action. M6G has a $t_{½ke0}$ nearly twice as long as morphine, a concern for "dose-stacking" and delayed adverse events. These PK parameters of SL sufentanil may explain the better pain intensity and pain relief differences at 1, 2, and 4 hours ($p < 0.01$), a longer interdosing interval, and fewer oxygen desaturations ($p=0.028$) than IV PCA morphine in a recently conducted randomized, active comparator study in 359 patients after open abdominal or major orthopedic surgery who received either the System or IV PCA morphine 1 mg q6 min. Additionally, in this study, M6G (and M3G) plasma concentrations were significantly increased in the presence of renal impairment ($p < 0.001$).

CONCLUSION

Context sensitive half-time and effect-site equilibration time are properties that better describe the choice of opioids for PCA than the traditional venous PK parameters. The Sufentanil NanoTab PCA System was designed using these principles and may provide a viable alternative to traditional IV PCA analgesia.

[i] Data on file, AcelRx Pharmaceuticals, Study IAP102.

[ii] Data on file, AcelRx Pharmaceuticals, Study IAP309.

Table 1. PK Parameters with Different Routes of Administration of Sufentanil

	IV	SL	BU	PO
Bioavailability (%)	100	57	78	6
Cmax (pg/mL) mean	361.1	37.7	53.0	3.3
Tmax (h) median	0.07	0.83	0.85	1.11
$CST_{½}$ (h) median	0.14	2.50	2.28	2.00

IV = intravenous, SL = sublingual, BU = buccal, PO = oral

SUMMARY:

The context sensitive half-time ($CST_{½}$ or the time required from C_{max} to 50% of C_{max}) and effect-site equilibration time ($t_{½ke0}$) are properties that better describe the choice of opioids for PCA than the traditional venous PK parameters. The Sufentanil NanoTab PCA System, a novel preprogrammed hand-held device which delivers sublingual sufentanil 15 mcg with a 20 min lockout, was designed using these principles and may provide a viable alternative to traditional IV PCA analgesia. It is currently in Phase 3 development.

Status: Complete