

ANESTHESIA ABSTRACTS

PROVIDING THE CLINICAL ANESTHETIST WITH UP-TO-DATE RESOURCES FOR EVIDENCE BASED PRACTICE.



Table of Contents

EDITOR

Michael A. Fiedler, PhD, CRNA

CONTRIBUTING EDITORS

Mary A. Golinski, PhD, CRNA

Dennis Spence, PhD, CRNA

ASSISTANT EDITOR

Heather Whitten, MEd.

Pharmacology — Pain

- CE** Pharmacokinetic properties of a sufentanil sublingual tablet intended to treat acute pain3
- CE** Sufentanil sublingual tablet system for the management of postoperative pain following open abdominal surgery: a randomized, placebo-controlled study6

Pharmacology — Geriatric Anesthesia

- CE** Intraoperative ketamine for prevention of depressive symptoms after major surgery in older adults: an international, multicentre, double-blind, randomised clinical trial.....9

www.AnesthesiaAbstracts.com

A Publication of Lifelong Learning, LLC

© Copyright 2019

1 Pharmacology CE credit.*

None of the editors or contributors have any real or potential conflicts of interest to disclose.

 Indicates Continuing Education Credit is available for this abstract and comment during the CE approval period. Continuing Education Credit is available to individual subscribers on the Anesthesia Abstracts web site at www.AnesthesiaAbstracts.com.

New health information becomes available constantly. While we strive to provide accurate information, factual and typographical errors may occur. The authors, editors, publisher, and Lifelong Learning, LLC is/are not responsible for any errors or omissions in the information presented. We endeavor to provide accurate information helpful in your clinical practice. Remember, though, that there is a lot of information out there and we are only presenting some of it here. Also, the comments of contributors represent their personal views, colored by their knowledge, understanding, experience, and judgment which may differ from yours. Their comments are written without knowing details of the clinical situation in which you may apply the information. In the end, your clinical decisions should be based upon your best judgment for each specific patient situation. We do not accept responsibility for clinical decisions or outcomes.

* This program has been prior approved by the American Association of Nurse Anesthetists for 20 Class A CE credits; Code Number 1037484; **Expiration Date 03/31/2022.**

**CE PHARMACOKINETIC PROPERTIES OF A SUFENTANIL SUBLINGUAL TABLET
INTENDED TO TREAT ACUTE PAIN**

Anesthesiology 2018;128:943-52

DOI: 10.1097/ALN.0000000000002145

Fisher DM, Chang P, Wada DR, Dahan A, Palmer PP

Abstract

Purpose The purpose of this study was to describe the pharmacokinetic properties of 15 to 30 µg sublingual sufentanil tablets.

Background AcelRX Pharmaceuticals has developed two sublingual sufentanil delivery systems: Dsuvia, which is available in the USA, and Zalviso, which is available in Europe. Dsuvia consists of a single-dose applicator prefilled with a small 3 mm 30 µg sufentanil tablet. Zalviso is a patient-controlled analgesia system with a 20 minute lockout. Controlled by thumb-print, it delivers a 3 mm 15 µg sublingual tablet. Both are administered under the tongue which enables transmucosal absorption of sufentanil. In this report, the investigators described the pharmacokinetic results from 11 clinical studies on the two drug delivery systems; 4 volunteer studies and 7 postsurgical patient studies.

Methodology Blood was sampled from 122 healthy volunteers and 944 postsurgical patients enrolled in 11 different studies; 4 volunteer studies and 7 postsurgical studies. The investigators analyzed:

- maximum plasma concentration
- time to maximum plasma concentration
- terminal elimination half-life
- plasma half-time
- bioavailability %

They examined the effect of weight, age, renal impairment, and hepatic impairment on the pharmacokinetic results and evaluated the impact of inhibition of cytochrome P450 3A4 on the enzymatic degradation of sufentanil. Dosing and sampling regimens are listed in Table 1. Statistical analysis was appropriate.

Result The maximum plasma concentration was markedly less with 30 µg sublingual sufentanil than 30 µg intravenous sufentanil (64 pg/mL vs. 1,074 pg/mL). The time to maximum plasma concentration following a sublingual dose was 1 to 1.2 hours, with a range of 0.5 to 2 hours. After a single sublingual dose of sufentanil, the plasma half-time was 2.5 ± 0.9 hours. This plasma half-time was almost identical even after 12 hourly doses of 30 µg sublingual sufentanil (2.5 ± 0.7). Repeated administration of 30 µg sublingual sufentanil at 1 hour intervals did, however, result in a 2 to 3 times higher peak plasma concentration compared to a single dose.

The mean terminal elimination half-life of sublingual sufentanil ranged from 13 to 16 hours. **[Editor's**

Note: other studies have shown the elimination half-life of IV sufentanil to be about 2.5 hours.]

Bioavailability ranged from 52-58%.

Table 1. Studies in this Report

Study Population	n	Number of Doses x μg or Dose in μg	Minutes between doses
Volunteers	40	1 x 15 μg 40 x 15 μg	20
Volunteers	24	1 x 15 μg (IV) 1 x 15 μg (sublingual) 1 x 15 μg (oral)	- - -
Volunteers	19	2 x 15 μg *	4,320
Volunteers	39	1 x 30 μg (IV) 2 x 15 μg 1 x 30 μg 12 x 30 μg	- 20 - 60
Knee replacement	69	5 μg , 10 μg , 15 μg	20
Open abdominal/orthopedic	162	15 μg	20
Open abdominal	98	15 μg	20
Knee or hip replacement	288	15 μg	20
Bunionectomy	80	20 μg , 30 μg	60
Open or laparoscopic abdominal	107	30 μg	60
Mixed surgical	140	30 μg	60

Note: * Hepatic cytochrome P450 inhibition prior to second sufentanil dose and continued for three days.

Swallowing the tablet resulted in less systemic absorption compared to sublingual administration, with a bioavailability of only 9% rather than the 52% following sublingual absorption. Hepatic cytochrome P450 inhibition increased the plasma concentration by 19% ($P = 0.047$) and increased the total area under the curve by 77% ($P < 0.001$). Hepatic cytochrome P450 inhibition likewise increased the terminal elimination half-time by 50%, but the plasma half-time did not increase significantly.

For every 1 Kg increase in body weight above 80 Kg, sufentanil clearance increased 0.5%. Clearance

decreased 1.6% per year for patients over 56 years old. Hepatic cytochrome P450 inhibition decreased clearance by 37%. Bioavailability decreased 33% with repeated dosing. Hepatic and renal impairment did not impact clearance.

Conclusion Administration of a 30 μg sublingual sufentanil tablet had a peak onset of approximately 1 hour and takes about 3 hours for the plasma concentration to drop below the analgesic threshold. Older and lighter patients and administration of a cytochrome P450 inhibitor may decrease clearance.

Comment

This week I had the opportunity to have Dr. Palmer, the co-founder of AcelRX Pharmaceuticals, speak to my anesthesia department on Dsuvia. Therefore, I wanted to learn more about this drug. What this pharmacokinetic report demonstrated was that the onset is about 0.5 to 1.25 hours with a duration of action around 3 hours. The recommended dose is 30 µg sublingually as needed for acute pain with a minimum of 1-hour between doses and no more than 12 tablets in 24 hours.¹ In Europe, Zalviso (15-µg patient administered sublingual sufentanil) is available and patients can self-administer 15 µg every 20 minutes.²

The rate of adverse reactions occurring in 2% or more of postsurgical patients (sublingual sufentanil vs. placebo) was: nausea was 29% vs. 22%; headache 12% vs. 11%; vomiting 6% vs. 4%; dizziness 6% vs. 4%; and hypotension 5% vs. 4%. Respiratory depression occurred in less than 2% of patients.¹

I found sublingual sufentanil to be a novel drug that may have value in an emergency room or battlefield setting because it may be used in patients without an intravenous line. It could potentially be a cheaper alternative to patient-controlled analgesia with morphine or hydromorphone if you factor in the equipment and nursing labor costs. Sufentanil does not have active metabolites and does not build up in the blood stream compared to the transmucosal fentanyl lollipop, which is approved only in cancer patients that are non-opioid tolerant. Only time will tell if it will become widely available in the United States.

Dennis Spence, PhD, CRNA

The original article summarized here is available free full text at the following url:
<http://anesthesiology.pubs.asahq.org/article.aspx?articleid=2674298>

1. Dsuvia package insert: http://www.dsuvia.com/pdf/PL-6410_FINAL_110218.pdf
2. Zalviso package insert: <http://zalviso.eu/hcp/about-zalviso/prescribing-information>

The views expressed in this article are those of the author and do not reflect official policy or position of the Department of the Navy, the Department of Defense, the Uniformed Services University of the Health Sciences, or the United States Government.

CE **SUFENTANIL SUBLINGUAL TABLET SYSTEM FOR THE MANAGEMENT OF POSTOPERATIVE PAIN FOLLOWING OPEN ABDOMINAL SURGERY: A RANDOMIZED, PLACEBO-CONTROLLED STUDY**

Reg Anesth Pain 2015;40:22-30

DOI: 10.1097/AAP.0000000000000152

Ringold FG, Minkowitz HS, Gan TJ, Aqua KA, Chiang Y, Evashenk MA, Palmer PP

Abstract

Purpose The purpose of this study was to evaluate the efficacy and safety of the sufentanil sublingual tablet system (SSTS) to manage postoperative pain after open abdominal surgery.

Background Patient-controlled analgesia (PCA) pumps are used to deliver opioids to postoperative patients for pain relief after surgery. While they result in lower pain scores and higher satisfaction scores compared to other methods of pain relief, PCA does require setup time and the patient is tethered to an IV pole. IV poles may hinder mobility and there is the risk of programming errors and higher nursing costs associated with PCA setup and management.

The sufentanil sublingual system (Zalviso) has been developed by AxelRX Pharmaceuticals and is currently under review by the Food and Drug Administration. The SSTS system is a non-invasive, patient-activated, bedside system with a radio frequency identification thumb tag that delivers a 3 mm 15 µg sublingual sufentanil tablet to the patient on an as needed basis without nursing support. (It has a 20 minute lockout.) The 15 µg sufentanil tablet is equivalent to 3 to 4 mg of morphine. The bioavailability is 60%, and delivery of a sublingual

sufentanil tablet every 20 minutes is approximately equivalent to 1 mg of morphine delivered every 6 minutes via a PCA. The sufentanil sublingual tablet has an onset of 0.5 to 1 hour and an approximate duration of action of 3 hours. Highly lipophilic drugs like sufentanil are absorbed rapidly from sublingual tissues and undergo less first-pass metabolism than oral swallowed medications, thus increasing the bioavailability.

The investigators of this phase 3 study sought to examine the efficacy and safety of the sufentanil sublingual system compared to a placebo sublingual system in patients undergoing open abdominal surgery.

Methodology This was a prospective, randomized, double-blind, multi-center study of 178 ASA I to III adult patients undergoing open abdominal surgery. Exclusion criteria included opioid tolerance, chronic pain, diagnosed sleep apnea, total laparoscopic surgery, oxygen dependence; or requirement for perioperative gabapentinoids, steroids, or anti-inflammatory drugs; or need for regional anesthesia or local wound infiltration. Patients were randomized to receive either sufentanil sublingual 15 µg or a placebo delivered via the same SSTS system. Pain was

evaluated with an 11-point numeric rating scale. Breakthrough pain was managed with 2 mg IV morphine only 10 minutes after SSTS drug delivery and no more than once per hour. Patients who required additional analgesia were discontinued from the study. Patients who could not maintain an oxygen saturation of 95% or more and a respiratory rate of 8 or more were not allowed access to the study drug and were withdrawn from the study.

Pain intensity and pain relief scores were measured at 15, 30, 45, and 60 minutes, every 1 hour for 12 hours, then every 2 hours for 48 hours, and every 4 hours from 52 to 72 hours. Pain intensity and pain relief scores were obtained just prior to IV morphine administration.

The primary outcome was time-weighted summed pain intensity difference over 48 hours (SPID48). This outcome measure is required by the FDA to demonstrate efficacy. A higher score reflects better pain relief. Secondary outcomes included summed pain intensity difference (SPID) and pain intensity difference (PID) scores at each time point; proportion of patients discontinuing the study or requiring additional analgesics for breakthrough pain, and rate of adverse events. Statistical analysis was appropriate.

Result There were 119 subjects randomized to the SSTS group and 59 to the placebo group ($N = 178$). There were 172 subjects who received either sublingual sufentanil or placebo, with 61% completing the 48-hour study period and 23% completing the 72-hour period. No significant

differences were seen in most demographic and clinical characteristics. A higher percentage of patients in the SSTS group were <65 years old (80% vs. 61%, $P = 0.016$) and a lower percent were female (70% vs. 84%, $P = 0.042$). Over half of all patients enrolled had a BMI <30 Kg/m². A lower percentage of patients in the placebo group completed the study at 48-hours than patients in the SSTS group (32% vs. 17%, $P = 0.035$).

Fewer patients in the SSTS group required IV morphine for breakthrough pain (33% vs. 67%, $P < 0.001$). Patients in the placebo group withdrew from the study for inadequate pain relief earlier ($P = 0.022$) and needed rescue IV morphine sooner than those who received sublingual sufentanil ($P < 0.001$).

The SPID48 was significantly higher in the SSTS group than the placebo group (105 vs. 56, $P = 0.001$). (Higher scores reflect better pain relief) The SPID, PID, and total pain relief scores throughout the study period were significantly better in the SSTS group ($P < 0.05$). The mean total number of IV morphine doses was significantly lower at 24 hours (1.3 vs. 2.3, $P < 0.001$), 48 hours (1.8 vs. 3.8, $P = 0.002$), and 72 hours (1.9 vs. 4, $P = 0.003$) in the SSTS group compared to the placebo group.

Overall, 24% of subjects in the SSTS group and 26% in the placebo group experienced an adverse event ($P = NS$). The most common adverse events in both groups was nausea (SSTS 14% vs. placebo 22%), followed by pruritus (SSTS 4.4% vs. placebo 0%), vomiting (3.5% both groups), oxygen saturation

decreased (SSTS 3.5% vs. placebo 1.7%), and dizziness (SSTS 2.6% vs. placebo 1.7%). Overall satisfaction with the sublingual tablet delivery system was very high, with 96% of the SSTS group and 92% of the placebo group being satisfied with the device (P = NS).

Conclusion The sufentanil sublingual tablet system (SSTS) was safe and more effective than placebo for providing postoperative analgesia after open abdominal surgery.

Comment

The SSTS is a novel delivery system which has been used for a number of years in Europe. The results of this study demonstrated the SSTS is an effective and safe alternative to as needed IV morphine for pain relief after open abdominal surgery in patients who are NOT on an enhanced recovery after anesthesia protocol (ERAS) or have received regional anesthesia or wound infiltration with local anesthetics. These patient populations were excluded so that investigators could minimize confounding effects of other drugs and analgesic regimens on postoperative pain.

Whether or not the same results would be seen in an active comparison group that received a PCA of morphine or hydromorphone with or without an ERAS protocol is unknown and requires more study. In reality, this would be more realistic in clinical practice. Unfortunately, even four years after publication of this study, the SSTS drug delivery system (Zalviso)¹ is still in clinical trials and is not available in the United States. If the device ever gets

FDA approval, I imagine many hospital administrators would have to be convinced that the savings achieved through reduced nursing/pharmacy labor costs for traditional PCA delivery systems were greater than the cost of the SSTS before they brought it on formulary.

Dennis Spence, PhD, CRNA

Notes: SSTS is a novel sufentanil drug system (Zalviso)¹ that is currently approved for use in Europe and is not yet approved for use in the United States. However, Dsuvia (30 µg sublingual sufentanil delivery system)² is available in the USA.

1. Zalviso package insert: <http://zalviso.eu/hcp/about-zalviso/prescribing-information>
2. Dsuvia package insert: http://www.dsuvia.com/pdf/PL-6410_FINAL_110218.pdf

The original article summarized here is available free full text at the following url:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4272222/>

The views expressed in this article are those of the author and do not reflect official policy or position of the Department of the Navy, the Department of Defense, the Uniformed Services University of the Health Sciences, or the United States Government.

CE **INTRAOPERATIVE KETAMINE FOR PREVENTION OF DEPRESSIVE SYMPTOMS AFTER MAJOR SURGERY IN OLDER ADULTS: AN INTERNATIONAL, MULTICENTRE, DOUBLE-BLIND, RANDOMISED CLINICAL TRIAL**

Br J Anaesth 2018;121:1075-83

DOI: 10.1016/j.bja.2018.03.030

Mashour GA, Abdallah AB, Pryor KO, El-Gabalawy R, Visides PE, Jacobsohn E, Lenze E, Maybrier HR, Veselis RA, Avidan MS, and on behalf of the PODCAST Research Group

Abstract

Purpose The purpose of this study was to compare the effects of 0.5 mg/Kg ketamine, 1 mg/Kg ketamine, or placebo after induction on postoperative depression symptoms in adults over 60 years old undergoing major surgery.

Background A meta-analysis and several randomized controlled trials have found that subanesthetic ketamine is efficacious as a rapid-acting antidepressant in patients with major depression. It is unclear how ketamine works to reduce depression. Preclinical studies suggest the N-methyl-D-aspartate (NMDA) antagonist effects may reverse synaptic dysfunction induced by stress through suppression of burst firing in the lateral habenula and this may account for the rapid antidepressant effects. There are conflicting reports in postoperative populations that subanesthetic ketamine may reduce depressive symptoms. One study in healthy adults undergoing orthopedic surgery had reduced symptoms. However, a study on cesarean delivery patients found no effect on postpartum depression. The investigators of the Prevention of Delirium and Complications Associated with Surgical Treatments (PODCAST) study group conducted a prespecified analysis to examine the

effects of two doses of ketamine and placebo on postoperative depression in adult patients over the age of 60 years undergoing major open cardiac and non-cardiac surgery.

Methodology The PODCAST trial was a prospective, randomized, clinical trial at 10 sites in the USA, Canada, South Korea, and India. Patients >60 years old scheduled for major open cardiac or non-cardiac surgery were randomized in blocks of 15 in a 1:1:1 ratio to receive either ketamine 0.5 mg/Kg (Lo-Ketamine) or 1 mg/Kg (Hi-Ketamine) or placebo after induction but prior to skin incision. Ketamine 0.5 mg/Kg, administered over 40 minutes, is the usual antidepressant dose in the awake patient. Patients were excluded if they had a history of substance abuse, were taking anti-psychotic medications, or had a weight < 50 Kg or > 200 Kg. This was a pragmatic trial so decisions about anesthetic management were left to the discretion of the anesthesia team. Subjects, anesthesia providers, and data collectors were blinded to group assignment.

The primary outcome was postoperative depressive symptoms as measured by the Patient Health Questionnaire 8 (PHQ-8; 0-24 scale). Subjects with a

score of 10 or higher were considered to have symptoms suggestive of depression. The PHQ-8 was administered by trained data collectors at baseline and on postoperative day (POD) 3, and POD 30. Investigators collected demographic data and information on functional independence, comorbidity, and medical and surgical characteristics on enrolled subjects. Statistical analysis and sample size calculations were appropriate.

Result Data was analyzed from N = 670 subjects. No significant differences were found in demographic, comorbidities, and medical or surgical characteristics between the groups. On POD 3 n = 156 in the placebo group, n = 180 in the Lo-Ketamine group, and n = 169 in the Hi-Ketamine group completed the PHQ-8. On POD 30 n = 137 in the placebo group, n = 130 in the Low-Ketamine group, and n = 128 completed the PHQ-8.

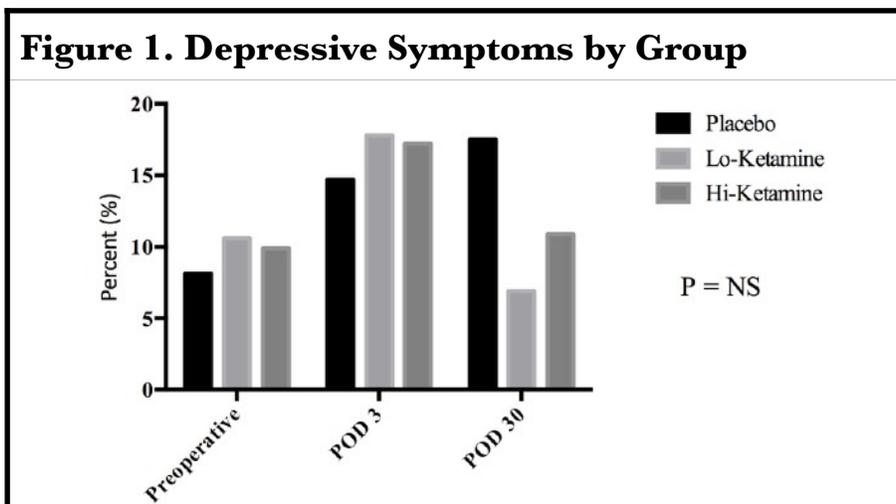
No significant differences were found in the incidence of depressive symptoms between the three groups or in the severity of postoperative depressive symptoms at POD 3 or POD 30 (Table 1). Overall, 9.6% of subjects at baseline, 16.6% on POD 3 and 12% on

POD 30 had symptoms suggestive of depression. Patients with a history of depression were more likely to have symptoms suggestive of depression postoperatively. However, approximately half the subjects with postoperative depressive symptoms on POD 3 (49%) and POD 30 (51%) had no prior history of depression. A history of depression was predictive of worsening depression postoperatively.

Conclusion Ketamine 0.5-1 mg/Kg, administered intraoperatively did not prevent depression or depressive symptoms after major open cardiac or non-cardiac surgery in adults >60 years old.

Comment

I thought this was a novel study that examined an outcome that most anesthesia providers would not think of - postoperative depression. What the results tell us is that postoperative new onset or worsening depressive symptoms occur in upwards of 17% of older patients undergoing major surgery. This is not surprising since major surgery is a significant life stressor.



What these results demonstrated was that subanesthetic ketamine does not decrease depressive symptoms like it does in awake, non-anesthetized patients. A meta-analysis found that 21-26% of patients with major depressive disorder had remission of symptoms at 7 days after subanesthetic ketamine administration.¹ The authors of this report speculated that prolonged general anesthesia may create unfavorable neural conditions at the cortical and subcortical levels of the brain which prevent the anti-depressant effects of ketamine.

As a side note, the original PODCAST study found that subanesthetic ketamine did not decrease the incidence of postoperative delirium in older adults, but that hallucinations and nightmares were significantly higher at the 1 mg/Kg ketamine dose.² Therefore, anesthesia providers may want to consider a lower dose of ketamine in older adults.

Dennis Spence, PhD, CRNA

1. Han Y, Chen J, Zou D, et al. Efficacy of ketamine in the rapid treatment of major depressive disorder: a meta-analysis of randomized, double-blind, placebo-controlled studies. *Neuropsychiatr Dis Treat* 2016;12:2859-67.

2. Avidan MS, Maybrier HR, Abdallah AB, et al. Intraoperative ketamine for prevention of postoperative delirium or pain after major surgery in older adults: an international, multicentre, double-blind, randomised clinical trial. *Lancet* 2017;390:267e75.

The views expressed in this article are those of the author and do not reflect official policy or position of the Department of the Navy, the Department of Defense, the Uniformed Services University of the Health Sciences, or the United States Government.