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Sublingual Absorption of Naloxone in a Large Clinical Population

Daniel M. Strickland[1]* and Jana K. Burson[2]

[1]WJ Medical Associates, West Jefferson, NC (DMS), US
[2]Half Moon Medical Associates, Cornelius, NC (JKB), US

Abstract

Background and Objectives: The combination of buprenorphine and naloxone (combo product) is a medication that is administered sublingually to treat opioid use disorder as part of medication assisted treatment. The naloxone component is believed to deter inappropriate use of the medication. True allergies to naloxone are infrequent, but many patients experience severe, unpleasant side effects that they associate with the combo product but not with the formulation containing buprenorphine alone (mono product). It is commonly contended that naloxone is poorly absorbed sublingually, so we sought to test the validity of that belief.

Methods: Using a sensitive LC-MS assay, we quantified the concentration of naloxone in the urine of 61 patients (Total specimens=686) prescribed the combo product. Because this study was retrospective it was neither intended nor possible to compare adverse side effects between patients prescribed mono versus combo products.

Results: We found that 92.7% of the patients prescribed the combo product had significant quantifiable concentrations of naloxone in their urine drug screens.

Conclusions and Scientific Significance: Contrary to popular belief, naloxone is absorbed sublingually. Such absorption may account for some of the unpleasant side effects experienced by patients treated with the combo products, but it was not possible to compare or quantify side effects in this retrospective study. We feel it is important that clinicians be aware of the possibility of significant sublingual absorption of naloxone when choosing therapeutic modalities for their patients.

Keywords: Buperenorphine; Naloxone; Opioid; Addiction; Sublingual; Drug screen

Introduction

Buprenorphine, alone or combination with naloxone, has been available since 2002 [1,2] to medical practitioners for the Medical Assisted Treatment (MAT) of opioid use disorder (ICD-10-CM: F11). Buprenorphine is considered a "partial" mu receptor agonist, which means it has binding affinity (in this case high) for the receptor, but the biological activity (effect) is less than that of "complete" agonists, such as morphine. Because of the high binding affinity, it will displace full agonists from the receptor, and thus can act as a partial antagonist [3]. Naloxone is a full antagonist at the mu receptor and was included in a formulation of 4: 1 buprenorphine: naloxone, in this paper referred to as a "combo" formulation. Buprenorphine alone formulations are commonly referred to as "mono" products.

Combo products were approved in the belief that they are less subject to abuse by either intranasal (snorting) or intravenous (IV) routes. Mendelson [3] states that "Buprenorphine and naloxone dose combinations should diminish the parenteral abuse liability of buprenorphine in opiate-dependent individuals by precipitating opiate withdrawal when taken parenterally, but not sublingually." Orman [4] and others have stated that the inclusion of naloxone in the combo product should prevent the parenteral use of the medicine but allow its sublingual dosing.

These conclusions appear to be based on the (common) belief that sublingual absorption of naloxone is poor compared to that of buprenorphine. "Misuse liability is limited by the presence of naloxone, which is not well-absorbed sublingually, yielding a clinical effect virtually identical to the mono product" [1]. However, the literature on the sublingual absorption of naloxone is confusing and sometimes contradictory. Chiang [5] concluded that, "… naloxone is poorly absorbed sublingually relative to buprenorphine" and "The addition of naloxone does not affect the efficacy of buprenorphine…" The National Alliance of Advocates for Buprenorphine Treatment also claim [6] that, "Taken sublingually, as directed, naloxone is clinically insignificant and has virtually no effect." Harris [7] using 16 mg sublingual tablets, reported that "So many naloxone concentrations were below the level of detection that comparisons between dose conditions could not be made. Only 5 of 8 subjects had more than 2 plasma concentrations of naloxone above the detection at the highest dose (16 mg: 4 mg)".

In apparent contradiction, however, the package insert for Suboxone [8] states that, "...Plasma levels of buprenorphine increased with the sublingual dose of SUBUTEX and SUBOXONE, and plasma levels of naloxone increased with the sublingual dose of SUBOXONE (Table 1). {NB: no naloxone concentrations are shown in that table.}

Supporting that statement was Heikman [9] who reported significant sublingual absorption of naloxone (as quantified by naloxone in urine) during different phases of treatment. The authors even concluded

***Corresponding author:** Daniel M. Strickland, MD PO Box 70, West Jefferson, NC 28640, US, Tel: (828) 394-9801; Fax: 844-542-5963; E-mail: strickd42@gmail.com

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Table 1: Urinary naloxone concentrations in patients taking buprenorphine/ naloxone products (combo products).

Active patients in database, N=561		Specimens with >1 ng/mL naloxone	Specimens with >30 ng/mL naloxone
Patients on mono product	499 (88.9%)	Patients using combo product at intake are excluded from count	
Patients on combo product (Total Specimens=686)	62 (11.1%)	671 (97.8%)	636 (92.7%)

that undetectable naloxone in a urine sample was indication of non-compliance with the prescribed combo product.

A Consensus Panel reporting in TIP 40 [10] from as recent as 2004, recommended the use of combo-therapy for all patients except pregnant women: "Because of the potential for naloxone to precipitate withdrawal in both mother and fetus, pregnant women who are deemed to be appropriate candidates for buprenorphine treatment should be inducted and maintained on buprenorphine monotherapy". It is notable that this publication is no longer available on the SMAHSA website [https://store.samhsa.gov].

Even a publication as recent as TIP 63 [11] states, "Although there are some publications with small sample sizes that indicate that the combination product appears to be safe in pregnancy, the safety data are insufficient at this time to recommend its use."

Preston [12], in a confusing combination of data and conclusions, administered up to 4 mg naloxone sublingually to opioid dependent patients and noted "That precipitated withdrawal was observed in five of nine subjects validates the biological delivery of naloxone by the sublingual route …"

Berkowitz [13] concluded that "Based on animal studies, the rapid onset of the narcotic antagonist action of naloxone can be related to its rapid entry into the brain, whereas its potency stems in part from its high lipid solubility which allows a high brain concentration to be achieved." Therefore, due to preferential distribution to brain tissue, a relatively low level of naloxone in the plasma may cause as much as a ten-fold higher concentration in central nervous system tissue.

Weinberg [14] stated, "… because sublingual naloxone absorption is not negligible (25%) the antagonist effects may make such a preparation undesirable." Simojoki [15], in a retrospective study of patients (involuntarily) switched from the mono product to the combo product, reported that 50% experienced side effects, predominantly gastrointestinal, fatigue, sweating, and headache, although the authors did not specifically correlate retention with these complaints. An FDA Advisory Committee [16] also offered the cryptic (and semantically strange) conclusion that, "… the delivery systems (sic) can be used by laypeople intranasally or sublingually is (sic) likely to play a critical role in reducing the number of deaths due to opioid overdose."

Opioid abusers, who obtain mono or combo products illicitly ("off the street") frequently report short term discomfort from SL use of the combo products (versus the mono product), although few are able to document intolerance. True IgE mediated reactions such as hives, oropharyngeal swelling, or respiratory distress are apparently uncommon, but troublesome side effects (pseudo-allergies) are frequently reported. The major side effects in our experience are headaches, nausea, diaphoresis, agitation, and general dysphoria, which have the effect of placing a premium on the "street" value of the mono product.

Increasingly, many states are placing legislative/regulatory limits on the prescribing (and even dispensing) of buprenorphine products, by imposing restrictions on the formulation and maximum dose permitted (TN, KY, WV) or the formulation permitted for take-home dispensing in Opioid Treatment Programs (VA) [17]. Pregnant patients and patients with documented intolerance are excepted, but that leaves the vast bulk of potential patients restricted to the combo product, regardless of side effects.

Such intolerance may limit continuation in MAT when combo-therapy is dictated by regulatory agencies. The purpose of this report is to demonstrate that sublingual absorption of naloxone is appreciable (not negligible) and may account for some of the intolerance reported by many patients in MAT that limit their ability to tolerate the combo product.

Methods

The purpose of our study was to further evaluate the sublingual absorption of naloxone from combo tablets, and to validate the findings of Heikman [9] in a large MAT clinic in which one author (DMS) is an independent provider. Because this was a retrospective study it was neither possible, nor our intention, to compare side effects experienced by patients administered mono products versus combo products. Indeed, the vast majority of our patients entered the program having obtained buprenorphine products illicitly, and most were prospectively aware of which product they could tolerate.

Our clinic has been treating opioid addicts for approximately 3 years, in a practice sometimes referred as an OBOT (Outpatient Based Opioid Treatment) program. Such programs/providers have met certain statutory requirements and are permitted to use Schedule III, IV, and V controlled substances for the treatment of opioid addiction [2]. Methadone (a Schedule II opioid) can only be used to treat addiction in a dispensing program called an OTP (Opioid Treatment Program), although buprenorphine can be dispensed in such programs without a DATA 2000 waiver.

We perform drug screening on every patient, at every visit, with a Point of Care test, often called a "dip" or a "cup" test. Every specimen is also sent to an external reference toxicology laboratory for "definitive" testing. Initially, the reference lab ran a panel that did not include naloxone testing. In the fall of 2016 our panel was expanded to provide quantitative reporting of analytes, including naloxone.

All urine specimens were obtained from patients as part of our usual and customary medical practice. No specimens were obtained specifically or solely because of this study analysis. To the contrary, the study was stimulated by the surprising finding of significant concentrations of naloxone in the panels reported by our reference lab.

Vital signs are obtained at every visit, to include temperature, respiratory rate, and blood pressure. During blood pressure measurements, the medical assistant checks for fresh needle marks in the antecubital fossa. Of course, recent opioid injections would be detected on both POC and outside testing, but after achieving an adequate blocking dose of buprenorphine we find that the use of IV opioids in our clinic population is virtually nil.

Our Electronic Health Record (EHR) is provided by Kareo, Inc. (https://www.kareo.com/ehr). It provides a clinical reporting tool that allows various search terms to be entered. We searched our active patient database through 31 Dec 2017. This paper reports on the results of that analysis, using the following search criteria:

1. Total Patients
2. Patients on mono product
3. Patients on combo product (buprenorphine:naloxone, OR Suboxone, OR Zubsolv, OR Bunavail)
4. Naloxone Result (ng/mL): <1
5. Naloxone Result (ng/mL): =OR>1
6. Naloxone Result (ng/mL): >30

Suboxone is marketed by Indivior Inc., North Chesterfield, VA, USA Zubsolv is marketed by Orexo US, Inc., Morristown, NJ, USA Bunavail is marketed by BioDelivery Sciences International, Inc., Raleigh, NC, USA

The urinary naloxone assays were performed by American Institute of Toxicology (a HealthTrackRx company, Denton, TX) *via* UPLC-MS/MS using an Acquity UPLC chromatography unit coupled with a XEVO TQD triple quadrupole mass spectrometer (both from Waters Corp, Milford, MA, USA). The mass spectrometer was equipped with an electrospray ionization source and operated in positive ionization mode. Separations were carried out using (A) 0.1% formic acid and 10 mM ammonium formate in ultrapure (18.2 MΩ) water (Thermo Scientific, Barnstead E-pure Ultrapure Water Purification System, Waltham, MA) and (B) 0.1% formic acid in LCMS grade acetonitrile (Fisher Scientific, Waltham, MA) under linear gradient conditions (A:B 95:5 to 40:60, over 7 min; flow rate 0.5 mL/min). Multiple reaction monitoring was used to detect two transitions of naloxone: m/z 328 > m/z 310 and m/z 328 > m/z 212. Limit of detection for naloxone was validated at 2 ng/mL, with a clinical reporting cutoff at 30 ng/mL and a maximum reporting limit of 5000 ng/mL. Quantitative and qualitative ion transitions were analyzed, validated and reported based on retention time (0.03 min tolerance) with respect to QC and internal standards, calculated concentration (area under peak curve), peak morphology, and quantitative to qualitative ion peak alignment criteria.

The method measures total naloxone by pretreating sample aliquots with beta-glucuronidase (in an acidic [~pH 4.5] buffer) to cleave the glucuronide-naloxone conjugates produced *via* hepatic metabolism. As dilution indicators, specific gravity (1.002 to 1.035), creatinine concentration, and pH were quantified.

Result

We queried the EHR database of all active patients as reported in Table 1. (NB: The EHR would not permit the mass searching of inactive patients.) Results were tabulated to confirm that all active patients were accounted for in the totals. We did not quantify the number of intake (initial) urine specimens with detectable naloxone levels, but such a finding was not uncommon. In fact, most of our new patients admitted to obtaining buprenorphine products "off the street" and their experiences helped persuade them to seek treatment in our clinic.

The naloxone concentration of >30 ng/mL was designated by the reference laboratory as a "clinical cutoff", a value typically employed in compliance drug monitoring. Lab "cutoff" values for any test are chosen with the aim of optimizing the balance between sensitivity and specificity (predictive value). The technology utilized by the external reference laboratory can quantify naloxone concentrations as low as 0.1 ng/mL (if clinically indicated), but in the case of this study we felt that a 1 ng/mL lower limit was adequate for our survey purposes. Of the 20 specimens with no detectable naloxone, most were explained by inadequate intake of prescribed medication, e.g. patient did not have enough money to buy their medication, or they changed their follow-up appt and ran out. Some were suspected of diversion.

Discussion

Of the 561 active patients in the database at time of query, 11.1% were prescribed the combo product. We understand that this is a relatively low percentage, but we feel that this practice is justified for several reasons: (1) most of our patients do not have prescription insurance and the generic combo tablets are considerably more expensive than the mono, and (2) many patients have the troublesome side effects mentioned previously. We feel that our first duty is harm reduction, so we listen to patient concerns and accommodate them as far as possible but practice active surveillance with regular (often observed) drug screening, and frequent, random pill counts. When there is clear evidence of non-compliance of any kind, especially diversion, that patient is typically dismissed from our clinic. Such patients are uniformly resistant to referral to a higher level of care, such as an OTP providing daily dosing.

It is commonly believed, even among addiction medicine specialists, that naloxone is poorly absorbed from sublingual dosing, and that abuse by injecting the combo product is inhibited by the presence of naloxone. However, Harris et al. [7] reported that intravenous buprenorphine:naloxone produced subjective effects like those of sublingual (SL) buprenorphine, but did not precipitate withdrawal, thereby disputing the commonly reported contention that the addition of naloxone discourages the IV administration of the combo product. Likewise, Bruce [18] evaluating a cohort of 41 habituated intravenous buprenorphine users in Malaysia who were switched to buprenorphine:naloxone, reported that "… overall 44% of subjects increased their daily amount of injection while 54% had no change in dose; only 1 subject reduced the amount of injection". The only symptom that was significantly associated with buprenorphine/NLX dosage was the report of 'stomach pains'.

Much of the confusion about the sublingual absorption of naloxone may be related to the original NDA for Suboxone [19,20] in which it was stated: "Most of the plasma levels of naloxone post oral and/or sublingual dosing were not detectable". The underlining was done by the authors of the report. The statement is true for oral, but looking at the actual data, it is not true for SL dosing.

Only 11.1% of our patients are prescribed the combo product. Of those, 97.8% of specimens had detectable urinary concentrations of naloxone, and 93% have values over the "clinical cutoff" of 30 ng/mL. The small number of samples with non-detectable levels occurred for various reasons, as explained in the Results section.

Because this was a retrospective study, we could not correlate the timing nor quantity of the morning dose with urinary levels of naloxone. Nor did we think it useful to normalize naloxone urinary concentration with urinary creatinine concentration or compare various parameters of buprenorphine, norbuprenorphine and naloxone. A Pearson regression analysis testing naloxone versus buprenorphine did not show a significant correlation (data not shown). Our goal was simply to confirm the results of Heikman and demonstrate that a significant amount of naloxone is absorbed sublingually. These data lend support to those reports that side effects of combo-therapy are common and may limit continuation in MAT when combo-therapy is dictated by various agencies. However, because this study was retrospective we could not correlate nor compare unpleasant side effects of patients

prescribed combo products versus mono products. For the most part, patients entering our program had illicitly used both products and knew in advance which formulation they could best tolerate.

The side effects are real, but variable from patient to patient, which is true of all medications. Many patients tolerate the combo product well, when given a chance, but we feel strongly that we should listen to patients when they describe unpleasant effects from combo therapy, and not just automatically assume that they want to misuse the medication, or divert. However, along with observed urine specimens and "pill counts", we do feel that the quantification of naloxone in urine on all patients can sometimes help to detect non-compliance and/or diversion.

The US Department of Health and Human Services and the National Institutes of Health have identified 5 major priorities in combating the opioid "epidemic" in the US [21], the first of which is: "Improving access to treatment and recovery services." We hope that the results of this study will support the efforts of those providers and agencies to provide, and indeed to expand, MAT services to patients with opioid use disorders.

We feel that certain legislative/regulatory impositions on the practice of medicine are not evidence-based, and are obstructive to the legitimate efforts of opioid addicts struggling to cease illicit substance use and "get their lives back." In the opinion of the authors, there appears to be a disproportionate emphasis on interdicting the diversion of buprenorphine, instead of focusing on the relatively more dangerous pure opioid agonists.

We have heard countless successful MAT patients state categorically that if the combo product were the only formulation available they would go back to illicit pure agonist use, as expensive and as destructive and dangerous as that may be. A secondary (but significant) problem is cost: the generic combo product costs considerably more than the mono product. For our patients, most of whom have no prescription medical insurance, the cost variation may mean the difference between success and failure in a program. Prices for various locations can be obtained at such sources as https://www.goodrx.com.

Conflict of Interest

No funding or support was received for this project.

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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