Pharmacokinetics of Suboxone

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Suboxone, a sublingual tablet formulation comprised of a 4:1 ratio of buprenorphine and naloxone is “the most widely used formulation of buprenorphine to treat opioid dependence in the USA” (Ling, 2009, p. 1). Its value as a treatment for opioid use disorder can be attributed to the pharmacokinetic effectiveness of suboxone’s: 1) absorption, 2) distribution, 3) metabolism, and 4) elimination when administered sublingually. This paper will address the pharmacokinetic characterization of suboxone, how it affects the blood-brain and placental barrier along with the physiological, psychological, and possible side effects when used as a treatment for opioid use dependence.

Interestingly when buprenorphine is taken orally (whole) it is not well absorbed but when absorbed sublingually through the saliva (the mucosa of the oral cavity) the rate of absorption is rapid and increases significantly (Ling, 2009). The approximate time for the complete dissolution of suboxone is approximately 7-10 minutes under the tongue (Orman & Keating, 2009). Though the absorption of buprenorphine is rapid in the oral mucosa, systemic circulation is slower (Orman & Keating, 2009). Suboxone’s bioavailability, which is “the amount of drug to reach systemic circulation” sublingually ranges from 30% to 55% compared to 14% when swallowed (Coe et al., 2019, p. 95; Wesson & Smith, 2010). Therefore, the sublingual form of buprenorphine is primarily chosen when treating opioid dependence due to its increased bioavailability (Wesson & Smith, 2010). Research studies have shown the rate and extent of absorption known as Cmax and the blood concentration-time known as AUC of buprenorphine increase linearly when the suboxone’s dosage is increased (Ling, 2009).

After absorption in the oral mucosa, buprenorphine is “widely distributed throughout the body reaching peak plasma concentration at 60 minutes and having a terminal half-life of approximately 32-37 hours” (Ling, 2009, p. 2). Buprenorphine binds highly to plasma proteins,

"approximately 96% of which is primarily to alpha and beta globulin" (The National Alliance of Advocates for Buprenorphine Treatment [NAABT], 2019). Interestingly, studies have found that naloxone does not affect the pharmacokinetics of buprenorphine (Ling, 2009). The formulation of adding naloxone to buprenorphine to produce suboxone was done to discourage the abuse of buprenorphine by precipitating withdrawal symptoms when used intravenously. As a result, the effect of naloxone is bioavailable and precipitates withdrawal only when administered intravenously (Coe et al., 2019). When administered sublingually the absorption of naloxone is low and barely detectable in the plasma (Orman & Keating, 2009).

Unlike what occurs in absorption buprenorphine and naloxone both go through extensive hepatic metabolism (Orman & Keating, 2009). It is important to note, though buprenorphine is absorbed well in the gut and mucosal surfaces it is rapidly metabolized primarily in the liver to norbuprenorphine by the cytochrome P450 3A4 enzymes (Wesson & Smith 2010). The metabolism of buprenorphine occurs through N-dealkylation and glucuronidation (Orman & Keating, 2009). When buprenorphine is converted to norbuprenorphine it has little ability to cross the blood-brain barrier making its effects negligible (Welsh & Valadez-Meltzer, 2005). Naloxone undergoes glucuronidation directly along with N-dealkylation resulting in a metabolized form of naloxone-3-glucuronide and a "reduction of the 6-oxo group" (Orman & Keating, 2009, p. 9).

The impact of hepatic impairment and how it affects the pharmacokinetics of buprenorphine and naloxone is not known. However, since both drugs are metabolized primarily by the liver clients with moderate or severe hepatic impairments should be monitored. Obtaining a baseline of a client's liver enzymes before and during suboxone treatment is recommended in all buprenorphine package inserts (Coe et al., 2019). Suboxone's dosage may also need to be

adjusted to account for the increased possibility of higher plasma concentrations of buprenorphine and naloxone (NAABT, 2019; [Orman & Keating, 2009]). Clients taking protease inhibitors along with suboxone should also be monitored closely by a physician because the combination of these two drugs could potentially slow down the metabolism of buprenorphine (Wesson & Smith, 2010).

The elimination of buprenorphine is excreted mainly through the fecal route (Ling, 2009). While naloxone is excreted primarily in urine (Orman & Keating, 2009). How renal impairments affect the pharmacokinetics of naloxone is unknown. While no differences were found in the pharmacokinetics of buprenorphine in a study conducted with clients on dialysis, caution is recommended when administering suboxone to clients with severe renal impairment (Orman & Keating, 2009).

Buprenorphine is classified as a Category C drug by the Federal Drug Administration (FDA), which means data to establish whether administering suboxone is safe during pregnancy is insufficient (Wesson & Smith, 2010). Despite this lack of data, in 2017 The American College of Obstetricians and Gynecologists put out guidelines stating buprenorphine was safer than methadone treatment or medical withdrawal and is the treatment of choice for pregnant women who are opioid-dependent (Velander, 2018). The first pass hepatic metabolism of naloxone which studies show leads to a minimal placental transfer of naloxone also contributes to suboxone as the treatment of choice for opioid-dependent pregnant women (Velander, 2018).

Physiologically as a treatment for OUD, the combination of buprenorphine as a partial opiate agonist alongside naloxone decreases its potential for abuse and provides a safer treatment option for relieving the cravings and withdrawal of OUD. In a study conducted to examine the cardiovascular and respiratory effect while using suboxone for OUD, no significant differences

were found in “any of the treatment conditions for blood pressure, heart rate, respiratory rate, oxygenation, or skin temperature across time” (NAABT, 2019).

Despite suboxone’s high safety profile and milder side effects compared to other opioids, clients still need to be aware of the possible side effects of suboxone. Such as constipation, nausea, headache, urinary retention, and sedation (Welsh & Valadez-Meltzer, 2005) A decrease in respiratory rate may also be observed (Welsh & Valadez-Meltzer, 2005). It is also important for clients to know that the risk of a fatal overdose occurring increases when buprenorphine is mixed with benzodiazepines (Welsh & Veladez-Meltzer, 2005).

Psychologically, the goal of suboxone treatment is to aid in supporting the client from relapsing without creating physical dependence on another drug (Campbell & Lovell, 2012). The flexibility in treatment with suboxone empowers those battling with OUD while normalizing addiction treatment and removing the stigma associated with OUD through “office-based pharmacotherapy” (Campbell & Lovell, 2012, p. 137). Treatment with suboxone allows the client to get physiologic support for their cravings and withdrawal symptoms. Which in turn enables them to focus on seeking and receiving the psychological support they need to make the necessary changes in their lifestyle, maladaptive patterns, and behaviors to live a life free of opioid addiction. (Campbell & Lovell, 2012).

The pharmacokinetics of suboxone’s rapid absorption, systemic plasma distribution, hepatic metabolism, and fecal elimination contributes to its efficacy and safety in treating OUD. As a counselor, it is our ethical responsibility to have a basic understanding of the pharmacology behind the medication our client is currently taking or considering as an option. Without this basic knowledge, we are doing our clients an injustice which could lead to harm. Therefore, let us strive to have a discerning heart that seeks out and acquires knowledge (Proverbs 18:15 NIV).

References

Coe, M.A., Lofwall, M.R., & Walsh, S.L. (2019). Buprenorphine pharmacology review: Update on transmucosal and long-acting formulations. *Journal of Addiction Medicine*, 13(2) 93-103. doi:10.1097/ADM.0000000000000457

Orman, J. S., & Keating, G. M. (2009). Buprenorphine/Naloxone: a review of its use in the treatment of opioid dependence. *Drugs*, *69*(5), 577+. https://link.gale.com/apps/doc/A213856414/EAIM?u=nysl_se_nyac&sid=EAIM&xid=d75e2275

The National Alliance of Advocates for Buprenorphine Treatment. (2019, August 28). Package insert PDF. https://www.naabt.org/documents/packageinsert.pdf

Velander J. R. (2018). Suboxone: Rationale, science, misconceptions. *The Ochsner Journal*, *18*(1), 23–29.

Welsh, C., & Valadez-Meltzer, A. (2005). Buprenorphine: a (relatively) new treatment for opioid dependence. *Psychiatry (Edgmont (Pa: Township))*, *2*(12), 29–39.

Wesson, D.R., & Smith, D. E. (2010). Buprenorphine in the treatment of opiate dependence. *Journal of Psychoactive Drugs*, 42(5), 161-175.