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Clinical Use of Buprenorphine for Anesthesia and Pain Management in Japan

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Abstract

Buprenorphine (BUP) is a classic analgesic drug, and recent studies have reported a new, unique pharmacological profile of it. BUP can be used in patients with renal dysfunction and failure, and these patients can receive the same dose of BUP administered to those with normal renal function. BUP may have a local anesthetic-like effect to blockade voltage gated Na+ channels; it can be used as a local anesthetic peripheral nerve block adjuvant to prolong analgesia. BUP is useful for postoperative pain relief in patients with severe liver dysfunction in Japan. However, the prolonged metabolism of BUP and occurrence of delayed emergence from anesthesia may occur in these patients. Moreover, in Japan, the transdermal buprenorphine patch (TBP) is used for the reducing intractable chronic non-cancer pain such as low back pain or pain caused by osteoarthritis not opioid addiction.

Keywords Buprenorphine; Anesthesia; Postoperative pain management; Pain medicine; Chronic non-cancer pain

Introduction

Buprenorphine (BUP), a classic chemically synthesized opioid reported in 1967 by Bentley et al. [1], has been reconsidered as an analgesic for anesthesia or the management of postoperative pain and cancer pain. Moreover, recent studies have also reported a new, unique pharmacological profile of BUP [2].

On the other hand, transdermal buprenorphine patch (TBP) has been widely used in pain medicine since 2011 to reduce chronic non-cancer pain in Japan. However, the use is limited for reducing low back pain or joint pain in Japan. Simultaneously, BUP is reconsidered as a useful postoperative analgesic after general anesthesia with remifentanil.

Therefore, I will present the recent clinical significance of BUP in Japan for anesthesia, postoperative pain management, and chronic pain management in this short review.

Recent Knowledge of Pharmacokinetics of BUP

It is well known, BUP is synthesized from thebaine (paramorphine) [1], an opioid alkaloid, and it has a chemical structure similar to morphine (MOR) and codeine. BUP has the affinity of Ki of 0.16 nM against the human recombinant μ receptor and Ki of 0.06 nM against the κ receptor [3]. In addition, BUP has an efficacy of EC50>20,000 nM against the κ receptor compared to an EC50 of 0.76 nM for the μ receptor. Therefore, BUP is currently considered a partial agonist of μ-1 and μ-2 receptors and a partial antagonist of κ-1 receptor. However, recent investigations have reported that BUP is a potent, partial agonist of the μ-1, μ-2, κ, and δ subunits, especially the κ-3 subunit [2]. BUP has 40 times more than MOR in the analgesic effect; nevertheless, the binding effect to the mu receptor is lower for BUP than for MOR [4]. Moreover, as a partial agonist of the nociceptin/orphanin FQ (opioid receptor like-1) receptor, BUP induces an analgesic effect on the spinal cord and inhibits opioid tolerance, opioid-induced hyperalgesia, and the rewarding effect caused by opioids [5]. Norbuprenorphine (NBUP), a metabolite of N-dealkylation of BUP, is a full agonist of the δ receptor and partial agonist of the mu and κ receptors [6]. Compared to BUP, NBUP has a high affinity for the μ, κ, and δ receptors. However, because NBUP cannot pass through the blood-brain barrier (BBB), the pharmacological effect of NBUP is weak.

BUP is excreted in the feces through the bile, which undergoes glucuronidation in the liver, so the renal excretion rate is about 1%. Therefore, BUP can be used in patients with renal dysfunction and even in those on dialysis due to renal failure; these patients can receive the same dose of BUP administered to those with normal renal function [7]. BUP may also have a local anesthetic-like effect to blockade voltage-gated Na^+ channels [8]. Thus, BUP can be used as a local anesthetic peripheral nerve block adjuvant to prolong analgesia [9]. As the response from the μ receptor is slower to BUP than to other opioids, withdrawal symptoms of BUP are usually not seen, as there is a ceiling effect. Therefore, there is little risk of dependency, and tolerance is inhibited. The rewarding effect caused by opioids is also mild compared to that of MOR, as the rewarding effects are only observed at higher doses [7]. Therefore, BUP is considered an opioid with a low risk of abuse or addiction [10].

Clinical Use of BUP for Anesthesia in Japan

Usually, the injection of BUP is used to assist in the management of anesthesia [11]. Changes in the blood concentration of patients who received BUP intravenously and intramuscularly are equal, and the duration of BUP is reported as 6-9 hours. For the relief of postoperative pain, 4–5 μg/kg of a single dose of BUP is administered intravenously [12].

According to the several Japanese trial of BUP by Japanese researchers in 1982, the effective rates of BUP at 4 μg/kg, 6 μg/kg and 8 μg/kg to support anesthesia are reportedly 50.0%, 83.3%, and 83.9%, respectively (article in Japanese only). Therefore, in Japan, it is recommend administering 6 μg/kg of BUP to support anesthesia and 4-5 μg/kg of a single dose of BUP for postoperative pain relief.

Moreover, a continuous subcutaneous infusion of 0.6-0.7 mg/d and continuous intravenous infusion of 0.002 mg/kg/h of BUP are recommended for postoperative main management according reports by Gourlay or Bramley et al. [13,14].

I will mention the more common usage of BUP in Japan as below.

BUP for postoperative pain relief in hepatic dysfunction patients

As the previous report, BUP provides effective postoperative pain relief, and it did not compromise the recovery of patients who underwent major abdominal surgery with total intravenous anesthesia [15]. Especially, we considered that, in cases of partial liver resection cause of liver cancer, the use of BUP for postoperative pain management after remifentanil-based anesthesia with a volatile anesthetic has been indicated. Most patients with liver cancer caused by liver cirrhosis may have coagulation dysfunction. Thus, epidural analgesia cannot be chosen for postoperative pain relief [16,17].

For subsequent analgesia from the intraoperative period in the surgical theater to the postoperative period in the ward, we recommended the administration of 5 μg/kg of BUP before the end of surgical procedure and remifentanil-based anesthesia like the method of Kimoto et al [18]. There might be no significant difference regarding recovery from anesthesia to extubation between patients who underwent liver resection and did or did not receive small dose of BUP [19].

Usually, it is best to interrupt BUP therapy 6-8 hours before anesthesia [20], because the high affinity of BUP prevents the binding of other opioids such as fentanyl or remifentanil at commonly used clinical doses to receptor sites, which reduces their minimum alveolar concentration (MAC).

However, there are several studies about the usefulness of BUP for postoperative pain relief without delayed emergence from anesthesia [15,21,22]. Particularly, Albrecht et al. [15] emphasized the efficacy of piritramide over fentanyl and BUP. Since piritramide cannot be used in Japan, we use BUP for postoperative pain management, as it has the same effect as fentanyl. Since BUP undergoes hepatic metabolism, it is likely to have a prolonged effect in patients with liver disease [23]. Thus, severe liver dysfunction may prolong the metabolism of BUP and cause delayed emergence from anesthesia. In patients with hepatic dysfunction, the use of most analgesics is limited due to significantly impaired renal clearance, but this has been poorly studied in the clinical setting. On the other hand, BUP has the risk of postoperative delirium in elderly patients [24].

Transdermal BUP for chronic non-cancer pain treatment

In 2011, the TBP was first used in clinical practice for treating chronic musculoskeletal pain [25,26]. In Japan, we can only use TBP, not sublingual BUP or the BUP/naloxone compound for non-cancer pain relief. BUP with naloxone is a well-known therapeutic agent for opioid addiction. But, there is no clinical use of BUP to treat the opioid addiction. Therefore, BUP is evaluated as the analgesic only in Japan and that is different from that in other countries such as the United States or Europe [27].

TBP is useful for reducing chronic non-cancer low back pain and pain due to osteoarthritis; these types of pain are difficult to treat with non-opioid analgesics [28,29]. Three doses of TBP may be used (5 mg, 10 mg, and 20 mg); the maximum serum concentration are as follows: 84 ± 19 pg/mL, 140 ± 47 pg/mL, and 270 ± 67 pg/mL, respectively. The tendency to treat non-cancer chronic pain with TBP was retrospectively reviewed [27]. Safety index (odds ratio of the anti-nociceptive effect / odds ratio of respiratory depression) of BUP is 13.54, whereas the safety index of fentanyl is 1.20. This result indicates that the safety margin of BUP is wide compared to that of fentanyl [30]. Recently, Dowell et al. indicated that for patients with an opioid use disorder, clinicians should offer or plan to use evidence-based treatment such as medication-assisted treatment with BUP or methadone [31].

Regarding side effects, constipation, nausea, and vomiting are seen at a high rate. Therefore, it is necessary to combine BUP with antiemetics and laxatives. Often the incidence of constipation caused by BUP is less than that due to MOR. In patients taking oral P-glycoprotein inhibitors, there is a possibility that NBUP may easily pass through the BBB and thus enhance the analgesic effect [32]. Therefore, patients who are taking drugs such as verapamil, amiodarone, quinidine, an immunosuppressive agent, and HIV therapeutic agents that have the ability to inhibit P-glycoprotein may enhance the analgesic effect of BUP.

Conclusion

BUP is a well-known synthesized opioid analgesic with unique properties such as being a partial κ agonist and Na+ channel blocker [2,8]. However, further study is required to assess the safety of perioperative pain management and chronic pain management with BUP in the future.

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Conflicts of Interest

The author declares no conflicts of interest.

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References

1. Bentley KW, Hardy DG, Meek B (1967) Novel analgesics and molecular rearrangements in the morphine-thebaine group. II. Alcohols derived from 6,14-endo-etheno- and 6,14-endo-ethanotetrahydrothebaine. J Am Chem Soc 89: 3273-3280.
2. Pick CG, Peter Y, Schreiber S, Weizman R (1997) Pharmacological characterization of buprenorphine, a mixed agonist-antagonist with kappa 3 analgesia. Brain Res 744: 41-46.
3. Heel RC, Brogden RN, Speight TM, Avery GS (1979) Buprenorphine: a review of its pharmacological properties and therapeutic efficacy. Drugs 17: 81-110.
4. Pergolizzi J, Aloisi AM, Dahan A, Filitz J, Langford R, et al. (2010) Current knowledge of buprenorphine and its unique pharmacological profile. Pain Pract 10: 428-450.
5. Takahashi T, Okubo K, Kojima S, Nishikawa H, Takemura M, et al. (2013) Antihyperalgesic effect of buprenorphine involves nociceptin/orphanin FQ peptide-receptor activation in rats with spinal nerve injury-induced neuropathy. J Pharmacol Sci 122: 51-54.
6. Ohtani M, Kotaki H, Sawada Y, Iga T (1995) Comparative analysis of buprenorphine- and norbuprenorphine-induced analgesic effects based

on pharmacokinetic-pharmacodynamic modeling. J Pharmacol Exp Ther 272: 505-510.

7. Niscola P, Scaramucci L, Vischini G, Giovannini M, Ferrannini M, et al. (2010) The use of major analgesics in patients with renal dysfunction. Curr Drug Targets 11: 752-758.
8. Leffler A, Frank G, Kistner K, Niedermirtl F, Koppert W, et al. (2012) Local anesthetic-like inhibition of voltage-gated Na(+) channels by the partial Î¼-opioid receptor agonist buprenorphine. Anesthesiology 116: 1335-1346.
9. Ducharme S, Fraser R, Gill K (2012) Update on the clinical use of buprenorphine: in opioid-related disorders. Can Fam Physician 58: 37-41.
10. Kirksey MA, Haskins SC, Cheng J, Liu SS (2015) Local Anesthetic Peripheral Nerve Block Adjuvants for Prolongation of Analgesia: A Systematic Qualitative Review. PLoS One 10: e0137312.
11. Yonemura E, Fukushima K (1990) Comparison of anesthetic effects of epidural and intravenous administration of buprenorphine during operation. J Anesth 4: 242-248.
12. Budd K (1984) Buprenorphine. In: Bullingham RES, ed. Opiate analgesia. W.B. Saunders Company, Philadelphia, London, Toranto.
13. Gourlay GK, Kowalski SR, Plummer JL, Cousins MJ, Armstrong PJ (1988) Fentanyl blood concentration-analgesic response relationship in the treatment of postoperative pain. Anesth Analg 67: 329-337.
14. Bromley L (1993) Improving the management of acute pain. Br J Hosp Med 50: 616-618.
15. Albrecht S, Fechner J, Geisslinger G, Maass AB, Upadhyaya B, et al. (2000) Postoperative pain control following remifentanil-based anaesthesia for major abdominal surgery. Anaesthesia 55: 315-322.
16. Yukioka H, Fujimori M (1992) Epidural opioids for postoperative pain relief following hepatectomy. Osaka City Med J 38: 67-77.
17. Yorozu T, Morisaki H, Kondoh M, Toyoda Y, Miyazawa N, et al. (1996) Epidural anesthesia during upper abdominal surgery provides better postoperative analgesia. J Anesth 10: 10-15.
18. Kimoto M (2011) Effect of buprenorphine on postoperative analgesia following remifentanil-based anesthesia. Masui 60: 656-660.
19. Iskandarov E, Srinivasan PK, Xin W, Bleilevens C, Afify M, et al. (2016) Protective Effects of Adenosine Receptor Agonist in a Cirrhotic Liver Resection Model. Hepatitis Monthly 16: 8.
20. Goyenechea Jaramillo LA, Murrell JC, Hellebrekers LJ (2006) Investigation of the interaction between buprenorphine and sufentanil during anaesthesia for ovariectomy in dogs. Vet Anaesth Analg 33: 399-407.
21. Murphy EJ (2005) Acute pain management pharmacology for the patient with concurrent renal or hepatic disease. Anaesth Intensive Care 33: 311-322.
22. Hogue C, Bowdle A, O'leary C, Duncalf D, Miguel R, et al. (1996) A multicenter evaluation of total intravenous anesthesia with remifentanil and propofol for elective inpatient surgery Anesth Analg 83: 279-285.
23. Sen S, Arulkumar S, Cornett EM, Gayle JA, Flower RR, et al. (2016) New Pain Management Options for the Surgical Patient on Methadone and Buprenorphine. Curr Pain Headache Rep 20: 16.
24. Ito G, Kanemoto K (2013) A case of topical opioid-induced delirium mistaken as behavioural and psychological symptoms of dementia in demented state. Psychogeriatrics 13: 118-123.
25. Khanna IK, Pillarisetti S (2015) Buprenorphine-an attractive opioid with underutilized potential in treatment of chronic pain. J Pain Res 8: 859-870.
26. Kress HG (2009) Clinical update on the pharmacology, efficacy and safety of transdermal buprenorphine. Eur J Pain 13: 219-230.
27. Hamaguchi S, Ikeda T (2013) Buprenorphine transdermal patch (Norspan tape). Masui 62: 799-807.
28. Plosker GL (2011) Buprenorphine 5,10 and 20 Î¼g/h transdermal patch: a review of its use in the management of chronic non-malignant pain. Drugs 71: 2491-2509.
29. Plosker GL, Lyseng-Williamson KA (2012) Buprenorphine 5, 10 and 20 Î¼g/h transdermal patch: a guide to its use in chronic non-malignant pain. CNS Drugs 26: 367-373.
30. Yassen A, Olofsen E, Kan J, Dahan A, Danhof M (2008) Pharmacokinetic-pharmacodynamic modeling of the effectiveness and safety of buprenorphine and fentanyl in rats. Pharm Res 25: 183-193.
31. Dowell D, Haegerich TM, Chou R (2016) CDC Guideline for Prescribing Opioids for Chronic Pain--United States, 2016. JAMA 315: 1624-1645.
32. Brown SM, Campbell SD, Crafford A, Regina KJ, Holtzman MJ, et al. (2012) P-glycoprotein is a major determinant of norbuprenorphine brain exposure and antinociception. J Pharmacol Exp Ther 343: 53-61.