Midazolam for the Treatment of Phantom Limb Pain Exacerbation : Preliminary Reports†

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Abstract

Phantom pain is one of the most difficult intractable pains to manage. The pain may result from the imbalance of self-sustaining neural activity that exceeds the inhibitory control. The management of acute severe exacerbation of phantom pain is extremely difficult. Midazolam acts by potentiation of gamma aminobutyric acid (GABA) and enhance the inhibitory action of glycine receptor at spinal neurons. We describe two preliminary reports of complete pain relief of severe phantom pain exacerbation by intravenous midazolam 3-5 mg.

Key word : Phantom Pain, Midazolam

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Phantom pain is one of the most difficult intractable pains to manage. The gate control theory of pain is commonly used to explain phantom limb pain(1). When the self–sustaining spinal neuronal activity exceeds the inhibitory control, the pain may occur in the phantom limb (2). The management of acute severe exacerbation of phantom pain is extremely difficult. Exacerbation of pain may be produced by physical and emotional stimuli(3), including spinal anesthesia(4-8). No therapy has been uniformly effective except two cases by intravenous thiopental(8). The proposed explanation is that the thiopental diminishes facilitation and enhances inhibition at synapses throughout the central nervous system But its used is possibly limited

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by the ultrashort action and the anti-analgesic effects at the subanesthetic dose[9]. Midazolam is the benzo-diazepine that act by potentiation of gamma aminobutyric acid (GABA) - the major inhibitory neurotransmitter in the central nervous system and enhance the inhibitory action of glycine receptor at spinal neurons[10]. We proposed that midazolam may be as effective to treat phantom pain exacerbation with the benefit of intermediate action. We describe two preliminary reports of complete pain relief of severe phantom pain exacerbation with intravenous midazolam.

PRELIMINARY REPORTS

Case 1.

A 57 year-old man with chronic arterial occlusion with chronic ulcers and gangrene of the toes was scheduled for debridement of right foot ulcers in Ramathibodi Hospital in October 1997. He had a history of left below-knee amputation 3 years ago due to gangrene of the foot. After the amputation, he experienced occasional phantom discomfort at his absent foot that required no treatment. He had a history of essential hypertension for 5 years with inadequate control. There was no history of diabetes mellitus or smoking. The recent analgesic for right foot ulcer was oral ibuprofen 400 mg as needed.

Spinal block was choosen to provide anesthesia for the debridement of right foot ulcers. Guage 25 needle was inserted at L4-5 interspace. Ten mg of heavy bupivacaine in right lateral position was given. Pin-prick testing revealed complete analgesia extending up to T12 level bilaterally. He was unable to elevate either his leg or stump. On cleansing the skin for surgery the patient started to complain of severe shooting pain over his absent foot. He extremely restless and continued to complain of severe unbearable pain while the surgeon was operating on the right foot. Attempts were made to relieve the patient's distress with 5 mg of intravenous morphine. There was no improvement. The incremental dose of intravenous midazolam 3 mg was given and the phantom pain began to disappear. He was not asleep but able to freely communicate about his "strange feeling". After the spinal anesthesia wore off, there was no recurrence of the phantom pain.

Case 2.

A 24-year-old woman was admitted to Ramathibodi Hospital on August 1998 due to severe phantom pain after the traumatic amputation of her right hip 2 months ago. The treatment for her phantom pain was intravenous lidocaine infusion 3 mg/kg over 60 minutes daily, baclofen 450 mg/day amitryptyline 50 mg at bedtime and paracetamol 1 g every 6 hours that afforded pain relief from the visual analog scale (VAS) 10 to 0-3. She only experienced some throbbing discomfort over her stump after the third dose of intravenous lidocaine. However, after 6 hours of minimal pain, she complained of severe electric shock-like phantom pain exacerbation. Attempts to alleviate her pain include intravenous morphine 5 mg and intravenous lidocaine 150 mg over 30 mins. All offered no relief. The increment dose of intravenous midazolam 5 mg was given. The pain diminished and disappeared after 3 minutes. She was able to sit up and eat her meal. No phantom pain recurred during her stay for 1 month in the hospital and she only felt some phantom discomfort occasionally. Her home medications were amitryptyline 50 mg at bedtime and paracetamol 1 g as needed.

Two months later, she was admitted again with another episode of phantom pain exacerbation. Intravenous midazolam 5 mg offered complete pain relief.

DISCUSSION

Phantom limb pain may originate from the abnormal firing of the central nervous system [8]. Two neurophysiologic theories of phantom pain are peripheral and central mechanisms[11]. The peripheral mechanism theorized that the phantom pain originate from the cut end of nerves[2] but does not fully explain the problem because the complete sensory blockade does not provide pain relief in most patient. The central mechanism - the "gate control theory[12]" is widely accepted to explain the phantom pain. The theory proposed that a portion of brainstem reticular formation exerts a tonic inhibitory influence on transmission at all synaptic levels of the somatic sensory system (pattern generating mechanism). After amputation, there is significant destruction of sensory afferents, the wide-dynamic

range neurons of the spinal dorsal horn are freed from inhibitory control[2]. If the self-sustaining spinal neuronal activity exceeds a critical level, pain may be experienced in the absent limb[13].

Pain may recur long after resolution of phantom limb pain if the patient undergoes regional anesthesia[1]. There have been 13 case reports of phantom pain exacerbation induced by spinal anesthesia[4-8]. Following the loss of sensory input after spinal block, the decreased inhibition of the "pattern generating mechanism" and the increased self-sustaining neuronal activity result in the phantom pain. Several drugs including fentanyl with diazepam, morphine, pethidine and thiopental have been used in an attempt to alleviate the pain[4-8]. No drug was given in two cases, one case suffered the pain until the spinal anesthesia disappeared, and another case suffered for 12 hours after spinal anesthesia wore off[8]. Only intravenous thiopental 50 mg was effective in abolish the pain in two cases[8]. The proposed explanation for the effectiveness of thiopental is that the barbiturates diminish facilitation and enhance inhibition at synapses throughout the nervous system[14]. However, thiopental action is ultrashort and at subanesthetic dose may have the anti-analgesic effect which may be unsuitable.

Midazolam has a chemical structure that is different from other therapeutic benzodiazepines[10]. At pH greater than 4 the diazepine ring closes. The closed ring form is lipophilic at physiologic pH. This permits easy passage across neuronal tissues and blood-brain barrier [15]. The pharmacologic effect of benzodiazepine are mediated by a facilitation of gamma aminobutyric acid (GABA) and glycine mediated action[10]. GABA is an important inhibitory neurotransmitter in both peripheral and central nervous system[16]. Synapses use GABA as the chemical mediator to modulate the activity of other neuronal systems that secrete dopamine and serotonin[17]. Anesthetic agents can increase the concentration of GABA in critical regions of the brain and the increased concentration of this inhibitory neurotransmitter may attribute to anesthetic effects of certain drugs[18]. Glycine, the simplest alpha amino acid is the major inhibitory transmitter of the spinal cord and may mediate inhibition of motor neurons originating in the spinal cord and brainstem[10]. There are reports of segmental spinal analgesia when administering midazolam intrathecally[19]. Midazolam was effective in abolishing the phantom pain exacerbation in our one case during spinal anesthesia and another case of spontaneous exacerbation.

The explanation for why midazolam is effective may be as follows: 1) the loss of inhibition at the gate control of pattern generating mechanism is restored by facilitation of GABA ergic inhibition in the nervous system and abolish the self-sustained neuronal activity[8,10,17] 2) the affinity for glycine receptor in spinal cord further augments the inhibitory effect on spinal neurons[10].

We conclude that intravenous midazolam is effective for abolishing the exacerbation of phantom pain either after spinal anesthesia or spontaneously. When faced with severe phantom exacerbation which does not respond to other treatment, we recommend that midazolam should be tried immediately.

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การใช้ไมดาโซแลมในการบำบัดรักษาอาการปวดแฟนทอม : การรายงานเบื้องต้น

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ความปวดที่เกิดขึ้นจากตำแหน่งของร่างกายส่วนที่ถูกตัดขาดไป (phantom pain) เป็นอาการที่ยากต่อการรักษา โดยเฉพาะความปวดรุนแรงที่อาจเกิดขึ้นเป็นครั้งคราว ซึ่งเกิดจากความผิดปกติในสมดุลของกลไกการยับยั้งและกระตุ้นกระแสประสาท (gate control theory) ยา midazolam ซึ่งมีฤทธิ์กระตุ้นสารสื่อประสาท gamma aminobutyric acid (GABA) และกระตุ้น glycine receptor ซึ่งมีฤทธิ์ยับยั้งประสาทไขสันหลัง จึงน่าที่จะบรรเทาความปวดรุนแรงได้ ผู้รายงานได้รายงานเบื้องต้นของการรักษา phantom pain exacerbation ในผู้ป่วย 2 รายซึ่งมีอาการปวดรุนแรงด้วยยา midazolam 3-5 มก. ทางหลอดเลือดดำอย่างได้ผล

คำสำคัญ : ความปวดแฟนทอม, มิดาโซแลม

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