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Naloxone Does not Affect Pain Relief Induced by Electrical Stimulation in Man

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Summary

We wished to determine if pain relief that resulted from transcutaneous (TNS) or spinal cord electrical stimulation in patients with chronic pain was due to activation of an endogenous opiate-related pain control system. Naloxone (0.4–10 mg) or saline was injected in double-blind fashion intravenously into opiate-naive subjects with chronic pain who achieved 30% or greater pain relief with spinal cord stimulation (4 patients) or TNS (9 patients). Subjects rated their pain during stimulation and 2, 5, 10 and 15 min after the injection. Two days or more later the procedure was repeated using the alternate agent (naloxone or saline). Naloxone did not decrease the pain relief induced by stimulation, and therefore the effects of stimulation are probably not mediated by the endogenous opiates.

Introduction

Electrical stimulation is now in common use for pain control. In a double-blind study using electrical stimulation and a placebo device, Thorsteinsson et al. [25] demonstrated that transcutaneous nerve stimulation (TNS) relieved pain more effectively than mock stimulation. TNS appears to be most effective at relieving pain associated with peripheral nerve injuries, chronic lumbar and cervical syndromes, amputation stumps, and arthritis [15] and in treatment of postoperative pain [26].

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Peripheral nerve stimulation often constitutes an effective therapy for pain originating from peripheral nerve injury when a definitive operation is not available [3]. Stimulation via posteriorly placed electrodes on the spinal cord (epidural stimulation) is primarily used for patients with lumbosacral spine disorders not amenable to direct treatment [15,19].

The mechanism by which epidural and transcutaneous electrical stimulation reduces pain in man is not established. One possibility is that the effect results from activation of an endogenous opiate-related pain modulating system involving enkephalins [11,16,20]. If true, the narcotic antagonist naloxone might be expected to abolish pain relief induced by electrical stimulation. Also, the onset of antagonism by naloxone of pain relief induced by electrical stimulation should correspond to the time of onset of naloxone reversal of opiate-induced pain relief, viz. 2 min [13].

In this study opiate-naive subjects were engaged in a prospective double-blind randomized cross-over study of the effect of naloxone (0.4–10.0 mg) vs. placebo on pain relief induced by electrical stimulation.

Methods

(a) Subjects

Subjects consisted of 12 patients with chronic pain, 1 of whom was studied twice. The patients met the following criteria: (1) 30% or greater reduction in pain with use of electrical stimulation, (2) no intake of narcotics for at least 3 days before the study, and (3) electrical stimulation relieved pain for at least 30 days successfully. The patients were allowed to manipulate the stimulus frequency to effect maximum pain relief and all chose frequencies between 10 and 100 Hz. There were 4 male and 9 female subjects, and age ranged from 14 to 62 years old. Three of the subjects had cervical spondylosis, 9 had lumbar spondylosis (5 of whom were studied in the epidural group), and one had knee pain thought to be secondary to trauma. Five of these patients received epidural stimulation, and the rest received transcutaneous stimulation.

(b) Methods for measurement of pain

Pain was measured by the technique of magnitude estimation [2,23,24]. The magnitude estimation task allowed construction of a ratio scale so that percentage change in pain could be derived.

The subjects were instructed as follows:

> Decide on a number which you will assign to your current level of pain. If your pain doubles, then your rating should double. For example, if you call your pain right now '100,' and the pain doubles, then you would call it '200.' If the pain becomes half as much as it was originally then it would be called '50.' No pain is '0.' So that you understand this better, a simple demonstration will be performed.

Understanding of the task was assured by having the subject rate repeated pressure

stimulation applied to the skin. Subjects were told that injection of the test substance might either make pain worse or better, or have no effect.

(c) Procedure

At the time the testing session began, stimulators were in operation for at least 45 min. Subjects were instructed in the techniques of pain measurement, and chose a modulus to represent the level of pain before the injection. Subjects were also asked to estimate the level of pain immediately prior to application of the electrical stimulation.

The order of delivery of the test substance (saline or naloxone) was determined in a randomized manner. The substance was administered double blind as an intravenous bolus. Subjects were observed for signs of narcotic withdrawal and none were observed. The dose of naloxone was as follows: 5 subjects received 0.4 mg, 1 subject received 0.8 mg, 5 subjects received 1.6 mg, and 2 subjects received 10 mg. Ratings of pain were obtained at 2, 5, 10, and 15 min after injection. After a minimum of 48 h had elapsed, the procedure was repeated and subjects were given the alternate agent (naloxone or placebo).

TABLE I

RATING OF PAIN INTENSITY BEFORE AND AFTER INJECTION OF NALOXONE AND PLACEBO IN PATIENTS RECEIVING TRANSCUTANEOUS OR EPIDURAL ELECTRICAL STIMULATION

	Patient	Dose of naloxone (mg)	Pain intensity before electrical stimulation	Pain intensity after injection [a]	
				Placebo [b]	Naloxone
Transcutaneous	EH	0.4	2.5	0.87	1.03
	NP	0.4	2.0	1.00	0.77
	CD	0.4	1.6	0.5	0.5
	PB	0.4	1.5	1.0	0.5
	CZ	1.6	2.7	1.67	2.67
	NM	1.6	2.0	0.77	0.77
	DD	1.6	2.0	1.07	1.00
	NB	10.0	1.8	0.67	0.43
	CD	10.0	3.0	0.5	1.0
Epidural	MN	0.4	4.5	1.33	1.27
	JW	0.8	1.8	1.03	0.8
	JH	1.6	2.0	0.6	1.0
	DH	1.6	1.6	0.87	1.1
Mean	–	–	–	0.93	0.97
S.D.	–	–	–	0.31	0.53
S.E.	–	–	–	0.08	0.14

[a] Values are normalized ratings of pain relative to pain level during electrical stimulation and prior to injection of placebo or naloxone.

[b] The naloxone and saline groups failed to differ either overall ($t = 0.40$) or separately for the TNS ($t = 0.47$) or the epidural group ($t = 0.09$).

Results

Subjective ratings of pain were normalized by dividing each rating by the modulus (the arbitrary number selected by the subject to correspond to the level of pain immediately prior to injection). The results at 2, 5, 10, and 15 min post injection were similar for a given subject. The results at 5, 10 and 15 min were averaged for each subject and these values are shown in Table I separately for the TNS and epidural stimulation groups. The pain relief induced by stimulation prior to injection of the test substance, as well as the dose of naloxone are also listed. The effect of naloxone was no different than that of saline. For each subject the naloxone and saline effects were compared and the results analyzed by doing a matched paired t test. The naloxone and saline groups failed to differ either overall ($t = 0.40$) or separately for the TNS ($t = 0.47$) and epidural group ($t = 0.09$).

Considering the saline and naloxone groups separately there was a $7 \pm 8\%$ (S.E.M.) reduction in pain for the saline group and $3 \pm 14\%$ reduction in pain for the naloxone group which in either case was not significantly different than 0. Thus in this group of patients there was little or no overall placebo response after saline or naloxone injection.

Various doses of naloxone were administered and the dose for each subject is indicated in Table I. Though the numbers for each group were too small to draw conclusions a graded response in relation to the dose of naloxone was not apparent.

Discussion

Naloxone did not alter the pain relief induced by electrical stimulation. This result suggests that the therapeutic effect of electrical stimulation does not result from activation of the opiate-related pain modulating system.

The results reported here are in agreement with a similar study by Abrams et al. [1], in which naloxone in doses of 0.4–1.2 mg was used. Our study adds to this previous work by determining the effects of higher doses of naloxone (1.6–10 mg) and also by showing that naloxone fails to reverse pain relief induced by spinal cord electrical stimulation.

It might be argued that the dose of naloxone used in this study (as high as 10 mg) was insufficient to block binding of endogenous opiates at synaptic receptor sites. This seems an unlikely possibility in that naloxone even in small doses (0.4 mg) fully reverses the analgesia produced by potent doses of clinically useful narcotics [27]. If the binding characteristics of the endogenous opiates met-enkephalin and leu-enkephalin, are at all similar to that of narcotics then certainly a 10 mg dose of naloxone should be more than sufficient.

The parameters of stimulation used in this study were varied by each individual patient to maximize pain relief. The stimulation itself was not painful. The frequency of stimulation ranged from 10 to 100 Hz. Other investigators have used other kinds of electrical stimulation and have reported that naloxone partially reverses the pain relief [7,18,22]. Sjölund and Eriksson [22] purported to show that naloxone did not

reverse the pain relief induced by TNS delivered continuously at a frequency of 100 Hz whereas, naloxone did partially reverse pain relief induced by pulsed (2 Hz), high intensity, high frequency (100 Hz) TNS. However, there are a number of problems with the experiment. First, no statistical analysis was provided. Also, subjects were preselected for having an inhibition of pain relief by naloxone, the rationale for which is not clear. Furthermore, it is not known if the subjects were opiate naive. Finally, patients were given saline and naloxone in a double-blind manner at 30 min intervals, in disregard of the observation that the clinical effects of naloxone appear to last for at least 1–4 h [13]. In light of this latter point in particular, it is not clear how to interpret the results of the experiment.

Chapman and Benedetti [7] reported that the analgesia induced by transcutaneous electrical stimulation of the ipsilateral cheek in treatment of acute dental pain was partially reversed by 0.4 mg of naloxone. However, the effects on pain of naloxone by itself prior to stimulation were not assessed. The omission of this control is particularly noteworthy in light of recent work of Gracely et al. [9] who showed that acute pain in patients undergoing dental procedures was increased by naloxone. It is likely, therefore, that the effect observed by Chapman and Benedetti resulted from enhancement of pain by naloxone independent of any reversal effect on pain relief brought about by electrical stimulation.

The mechanisms by which TNS and spinal cord stimulation relieve pain remains in question. Evidence has accumulated in animal experiments that stimulation of multiple areas throughout the central nervous system affects transmission of nociceptive-specific and other sensory pathways, independent of enkephalinergic receptors [6,8,10]. It is therefore possible that electrical stimulation somehow activates one or several of these areas and thereby affects pain perception without activation of opiate-related pathways. In the case of TNS it is also possible that peripheral nervous system factors may play a role as has been suggested by certain authors [3–5,12].

Naloxone in comparison to placebo in our group of patients had no effect on the ongoing level of chronic pain. These data suggest that the alleged opiate-related endogenous pain control system does not modulate the intensity of chronic pain. This result is in agreement with a previous study by Lindblom and Tegner [14] but contrasts with the results noted by Gracely et al. [9] in patients with acute pain. It is possible that chronic pain, as distinguished from acute pain, is associated with diminished levels of endorphins, changes in the number of opiate receptors, or opiate receptor binding affinity. Chronic pain might be associated with increases in inactive opiate receptors, or increases in enkephalin-degrading peptidases. Furthermore, chronic pain patients may have compensatory changes in (1) a 'second messenger' or (2) alternate neuronal systems concerned with pain. Finally, it is possible that an opiate-related endogenous pain control system is not involved in modulating pain in patients with chronic pain.

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