Summary

Ten patients with organic nerve injury causing chronic neuropathic pain were tested for the effects of intravenous lidocaine versus saline upon psychophysical somatosensory variables. The variables assessed were the subjective magnitude of pain, area of mechanical hyperalgesia and presence and magnitude of thermal heat/cold hyperalgesia.

The study methods applied to evaluate these conditions were the conventional testing of somatosensory submodalities with area mapping and the subjective magnitude estimation of spontaneous pain. It was found that spontaneous pain and mechanical hyperalgesia were consistently improved, transiently, by intravenous administration of lidocaine in all 10 patients; areas of hyperalgesia which extended beyond the territory of the nerve also improved transiently. Spontaneous pain and mechanical hyperalgesia, but not hypoesthesia, were transiently improved by injection of saline in only 1 of the 10 patients. This outcome is probably due to a placebo effect. This improvement is in keeping with the inhibition of anomalous neural impulses which can be generated anywhere along the sensory channels responsible for generating spontaneous pain and hyperalgesia.

Thus, intravenous lidocaine is proposed as a diagnostic aid in the examination of patients complaining of complex sensory disorders associated with nerve injury. The transient pain relief may allow a fuller identification of the area of sensory loss.

Key words: Chronic neuropathic pain; Lidocaine; Sensory disorder

Introduction

Patients affected by peripheral nerve or root lesions sometimes report spontaneous pain together with mechanical and thermal hyperalgesia and sensory loss (Ochoa et al. 1985). This association of positive and negative symptoms may, in some cases, be referred to a deep structure or to a cutaneous territory not matching the classical anatomical distribution of roots, plexuses or nerves. Thus the clinical presentation of such symptoms is complex and may not be recognized as organic or, if it is, the affected peripheral nerve may be difficult to identify. The aim of the present study is to make the clinical picture simpler by first inducing a pain-free state, if possible, in patients affected by neuralgia and complex sensory disorders.

The drug selected to induce this temporary analgesia was lidocaine. It was selected on the basis of its reported analgesic action on painful neuralgia, at doses inducing no sedation and no important side effects (Boas et al. 1982). Its intravenous administration caused a relatively pain-free state of rapid onset and short duration. Due to previous clinical psychophysical studies (Nathan 1960; Hodge and King 1976; Lindblom and Meyerson 1976) some modifications and improvement of sensation following pain relief in neuralgia could be expected. Therefore, clinical sensory testing was performed to evaluate possible modifications of the sensory function after lidocaine injection. Furthermore, the site of the lidocaine action, its mechanism and possible pathophysiological interactions between spon-
taneous pain and the disorder of other sensory modalities, were also explored.

Subjects

The study was proposed to patients affected by pain and sensory disorder, following lesions of the peripheral nervous system, and under treatment at the Pain Clinic. They were given exhaustive information on the purpose and methods of the study and volunteers were invited. Ten patients (7 females and 3 males), all with a normal electrocardiogram (ECG) and cardiac function and without demonstrable lesions of the central nervous system (CNS), were selected.

(1) A man aged fifty-five had complained of pain deep in the right abdomen for several years. After gallbladder surgery the original pain was slightly reduced, but a new pain appeared. The patient described the new pain as “being in the skin – touching the skin is unpleasant and there is a numb feeling”. On examination there was a 3-cm-long surgical scar on the upper right abdomen; surrounding the surgical scar, in an area 10 cm in diameter, there was mild hypoesthesia to all sensory modalities and allodynia (Lindblom et al. 1986) to mechanical dynamic stimulation. At the medial aspect of the scar there was a painful Tinel sign (Tinel 1915).

(2) A woman aged sixteen had swelling of the forearms, hands and fingers associated with pain in the same areas and numbness of the 4th and 5th fingers of the right hand. She was diagnosed as having a thoracic outlet syndrome and underwent surgical scalenectomy on the right side. After surgery she reported improvement in the swelling of the right arm and hand, but the pain in this limb was unchanged and the 4th and 5th fingers were still numb. Moreover, after surgery, she complained of a new pain localized in the neck and upper part of the chest on the right side. Clinical examination revealed a 2-cm-long surgical scar along the right clavicle. There was mild hypoesthesia to all sensory modalities on both sides of the 4th and 5th fingers and along the distal forearm on the ulnar side. In the lower part of the neck and upper part of the right chest she had allodynia to light touch and decreased pinprick, cold and warm perception.

(3) A woman aged thirty-eight, after surgery for a partial mastectomy, complained of pain in the right arm, shoulder and upper part of the right chest and occasional sudden whitening and cooling of all fingers in the right hand. Clinical examination revealed a 3-cm-long surgical scar along the inferior lower quadrant of her right breast. A painful Tinel sign was present on the chest near the scar. Sensory examination confirmed hypoesthesia to all modalities in the area of referred pain. Her right hand was often colder than the left.

(4) A woman aged fifty-one complained of unbearable continuous pain in the left shoulder, chest, axilla and arm after partial mastectomy. She had allodynia to static mechanical and cold stimulations. On examination she had a surgical scar about 6 cm long, extending from the left side of the chest at mid-thoracic level to the inferior external quadrant of her right breast. There was a painful Tinel sign close to the area of the surgical scar. Her left hand was colder than the right and she had reduced sensation to light tactile, cold and warm stimuli in the painful area. Despite her hypalgesia to mechanical stimuli she had hyperalgesia to pinpricking.

(5) A woman aged sixty-seven had had a complete mastectomy in 1979 and has reported pain in the shoulder, arm and chest on the left side since awakening from the anesthesia. Since then the pain has remained confined to the same area but has increased in intensity. She had an extensive surgical scar on the left side of the chest and along the scar there were two small areas sensitive to tapping. From one area she also felt an electrical sensation which spread when it was touched. The area of maximal pain was also hypalgesic to light tactile, pinprick, cold and warm stimuli.

(6) A woman aged forty-seven had undergone saphenous vein stripping on the right leg under spinal anesthesia; at the end of the surgical procedure she felt a sudden intense pain along the medial aspect of her right leg. Two years later the pain was unchanged; it increased with warming and light mechanical repetitive stimuli like the blowing of the wind on her leg. On examination she had two small surgical scars on her right leg, one just below the knee and one above the ankle. She had lost all sensation in a cutaneous territory which included, but was larger than, the right saphenous nerve; furthermore the numbness extended to the foot. She had allodynia to touch on the medial side of the right ankle and a painful Tinel sign on the medial side of her right knee. In this location surgical exposure revealed a neuroma in continuity, originating from branches of the saphenous nerve. However, removal of the neuroma did not improve her pain. She obtained partial pain relief by dorsal column stimulation.

(7) A man aged sixty-three (Fig. 1 a, b) complained of pain in the right shoulder, axilla and chest. The pain had appeared over a period of time 22 months earlier. He had had a comprehensive neurological evaluation including electromyographic (EMG) examination of the upper arm and computerized tomography (CT scan) of the cervical spine 1 month prior to our evaluation. All these tests were normal, as were the same tests which we repeated. The only abnormality we found was a
mild sensory impairment for all sensory modalities in the painful area. After the lidocaine study it was possible to identify the area of hypoesthesia corresponding to the cutaneous territory of the right intercosto-brachial nerve. This finding led to a radiological study of the lower brachial plexus and the diagnosis of a Pancoast's syndrome.

(8) A man aged thirty-four had undergone an 8th left cervical preganglionic radiculotomy 4 years earlier to treat a neurinoma compressing the spinal cord. He complained of intense pain in the whole upper left limb; this pain had appeared after awakening from anesthesia. On clinical examination he had complete motor and sensory loss in the left 8th cervical root territory. He also had allodynia to mechanical stimulation in the distal cutaneous territory of the left 8th cervical root.

(9) A woman aged sixty-three suffering from diabetes reported the sudden onset of intense pain and paresthesiae along the lateral aspect of the right leg, dorsum of the foot and first toe. A clinical and EMG examination documented signs of a right 5th lumbar root lesion. A CT scan and magnetic resonance imaging (MRI) of the lumbar spine were normal.

(10) A woman aged fifty-seven had had surgery for a coronary bypass, performed with the left saphenous vein as graft, 5 years earlier. She awakened from the anesthesia complaining of severe deep and superficial pains in the left knee. On sensory examination she reported pain and sensory loss in the medial and lower aspect of the left knee and upper third of the leg. She also had allodynia to light mechanical and to warm stimuli in the affected area and a painful Tinel sign on the medial side of the knee.

Material and methods

All patients underwent a preliminary comprehensive cardiological and general neurological evaluation which included a clinical sensory examination.

The first step of the study was an intravenous infusion of a 5% dextrose solution. A basal estimation of spontaneous pain was recorded on a visual analogue scale (VAS) (Scott and Huskisson 1976). Thereafter, injections of lidocaine or saline were given through the intravenous line. At 5, 15 and 35 min further VAS estimations were made. A statistical analysis (t test) of all the VAS values for each time group of the lidocaine and saline observations was made. The patients were advised that the test performed was to identify a drug which could act on pain; they were also informed that the
injection could increase, decrease or leave the pain unchanged. Both patients and observers were blind to the injections. The presence of hyperalgesia to pinprick and allodynia to mechanical, warm and cold stimuli was clinically assessed. The areas of sensory loss for warm, cold and touch were identified. Borders of the area were drawn on the skin with a dermographic marker and photographed. The tested area was blocked from the patients' view so they were not able to observe the precise delineation at the time of the drawing. Pinprick was tested with a hypodermic needle and mechanosensitivity, dynamic and static, was tested with cotton wool. Cold and warm were tested using Lindblom rollers (Lindblom 1985) kept in ice or in a warm bath at 40°C. The outline of the area of sensory loss to cold sensation was left on the skin and cold perception was retested after intravenous injection of lidocaine or saline. This sensory modality was selected for mapping during the test as all the patients perceived the borders between normal and decreased perception to cold better than when the other sensory modalities were used. Each test was repeated at least twice.

The injection of lidocaine was 1.5 mg/kg (20 mg/ml). The dose of the saline injection was the same as each subject's lidocaine injection; injection time was 60 sec. ECG, pulse and blood pressure were constantly monitored during the study. The temperature of the room was kept at 24°C and noise and variation of luminance were avoided. Two of the patients (nos. 4 and 6) who had a painful Tinel sign were also given a lidocaine injection directly into the mechanosensitive area. The dose given was equal to the intravenous one.

Results

After all injections, the ECG, pulse rate and blood pressure remained stable. The intravenous injection of lidocaine produced an immediate lightheadedness and dizziness in 4 patients, a condition which lasted for less than 3 min. All patients experienced pain relief which appeared in less than 1 min and lasted for at least 15–20 min; in 1 patient it lasted 35 min. In patients who had a painful Tinel sign (nos. 1, 3, 4, 5, 6, 10) pain to tapping disappeared for as long as the disappearance of spontaneous pain, as did allodynia to cold and mechanical stimuli (reported by nos. 1, 2, 4, 6, 8, 10). At the time of the test none of the patients considered the intensity of the pain unbearable. All patients reported significant (P < 0.001, t test) pain relief, VAS estimation, at 5 and 15 min after the lidocaine injection (Fig. 2). Thirty-five minutes after injection all patients reported the reappearance of pain of the same quality and intensity as before. The VAS estimation of intensity was not significantly modified from the baseline values recorded before the test.

Before lidocaine injection the patients reported pain and sensation impairment in broad superficial areas of the body which did not match the expected distribution of the supposed damaged peripheral nerve; after this injection a shrinkage of the area of hypesthesia was observed. One patient proved the exception; this was patient no. 8 in whom the area of sensory loss, initially matching the territory of the amputated cervical root, did not change after injection of lidocaine. Injection of saline modified the VAS estimation of pain only in patient no. 5; in the other patients it had no effect (Fig. 3). The territory of sensory loss did not change after saline injection in any of the patients. In the 2 patients who had local injections of lidocaine in the supposed neuroma site (Tinel-positive area), pain induced by tapping was abolished, but the spontaneous pain remained almost unchanged. Injection of saline in the neuroma increased pain in patient no. 4 and did not modify it in patient no. 6.

Discussion

Our observations indicate that intravenous lidocaine modifies pain sensation in patients with painful sensory disorders of neurogenic origin. These modifications include a reduction of spontaneous pain and the disappearance of evoked pain, together with improved sensory function. The modifications are dynamic since
they are rapidly induced by the drug and reverse with the fading of its effect. Furthermore, effects are obtained with low doses of the drug.

These results are based exclusively on a subjective estimation of pain and psychophysical testing. All our patients had a normal past psychiatric history, thus it was considered that they were affected by only organic diseases. The patients consistently described their symptoms and all had lesions of the peripheral nervous system which could cause their pain and sensory disorder. The study was carried out in a double-blind randomized condition, the patients being unable to see the sensory testing and drawing on the skin. None of the patients reported improvement of sensory function after saline injection and only one reported a mild reduction of spontaneous and evoked pain. This placebo-responding patient may represent an example of how the effects of lidocaine differ from placebo. It is unlikely that lidocaine induced a placebo effect stronger than saline because only 4 of the 10 patients reported a transitory lightheadedness with lidocaine; none of the others could tell the difference between the injections.

None of the subjects described in this paper had lesions of the CNS; however, 9 of them reported hypoesthesia and pain spreading outside the territory of the affected peripheral nerve, according to the anatomy described in classic studies (Sherrington 1893; Head and Campbell 1900; Foerster 1933; Keegan and Garrett 1948). Similar cases were reported by Richards (1945) and later by Sunderland (1952). Sunderland's interpretation of the phenomenon was an anatomical abnormality of peripheral nerve fiber distribution (Sunderland 1952). The described sensory disorder can better be explained by a functional reorganization of central sensory pathways following damage of the primary afferents (Devor and Wall 1978; Dykes 1984; Devor 1988). Furthermore, Kirk and Denny-Brown (1970) observed, in the monkey, that the postganglionic sectioning of neighboring roots, followed by their pre-ganglionic sectioning, led to a reduction of the intact root territory, and thus concluded “… the reduction in the size of the isolated root area 3 and 4 days after the second operation … is indicative of a functional rather than an anatomical change” (Kirk and Denny-Brown 1970). Later Hodge and King (1976) observed that modifications in the area of sensory loss could be pharmacologically induced in humans after cervical rhizotomy.

Nathan, Lindblom and Meyerson reported an improvement in sensory perception (Nathan 1960) and threshold (Lindblom and Meyerson 1976) after pain relief in patients. Nathan said “once the pain or paraesthesiae have been taken away the subject can make better use of the fewer remaining fibers. Or in other words, in the presence of local pain, tenderness, or paraesthesiae the accurate perception of stimuli is rendered difficult” (Nathan 1960). Along the same line of thought Lindblom and Verrillo (1979) affirmed “hypoesthesia is usually taken as a sign of denervation through the nerve lesion, however a ‘functional block’ produced by pain may be responsible for the sensory loss.” They defined such sensory disorders as symptoms of central nervous system involvement ‘central signs’, and suggested that sensitized wide dynamic range neurons (WDR) are probably responsible for both the spontaneous pain and the loss of sensory accuracy. The strengthening of synaptic afferents to WDR, as suggested by Devor (1984), could be one of the mechanisms responsible for both hyperalgesia and allodynia, and the supposed action of lidocaine on WDR could be interpreted as an inhibition of such synaptic strengthening.

The analgesic effect of systemic lidocaine on various kinds of pain, and particularly on neurogenic pain, is well documented both experimentally (Wiesenfeld-Hallin and Lindblom 1985; Woolf and Wiesenfeld-Hallin 1985; Chabal et al. 1989) and clinically (Bartlett and Hutaserani 1961; De Jong et al. 1969; Boas et al. 1982; Petersen et al. 1986; Kastrup et al. 1987); however, the mechanism and site of action of the drug remain unclear (Bartlett and Hutaserani 1961; Kastrup et al. 1987; Maciewicz et al. 1988; Chabal et al. 1989).

In our patients it can be postulated that the drug acted on the central nervous system because: the ‘central signs’ diminished, it was effective at a dose (De Jong and Nace 1968; Woolf and Wiesenfeld-Hallin 1985) that does not affect peripheral nerve transmission; and direct injection into peripheral nerves abolished evoked pain and sensory function but did not relieve spontaneous pain.

These considerations certainly need to be supported by stronger scientific evidence. In fact, although central modification of sensory function after peripheral nerve injury is a described phenomenon both experimentally and clinically (Nathan 1960; Kirk and Denny-Brown 1970; Hodge and King 1976; Lindblom and Meyerson 1976), its pathophysiological mechanism is unknown. If the hypothesis of Lindblom and Verrillo (1979) is correct, the complex effects of lidocaine could easily be explained as a direct action on WDR neurons. Furthermore Woolf and Wiesenfeld-Hallin (1985) showed in rats that, while peripheral nerve conduction is maintained, withdrawal reflexes are inhibited by systemic lidocaine, supporting a spinal action of the drug.

Our observation of limited pain relief through a peripheral nerve block has already been described by Nystrom and Hagbarth (1981). These authors showed, through intraneural recording from active neuroma fibers, that spontaneous neural activity was still present, together with spontaneous pain, in spite of a successful block induced by lidocaine on the peripheral evoked activity. Recently Arnèr et al. (1990) reported
that 39 consecutive patients had complete pain relief through a peripheral nerve block; however, they do not exclude the possibility of systemic diffusion and central action of local anesthetics injected peripherally.

As a conclusion to this study and on the basis of former observations on the preferential action of the drug at low plasmatic concentrations in neuralgia (Boas et al. 1982) the use of a small bolus of intravenous lidocaine is proposed as a clinical test. Such a test may implement the assessment of complex painful sensory disorders which could be secondary to neurogenic deafferentation and centralized dysfunction. Moreover, the response to intravenous lidocaine can predict the effects of similarly acting drugs given orally. On the other hand, we believe that care should be taken in evaluating pain relief obtained by peripheral nerve blocking since local anesthetics may spread and act centrally. The present clinical study, in agreement with an earlier one (Arnèr et al. 1990), supports the need for further investigations on the action of lidocaine.

Acknowledgements

Support for this research was provided by Istituto Scientifico H San Raffaele, Milan, and CNR, Italy. Pierre1 SpA kindly provided the lidocaine.

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