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ORIGINAL ARTICLE

Effectivity of Intravenous Lidocaine in Pain of Neuropathic Origin

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ABSTRACT

Background: In order to accomplish the goals of this research project, lidocaine was administered intravenously (IV) to patients who were experiencing neuropathic pain. The researchers had an interest in gaining a deeper understanding of the connections that exist between effect and concentration, as well as graded and quanta1 dose-response.

Study Place: Kulsoom International Hospital Islamabad

Study Duration: 6months (Feb 2021 To July 2021)

Methods and Materials: Fifteen patients received an intravenous dose of lidocaine at a rate of 8.35 milligrams per minute for a total of one hour. During the course of the study, both venous blood samples and visual analog pain scores were collected at regular intervals of ten minutes for duration of sixty minutes. In addition, blood samples were taken in order to determine the concentrations of lidocaine in the serum as well as the amount of water in the serum both at the start of the analgesia as well as when the patient had reached their maximum level of pain relief. In order to determine the levels of lidocaine, a technique known as gas chromatography was performed.

Result: In addition to graded dose-response curves for each participant and the group, a quanta1 dose-response curve was created. Besides graded dose-response curves, this was done. Also done: graded dose-response curves. The dose-response relationship for IV lidocaine showed large pain relief for modest dose changes. Despite moderate dosage increases, this was true. This was when the drug was given. The ED administered 370.0 mg of lidocaine, but the ED administered 415.5 mg (5 min of infusion). Similar to the link between concentration and effect, 0.60 pg/mL of lidocaine significantly reduced pain. It's intriguing that serum lidocaine concentration didn't correlate better with analgesia onset or end than free lidocaine concentration did. Free lidocaine concentration correlated with analgesic effect. Lidocaine concentration in the serum was a stronger predictor of analgesia.

Conclusion: This suggests that IV lidocaine's analgesic mechanism may not follow a concentration-effect connection. The evidence shows this. Intravenous lidocaine is significantly stronger than oral. The analgesic response to intravenous lidocaine is a quick "break in pain" over a narrow dosage and concentration range. This was true independent of lidocaine dose. It doesn't matter how much lidocaine is given.

INTRODUCTION

Patients who are experiencing neuropathic pain as a result of a number of disorders have been given lidocaine intravenously (IV) for a very long period in order to provide them with analgesia. Patients have been receiving this treatment for a very long time . Unfortunately, essential pharmacological interactions, such as dose-response curves, have not yet been exhaustively defined in their totality. This is the case despite significant progress being made in this area. Previous study that was carried out by Boas and colleagues utilized a method that started with a bolus injection of lidocaine at a dose of 2mg/kg, and then continued with a continuous infusion at a rate of 3 mg/min. This was done in order to get the desired results. The analgesic effect started working very immediately, and steady-state blood concentrations were reached in a relatively short amount of time after that. As a consequence of this, it was not possible to ascertain the dose-response relationships or the concentration-effect correlations. In addition, the significance of free lidocaine serum concentrations as opposed to total lidocaine concentrations in relation to the production of analgesia was not explored in this particular investigation. It is generally accepted that the free drug concentration provides a more accurate depiction of the active concentration. The purpose of this research was to determine the relationships between concentration and effect, as well as dose and response, for the clinical use of intravenous lidocaine in the treatment of neuropathic pain states that were brought on by a wide variety of various etiologies. For the purposes of this investigation, the environment in which the intravenous lidocaine was given, as well as the method by which it was given, were designed to be as realistically representative of clinical practice as was humanly possible. It was also investigated whether or not there was a connection between the free vs total serum concentrations of lidocaine and the various stages of analgesia that were experienced by the participants.

METHODS

Patients who were experiencing neuropathy were given the opportunity to take part in this exploratory study, but there was no attempt made to standardize their diagnosis in any way (i.e., central versus peripheral neuralgia, sympathetically maintained pain versus nonsympathetic mechanism, etc.). The participants were selected at random, with neither their gender nor their ages taken into consideration. Patients who entered the trial already suffering from hepatic or renal sickness were not permitted to participate in the investigation. Before participating in the study, every patient had been dealing with neuropathic pain for a period of at least half a year. Before being enrolled in the study, not a single patient had taken oral lidocaine, nor had they received an intravenous infusion of a local anesthetic in the previous six weeks. There was no randomization of the subjects, and they were not blinded in any way. The Human Research Committee of the institution gave its approval to the study, and informed consent was obtained from every patient who participated in the research. A battery of psychometric assessments, including the McGill Pain Questionnaire in its abridged form and the Multidimensional Pain Inventory, was administered to every subject prior to the start of treatment . Only the scales of the Multidimensional Pain Inventory that pertain to activities of daily living were scored in this study . The patient was provided with the McGill Pain Questionnaire in its condensed form once more shortly after the IV infusion was completed. The complete battery of tests was carried out once again one week and then again two weeks after the patient had received the infusion. The patient received intravenous lidocaine in a clean environment, with all of the necessary resuscitative drugs and equipment close at hand. During the operation, intravenous catheters were inserted into the contralateral limbs to allow for the administration of lidocaine and the collection of blood samples. An injection of procaine was given to the patient in order to numb their

pain before to the insertion of a catheter through the skin. Intravenous administration of lidocaine was performed at a rate of 8.35 milligrams per minute (500 mg in 250 mL of normal saline over 60 min). Subjective bioassays using a visual analog scale were used in order to determine the effect that lidocaine had on the amount of neuropathic pain that was felt by the participants. Before beginning the infusion, participants were asked to rate the amount of pain they were experiencing, and then they were queried again at predetermined intervals throughout the duration of the infusion. Prior to the intravenous delivery of lidocaine, a rudimentary neurologic examination was performed on the patient. This exam was repeated every ten minutes while the infusion was taking place and continued until it was finished. As part of the neurologic examination, the patient's alertness, orientation, pupillary size, extraocular muscle function, nystagmus, and VIIIth cranial nerve function were all evaluated. Additionally, the patient's gross motor strength, reflexes, and coordination were also evaluated. It would take roughly two to three minutes to complete the comprehensive exam. The patients were given the instruction to immediately report any subjective responses they experienced as a result of the infusion. These responses could include, but were not limited to, feelings of lightheadedness or circumoral numbness. Before initiating the intravenous infusion, three samples of the patient's blood, each milliliter in volume, were drawn in order to determine the lidocaine concentration. After that, more samples were collected at 10, 20, 30, 40, 50, and 60 minutes after the IV infusion had begun. Until it was time to do the analysis, the samples were stored in tubes that had been heparinized and refrigerated to a temperature of -25 degrees Celsius. When the initial onset of analgesia occurred as well as when complete pain relief was achieved, additional blood samples in the volume of 10 mL were taken in order to evaluate the serum and serum water concentrations of lidocaine. This was done in order to determine the optimal dosage of lidocaine for future use. Following the procedures of letting these samples to coagulate at room temperature and then centrifuging them to produce serum, the samples were stored as indicated above. In order to bring the pH of the serum up to the physiologic level, microliter quantities of either 0.1 M HCI or 0.1 M NaOH were utilized, depending on the circumstance. After this step was completed, serum water was collected by the use of an ultrafiltration technique , and the proportion of lidocaine that was bound to protein was calculated. Gas chromatography was utilized in order to ascertain the levels of lidocaine present in whole blood, serum, and serum water respectively.

RESULT

The findings were expressed as the concentration of lidocaine hydrochloride in micrograms per milliliter of fluid. The variability of the assay was typically lower than 5% over the whole range of concentrations that the samples represented. After graded dose-response curves were created for each patient, a logarithmic regression analysis was performed on both the individual patients and on the total group of patients. This step was undertaken after the graded dose-response curves were created. In order to achieve total analgesia, a quanta1 dose-response curve was developed by plotting the cumulative frequency distribution of responders versus log dosage. This was done in order to construct a quanta1 dose-response curve. Because of this, it was possible to determine the optimal dose needed to create the effect that was wanted. A quadratic regression equation was applied in order to make an estimation of the ED because there were no empirical observations of the ED. In this particular investigation, the dependent variable was defined as the proportion of patients who were successful in obtaining complete pain relief. The amount of lidocaine that was given to the subjects and the square of that amount served as the experiment's independent variables. On a plot that examined the relationship between the amount of lidocaine in the sample and the amount of time that had elapsed, logarithmic regression was utilized. Both individual concentration-effect curves for each patient and group curves that included all of the patients were generated during this study's data collection process When providing interval data, the mean as well as the standard deviation should be reported. A paired Student's t-test was carried out in order to determine whether or not there were significant differences between the group means for the interval data. P values that were less than 0.05 were considered to be statistically significant across the board. Results A total of thirteen people took part in the investigation as part of this study. There was an overall decrease in the amount of pain experienced by ten different patients. At the end of the infusion, the "incomplete" responders reported a reduction in their baseline pain of 57% (in the case of Patient 2), 39% (in the case of Patient 5), and 60% (in the case of Patient 8). A listing of each patient's age, gender, diagnosis, initial pain score before the infusion, and the dose of lidocaine required for full analgesia may be found . Both the time at which the initial onset of analgesia occurred (15.2 min +5.4) , as well as the predicted matching dose of lidocaine, had a significant amount of interpatient variability (120.0 mg +50.0). A value of 0.43 was determined to represent the coefficient of variation (CV) for these two variables. On the other hand, the amount of time that passed before the patient experienced total analgesia was 40 minutes and 7.2 minutes, and the amount of lidocaine that was projected to be effective was 370.0 milligrams and 20.4 milligrams. The coefficient of variation was extremely low (0.1), indicating that there was very little difference between patients. Both the graded dose-response curve and the concentration-effect curve for the entire group are depicted .However, a significant analgesic effect was not seen either one week or two weeks after the infusion had been administered. The Multidimensional Pain Inventory was utilized in order to determine how the use of analgesics impacted a person's capacity to carry out their day-to-day activities of living as they normally would. There was no obvious effect found on the individual's capacity to engage in activities of daily living either one or two weeks after receiving the injection. One of the patients had vertical nystagmus after the infusion had been going on for twenty minutes (lidocainel, blood = 1.20 pg/mL). In all of the neurologic tests that were performed, not a single one of them turned up any additional abnormalities of any type. In terms of the patients' subjective symptoms, six out of the thirteen patients reported feeling lightheaded at some time throughout the infusion. This feeling lasted for the entire duration of the treatment. During the course of the investigation, the amount of lidocaine that was found in whole blood ranged from 0.95 pg/mL to 3.08 pg/mL. In two of the patients, the sensation of lightheadedness resolved on its own over the course of the treatment. Two patients reported that they felt intoxicated, despite the fact that they looked to be awake and oriented at the time of their interviews. Their lidocaine concentrations in their entire blood were measured at 1.50 and 4.01 pg/mL, respectively. Whole blood lidocaine levels of 2.34 and 4.01 pg/mL were measured for two of the patients, and both of them exhibited symptoms consistent with being somewhat sedated. It was never necessary to adjust the rate of infusion provided to patients due to the patients' subjective reports of suffering toxicity at any stage. This was because there was no need to change the rate of infusion. Discussion In the treatment of neuropathic pain, the analgesic response to intravenous lidocaine is characterized by considerable increases in pain reduction for very little increments in dosage and blood concentration, as the findings of this study effort have shown. This effect was seen in each and every one of the patients who participated in the study.). In the current investigation, the free concentration of lidocaine did not have a greater link with the onset of analgesia or the achievement of complete analgesia than the serum concentration of lidocaine did. This was the case despite the fact that the serum concentration of lidocaine was significantly higher . As a result of this, one is led to conclude that the mechanism of analgesia to which IV lidocaine contributes may not be based on a standard concentration-effect relationship. This is because of the fact that IV lidocaine is administered at higher concentrations. It is essential to

point out that in the past, a lack of link between plasma concentrations and the symptomatic impact of oral mexiletine a lidocaine congener was regarded to be a false-negative finding. This was due to the fact that there was no correlation between the two variables.

Table 1: Patient Demographics and Response to Treatment

Patient	Age: Sex	Diagnosis	Complete analgesia?	complete analgesia (mg)
1	57:M	Intercostal neuralgia	Yes	400.7
2	62:F	Burning dysesthesia (L5)	Yes	376.8
3	40:M	Saphenous neuropathy	No	>498
4	68:F	Burning dysesthesia (L5)	Yes	381.3
5	30:F	Diabetic polyradiculopathy	Yes	452.4
6	59:M	Intercostal neuralgia	Yes	388.9
7	70:M	Phantom foot pain	No	>495
8	29:F	Central pain (Dejerine-Roussy syndrome)	Yes	399.3
9	48:M	Sympathetically maintained pain	No	>500
10	25:F	Diabetic neuropathy	Yes	289.1
11	46:M	Sympathetically maintained pain	Yes	395.1
12	41:F	Diabetic radiculopathy	Yes	395.1
13	55:F	Meralgia paresthetica	Yes	191.6
14	51:M	Central pain (spinal cord injury)	Yes	408.1
15	38:M	Sympathetically maintained pain	No	>500

DISCUSSION

This is something that ought not to be disregarded in any way . Even though free lidocaine concentrations weren't measured, the work of Brose and Cousins suggests that target blood concentrations may be important in the process of achieving analgesia with continuous subcutaneous infusions of lidocaine. Despite the fact that these concentrations were not tested, this is the conclusion that may be drawn. In this experiment, steady-state concentrations were not determined since a fixed-rate infusion was used. As a result, the results were not accurate. This made it possible to determine dose-response relationships and to investigate the interactions between concentration and effect across a broad range of lidocaine concentrations. Nevertheless, the relationship of free drug concentration, which is a more accurate reflection of the active concentration, should have held, regardless of the attainment of steady-state concentrations, as lidocaine concentrations were increasing relatively slowly, particularly at the time of achieving complete analgesia. This is because free drug concentration is a more accurate reflection of the active concentration than the total drug concentration. This is due to the fact that lidocaine concentrations were rising at a relatively slow rate. The half-life of lidocaine is only 1 hours; however, several authors have documented the production of protracted analgesia (days to weeks) with the administration of IV lidocaine. This is despite the fact that the half-life of lidocaine is only 1hours . This study also shows the existence of a pharmacodynamic response that is not traditional to blood or serum concentrations of lidocaine . The generation of prolonged analgesia was one of the topics that was investigated in this particular study, and the short-form McGill Pain Questionnaire was used to do so. In addition to this, the Multidimensional Pain Inventory was used to evaluate whether or not there was an increase in functional activity at the same time. After receiving the infusion, the patient was observed for one and two weeks to see if there were any signs of persistent analgesia or an increase in functional activity. However, neither of these things were seen. In contrast, the study that was carried out by Edwards and his colleagues (2) discovered that one third of patients who had a positive response to intravenous lidocaine experienced pain relief that lasted for longer than one week after the drug had been administered. The reasons for this discrepancy are unclear; however, they may be connected to the fact that this preliminary study examining blood concentrations included a significantly lower number of patients (n = 15) when compared to the larger descriptive study conducted by Edwards et al. , which included a total of 211 participants. In the larger study, Edwards et al that some patients did not experience complete alleviation from their pain after receiving the treatment. It is not known what produces their pain responses that are sometimes described as analgesic. Do you believe that a complete response would have been achieved if a higher dose of lidocaine had been administered? Certainly, the partial analgesic responses cannot be attributed to higher beginning intensities of pain (Table 1) or a preponderance of central or peripheral disorders in these incomplete responders. These factors do not play a role in these patients. These factors do not play a role in the individuals who provided incomplete responses (Table 1). [Because the site of action for intravenous lidocaine is not completely understood, a number of authors have hypothesized that the analgesic mechanism(s) involved are more likely to be central rather than peripheral. We are unable to draw any conclusions regarding the mechanistic site that is most prevalent based on the facts presented here because of the limited total number of patients and the prevalence of patients with a suspected peripheral origin for their pain.] This preliminary inquiry has a potential flaw in that there is no procedure to eliminate people who respond favorably to the placebo. This is something that could be regarded a drawback. Patients who agreed to take part in this study were transported to the Pain Center so that they may receive infusions of lidocaine through their intravenous lines. When it comes to the management of neuropathic pain, this particular therapeutic modality is considered to be a standard strategy. Patients suffering from neuropathic pain would have had intravenous lidocaine supplied to them regardless of any reaction to a placebo infusion that might have been given. Because of this, we came to the conclusion that incorporating placebo infusions in the study was not a prudent option . The findings of this study imply that large increases in analgesic response can be attained for relatively minor increments in dosage when intravenous lidocaine is used for the treatment of neuropathic pain. This is the conclusion drawn from the findings of the study. To put it another way, the dosage does not need to be increased by a significant amount at all. Extremely steep slopes were observed in both the graded dose-response curves (which included the complete group) and the quanta1 dose-response curves (which encompassed the linear component) This term refers to the occurrence of a circumstance in which the reaction is either complete or absent. Similar to how steep the link between concentration and effect was, pain scores showed an abrupt reduction over a range of 0.62 pg/mL of lidocaine . However, there was a link between the serum concentration of lidocaine and both of these outcomes. There was no correlation between the free concentration of lidocaine and the beginning of analgesia or the achievement of complete analgesia. Because of this, the idea that the pharmacodynamic response to intravenous lidocaine is not dependent on a conventional concentration-effect relationship is given more weight. In the future, research should be conducted with a particular emphasis on a number of topics that are of the utmost significance, such as the verification of this hypothesis and the clarification of the

implications of it. According to the findings of this study, the analgesic response to intravenous lidocaine for the treatment of neuropathic pain of varying etiology was best characterized by an abrupt "break in pain" over a narrow dosage and concentration range. This was the case even though the causes of the neuropathic pain were different in each patient. This was the case despite the fact that each patient's neuropathic pain was brought on by a unique combination of factors.

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