

Study Protocol

Title of Project: A Randomized Double Blind Placebo Controlled Crossover Trial of the Use of Subcutaneous Lidocaine Infusion (SCLI) for Chronic Cancer-related Pain.

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Background and Rationale

Pain related to cancer can be controlled by conventional pharmacologic treatment in the majority of cases. However there are circumstances in which our attempts to gain analgesia are thwarted either by therapeutic failure or intolerable side effects. Even when satisfactory analgesia is obtained, the need for daily exposure to medications (particularly opioids) can lead to side effects which can compromise quality of life. The concept of the use of parenteral lidocaine is mechanistically radically different. Here the drug is administered over a relatively short period of time and yet the potential relief extends both beyond the infusion time and the plasma half-life of this agent. An infusion lasting several hours can produce pain relief lasting weeks.

Mechanisms of action

Lidocaine blocks impulses travelling along nerves by inhibiting sodium channels. In high doses, complete neural blockade is seen. At low doses, lidocaine does not cause any change in conduction in normal nerves but prevents pain from being generated in damaged nerves. Lidocaine can also prevent damaged dorsal root ganglia from sprouting. Lidocaine is thought to suppress central sensitization thereby producing a clinically relevant effect which persists well beyond the presence of the drug in the blood ⁽¹⁻⁶⁾.

Animal studies have allowed further investigation of the mechanism(s) of action of lidocaine. Small doses of systemic lidocaine decrease allodynia in the animal paw withdrawal test, and larger doses produce a reduction in allodynia still measurable at 21 days after the infusion, consistent with the human data ⁽⁷⁻¹²⁾.

Human studies

Lidocaine has been found to be safe in multiple controlled clinical trials for neuropathic pain; better than placebo and as effective as other analgesics ⁽¹³⁻¹⁹⁾. Subcutaneous lidocaine levels were measured by Linchitz ⁽²⁰⁾ during long-term lidocaine infusion (26-56 days). The infusion rate varied between 100 and 180 mg/hr and the serum levels varied between 3.03 and 4.67mcg/ml with an average of 3.69 mcg/ml. Another study using a computer-controlled

intravenous infusion was able to demonstrate a relationship between blood-level and both analgesia and side-effects⁽²¹⁾.

Intravenous and subcutaneous lidocaine infusions have been found to be helpful in cancer pain control in descriptive studies⁽²²⁻²⁶⁾ and there have been at least 3 reviews, including a 2007 Cochrane review which conclude that lidocaine is an indispensable part of the armamentarium for treating intractable severe pain, particularly neuropathic pain⁽²⁷⁻³⁰⁾. Though it was made clear that further placebo-controlled testing of lidocaine infusion was required, this treatment modality has been recognised as having the potential to significantly alter clinical practice in the care of cancer patients who suffer from opioid-refractory cancer pain.

There has since been one double-blind randomized placebo-controlled crossover study of 4mg/kg intravenous lidocaine for opioid-refractory pain in cancer patients, which demonstrated a dramatic 75% reduction in pain intensity as compared with 26% for placebo, 82% of patients reporting a more than 50% reduction in pain scores as compared with 16% after placebo, and duration of benefit averaging 9.3 days, with associated reduction in opioid requirements, and no serious side-effects⁽³¹⁾. Though it is reasonable to assume that the subcutaneous route would have the same beneficial effects as a slow intravenous infusion, this has not yet been studied in controlled trials.

The clinical picture of lidocaine toxicity closely follows the blood level: 1-3mcg/ml is therapeutic, and is free of toxicity. This is the level seen in slow lidocaine infusions. Mild toxicity (light-headedness, dizziness, sedation) is seen at 4-6mcg/ml. At this level, stopping the infusion prevents further toxicity.

Cardiovascular Monitoring

Lidocaine infusion is rarely used in the palliative care setting. Informal communication with a variety of institutions suggests that this is because of the belief that cardiac monitoring would be required. When using lidocaine for treatment of cardiac arrhythmias it is usual to have electrocardiographic (ECG) monitoring, however cancer patients with severe intractable pain are often admitted to palliative care units (PCUs) or hospices. Equipment for resuscitation is often not available. The requirement for cardiac monitoring is appropriate if the patient is at high risk for arrhythmias (such as following cardiac arrest), or if the patient is unable to complain of side effects, however cancer patients without cardiac problems would have neither of these concerns.

Two large retrospective reports^(24,25) of lidocaine infusions being used in substantial numbers of American hospitalized hospice patients ("over 100" in one report, and 82 in another), reporting promising effects in uncontrolled

settings. In neither of these reports was electrocardiographic monitoring a part of the treatment protocol, and no significant adverse effects attributed to lidocaine occurred, despite some of the patients in the latter study having known cardiac disease. In the prospective cancer pain study⁽³¹⁾ all patients were monitored with 3-lead ECG during and for 2 hours after their 4mg/kg infusion (2mg/kg bolus, then 2mg/kg over 1 hour), and blood pressure was taken every 10 minutes. No cardiovascular toxicity was observed. Other studies have reported the same lack of toxicity when lidocaine is given in this way to non-cardiac patients⁽³²⁾.

Clinical Experience

The finding that a single bolus of lidocaine could produce an analgesic effect of three weeks or more, has led one of the investigators (SJ) and a colleague to use single bolus lidocaine therapy for chronic, largely non-cancer pain in Kelowna. Intermittent intravenous lidocaine infusions of 5-9mg/kg over 1-2 hours have also been used routinely for severe opioid-resistant cancer pain at the Vancouver Centre by another investigator (PH) for approximately 8 years. In Kelowna we have a considerable body of experience of over 10 years with over 3000 Subcutaneous Lidocaine Infusions (SCLI). Our clinical experience suggested a useful analgesic response in approximately half the patients, lasting from days to several weeks. We did not encounter toxicity-related problems and did not feel that ECG monitoring was required. In our early experience in the Kelowna General Hospital (KGH) non-cancer pain population we converted 60 patients receiving Intravenous Lidocaine Infusion (IVLI) over 1-3 hours, to SCLI over 4-10 hours. We found that these patients experienced pain relief as good as, or better than, that obtained by IVLI. We saw no toxicity. We now use IVLI only for our cancer pain patients and about 10 non-cancer patients who have refused to change the route of administration. SCLI starting with 8-12mg/kg (less in the elderly) at 1.5mg/kg/hr has not been associated with side effects other than some mild somnolence. All patients go home with the infusion and we have had minimal calls because of adverse effects. We believe that SCLI is the appropriate route to investigate for the reasons outlined above i.e. decreased cost, complexity and toxicity. At the KGH Pain Clinic we administer about 15-18 SCLIs weekly and find that most of such patients experience 15-21 days of pain relief following each SCLI.

Despite our positive experience, there are no published studies of SCLI, and access to this treatment in BC is limited to the Kelowna area. We believe that a randomized placebo controlled trial of the use of SCLI in cancer patients with inadequately controlled pain would be of significant value and may lead to improved access to this potentially very useful treatment modality.

Study Objectives

This study's primary objective is to test the hypothesis that a single infusion of subcutaneous lidocaine can cause a clinically useful reduction in cancer pain within 48 hours of infusion and lasting a minimum of 7 days. A clinically useful reduction in pain is defined by either a 2-point reduction (on a 0-10 scale) in the worst pain experienced over a 24-hour period, or a $\geq 30\%$ reduction in 24-hour opioid requirement. We will use a composite endpoint of reduction in pain without increase in 24-hr opioid requirement or no decrease in pain with a $\geq 30\%$ reduction in 24-hour opioid requirement.

The secondary objectives are 1) to determine whether any significant toxicities occur as a result of the infusion. For this study significant toxicity is considered as any adverse event which either leads to the infusion being terminated, or which leads to medical intervention, such as prescribing of another medication or equivalent treatment, 2) to determine the effect of Lidocaine infusion on QOL parameters as measured by the Patient Outcome Scale (POS) Questionnaire and 3) to determine the duration of response to lidocaine infusion.

Eligibility criteria:

- Male or female patients 18 years of age or older
- In or outpatients referred to the BCCA PSMPC Clinics with a diagnosis of cancer
- Subjects must have somatic, visceral or neuropathic pain related to cancer
- Pain intensity, measured by a worst pain score over the last 72 hours of ≥ 4 on a 0-10 numerical rating scale
- Must have tried at least one opioid medication without adequate response or with significant side-effects for at least one week
- For those with neuropathic pain, must have also tried at least one adjuvant analgesic, such as a tricyclic (unless contraindicated) or an anticonvulsant without adequate response or with significant side-effects for at least one week
- Life expectancy of > 3 months
- Must be able to communicate symptoms indicating potential toxicity of Lidocaine
- Must have a competent caregiver in the home overnight after each infusion
- Must be willing to remain within 30 minutes of the Cancer Centre during each infusion

Exclusion criteria:

- Clinically significant cardiac disease, i.e, cardiac failure, atrial fibrillation with slow ventricular rate (< 60), any degree of heart block

New analgesic treatment initiated in time frame which might have effect within one week of study drug.

Hyper or hypokalemia.

Liver failure (bilirubin ≥ 25 $\mu\text{mol/L}$).

Renal failure (eGFR $< 50\%$ of normal)

Uncontrolled hypertension ($> 160/90$).

Hypotension (systolic < 90).

Uncontrolled seizures.

Planned initiation of chemotherapy, radiotherapy or bisphosphonates within 30 days prior to treatment with study drug.

Received an investigational drug within 30 days prior to study.

History of allergy to lidocaine or other topical, local or infusional anesthetics.

Methods

Recruitment

Subjects will be recruited from the BCCA Pain and Symptom Management/ Palliative Care (PSMPC) clinics at 5 sites - Vancouver, Kelowna, Abbotsford, Centre for the North and Fraser Valley. All patients attending BCCA PSMPC clinics complete a detailed pain and symptom and palliative care assessment. This includes worst pain intensity over the last 3 days as well as pain impact on function, and a body map to indicate location of pain. All patients attending the PSMPC clinics at the Vancouver and Kelowna Centres will be screened for eligibility by the research nurse and attending physician and then approached either by the attending physician or the clinic nurse as to whether or not they would like to hear about the study. If they would, the physician or research nurse will give the subject the consent form. The subject will be given the opportunity to thoroughly review and ask any questions they may have. Potential subjects from the Abbotsford and Fraser Valley sites will be approached by a Pain and Symptom Management/Palliative Care Team physician or nurse at those sites and referred to Vancouver for completion of study procedures, including consent and treatment. Once the consent is signed blood will be drawn for creatinine/GFR, bilirubin level, electrolytes if not already done in the 30 days prior to recruitment.

Baseline Visit

The baseline visit will include: documenting of age, gender, weight, history and physical, cancer diagnosis, (PPS), Edmonton Classification System for Cancer Pain (ECS-CP), medication and allergy history, blood pressure, pulse rate and ECG result, and physician assessment of cause(s) of pain(s). Patients will complete BPI, POS questionnaires and will be given a Medication Use Log to record their pain medication use for 3 days prior to their treatment day. Subjects will be introduced to the Brief Pain Inventory (BPI) at this time. This is a widely accepted and validated pain

assessment tool which asks for pain severity over the 24 hours prior to completion, which makes it very suitable for repeated use in assessing response to lidocaine. It takes only a few minutes to complete. The pain assessment on the morning of the infusion will be the baseline point for determination of response in the study, but subjects will need to be familiar with it in order for repeated scoring throughout the study. Introducing the BPI at the baseline visit will allow it to be explained without the time pressure of needing to start the infusion.

At the baseline visit the subjects will be instructed as to discontinuation of their long-acting opioid on the morning of treatment as appropriate for the pharmacokinetics of the particular opioid: For those on Morphine, Oxycodone or Hydromorphone their long-acting dose will be omitted on the morning of the treatment, and the dose divided into three 4-hourly doses of the short-acting preparation of the same drug. In the absence of a response to treatment, the long-acting dose will be re-assessed at the end of the treatment day. If the subject does experience analgesia from the study drug then the dosing of the long-acting opioid will be adjusted as needed according to that response by telephone advice from the study physician.

For those using the Fentanyl patch, without supplemental short-acting opioid equivalent to 25% of their total daily oral morphine equivalent (OME) dose, the patch will be removed at bedtime of the night prior to the treatment, and a short-acting opioid substituted at a dose based on a current equianalgesic table; the choice of opioid being expected to be the subject's prior breakthrough opioid. In the absence of a response to treatment, the Fentanyl patch will be put back on by the end of the treatment day. For patients on methadone, without supplemental short-acting opioid equivalent to 25% of their total daily OME dose, their morning dose will be held and a short-acting opioid will be substituted following the same process as described above for the Fentanyl patch. The second methadone dose of the day will be given if no analgesic response is noted by the end of the infusion, so a maximum of one dose will be missed in the absence of response to the study drug. If the subject does experience analgesia from the study drug then the fentanyl patch or methadone dosing will be adjusted as needed according to that response by telephone advice from the study physician. The same breakthrough dose as per the subject's usual prescription will be available, so if patients derive no pain relief from the treatment they will not have any opioid dose reduction.

Those on the Fentanyl patch or methadone with at least 25% of their total daily OME taken as supplemental short-acting opioid, will continue their patch or oral methadone unchanged, as a response to the lidocaine leading to no need for breakthrough opioid doses would allow a 25%

reduction in OME, thereby protecting the patient from relative opioid over-treatment in the post-infusion period.

Prescriptions required for both treatment days will be provided at the baseline visit so that subjects have adequate supplies of short-acting opioid. The subjects will fill these prescriptions at their regular outside pharmacy. Those subjects not taking a long-acting opioid will not be instructed to make any changes to their opioid dosing prior to the treatments. Subjects will be instructed to bring all their medications to their treatments.

After the baseline visit, subjects will be scheduled for their first treatment within 14 days, and instructions sent to pharmacy accordingly. On the day prior to first treatment the subject will be randomized according to a predetermined schedule held in the dispensing pharmacy in a double-blind fashion to either placebo (D5W) or active drug (10 mg/kg preservative-free lidocaine). Both products will be administered subcutaneously via a Baxter infusor. All infusions will be made up to the same volume with D5W by a licensed pharmacist. The infusors are designed to deliver the whole contents at a constant rate over 5.5 hours, so the actual dose rate will vary depending on the subject's body weight.

Prior to the First Scheduled Treatment:

Subjects will be asked to complete a Medication Use Log for three days prior to the first treatment visit

First Treatment Day

On the day of infusion any long-acting opioid medication will be switched to short-acting as described above, because a dramatic response to lidocaine could theoretically reduce pain such that symptoms of opioid toxicity such as sedation could arise if the opioid dose was large. If this does occur the short-acting opioid dose can be reduced. It should be noted that this problem has only been seen in in-patients on high dose opioids and has not been observed in our experience with intravenous lidocaine infusions in ambulatory patients.

Subjects will be met by the study nurse who will complete the Day 1 assessment, including the Brief Pain Inventory, POS and Medication Use Log and a Holter monitor will be attached by a cardiology technician. The preferred location of insertion of the subcutaneous catheter (usually the abdomen) will be injected with 1ml of 1% lidocaine subcutaneously at least 2 minutes before insertion of the subcutaneous catheter in order both that the catheter insertion will be painless, and also for blinding, as the lidocaine infusion will produce a degree of numbness in the area once the infusion is started, whereas the placebo infusion (D5W) will not. The amount of lidocaine in 1ml of 1% solution is only 10mg, and will not cause

any systemic analgesia. The infusion (lidocaine or D5W placebo) will start between 0900 - 0930hrs.

Subjects will be monitored for pre infusion vital signs and then clinically for the 1st hour, with vital signs (blood pressure, pulse oximetry, pulse rate) measured every 15 minutes, and physician to be contacted if the vital signs fall outside of the defined parameters. The infusor will be inspected every 15 minutes during this first hour to ensure that it appears to be emptying at the expected rate. Adverse events will be documented. After the 1st hour, if stable, subjects will be allowed to leave the clinic with their caregiver but will be required to stay within 30 mins from the cancer centre and to return for infusor inspection and vital signs measuring halfway through the infusion (+/- 30 mins) and again within 1 hour of completion of the infusion (total 5.5 hours). They will be required to have a cell phone (one will be provided if they do not already have one) in order to be able to contact the study nurse/physician if they experience any adverse effects, and be able to return for assessment quickly. A patient lounge area will be available at the cancer centre if the patient wishes to stay in the building. Subjects will be provided with the telephone numbers for the study nurse and the physician. A physician will be at the cancer centre throughout all infusions and in the event of a serious adverse reaction will assess the patient immediately. Subjects and companions will be reimbursed reasonable expenses for lunch and parking at the Cancer Centre if needed.

Regular opioid dosing during the treatment day will be determined by discussion with the study nurse/physician, considering the subjects' pain levels. If the subject is responding sufficiently that sedation could result from relief of pain, the subject will be instructed by the nurse/physician to reduce their regular opioid dose. The magnitude of dose reduction will be individually determined according to pain levels and any sedation experienced.

Blood will be drawn for lidocaine level during the hour before the infusion is completed, and the infusor removed once empty (approximately 5.5 hours post)End of infusion outcomes, including BPI, POS, Medication Use Log and Adverse Events Log, vital signs will be collected and the patient will resume their normal or reduced dose of opioid at the time of their next scheduled dose, reduced as needed.

Subjects will remove their Holter monitor 4 hours after completion of infusion and will return the monitor as instructed according to site, for analysis the following day. The monitor tracings will be reviewed independently. The Holter monitors will be made available from the Cardiology Depts. at Vancouver General Hospital and Kelowna General Hospital, as well as Lifelabs in Prince George.

Subjects will be allowed to use breakthrough pain medications as needed during the study period. These doses will be documented.

Between Visits

Subjects' short-acting opioid consumption will be assessed by telephone after the infusions, and those who respond will re-start their long-acting opioid at a dose determined by their use of short-acting opioid and current pain experience. Those who have not responded will resume their prior long-acting and breakthrough opioid doses as prior to the infusion and have their next treatment within a minimum of 48 hours and maximum of three weeks of the pain returning to baseline... Pain control will be maintained between the infusions by the same opioid consumption as at baseline, including breakthrough as needed, and returning to the subject's prior opioid dosing regimen as soon as any effect of the infusion is perceived to have worn off. Long-acting opioid dosing will only be reduced if the patient feels they have sufficiently improved pain control following an infusion, so there will be no risk of confounding the study results or making pain worse. As noted in the eligibility/exclusion criteria, no new adjuvant analgesic (non-opioid medication) or procedure which may have an analgesic effect will be started or stopped during the study.

At 1000 am on Day 2 and Day 3, the BPI and POS will be completed. If there is a reduction in pain scores, the BPI and POS will continue to be completed on Day 7, 14 and 21 post each infusion, or until the worst pain score on the BPI #3 has returned to baseline. If there is no change, the questionnaires for Day 7 will be completed and the patient will be scheduled for the next follow up visit and treatment within a minimum of 48 hours and maximum of three weeks of the pain returning to baseline. The Medication Use Log is to be completed daily, and the Adverse Events Log completed if an adverse event occurs. Telephone contact will be made at a minimum twice a week until the pain is back to the pre-treatment level by the research nurse or physician and to adjust medications if necessary, and, once pain returned to baseline, once weekly telephone contact will be done til the 2nd treatment visit to review any condition or medication changes. Subjects will also be encouraged to call the physician at any time if they experience any adverse event or to report return to baseline pain score.

Once the worst pain score on the BPI (question #3) has returned to baseline and at least 48 hours have elapsed, the second treatment will be arranged. If there is a response the patient will continue with diaries and questionnaires weekly until the BPI score returns to baseline

Second Treatment Visit

This will be arranged within a minimum of 48 hours and maximum of three weeks of the pain returning to baseline but will be no earlier than 48 hours after the 1st treatment. The baseline weight will be used to determine the dose for the second treatment. At 1000 am on Day 2 and Day 3 post second treatment, the BPI and POS will be completed. If there is a reduction in pain scores, the BPI and POS will continue to be completed on Day 7, 14 and 21 post each infusion, or until the worst pain score on the BPI #3 has returned to baseline, at which time the end of study visit will be arranged within a minimum of 48 hours and a maximum of three weeks of the pain returning to baseline. If there is no change, the questionnaires for Day 7 will be completed and the patient will be scheduled for the end of study visit within a minimum of 48 hours and maximum of three weeks of the pain returning to baseline. The Medication Use Log is to be completed daily, and the Adverse Events Log completed if an adverse event occurs. Telephone contact will be made at a minimum twice a week until the pain is back to the pre-treatment level. Subjects will also be encouraged to call the physician at any time if they experience any adverse event or to report return to baseline pain score.

Final Visit Post Second Infusion (once the worst pain score on the BPI (question #3) has returned to baseline by phone assessment and at least 48 hours or a maximum of three weeks of the pain returning to baseline., At this visit subjects will again complete the Brief Pain Inventory and POS and their Medication Use Log and Adverse Events Log will be reviewed. This will be the end of the study.

Outcome measures:

Primary:

The primary outcomes measure is a binary variable indicating whether lidocaine caused a reduction in cancer pain within 48 hours of infusion and lasting a minimum of 7 days. Lidocaine will be considered to have caused reduction in cancer pain if the subject had either one of the following episodes lasting a minimum of 7 days:

1) A 2-point reduction in severity of pain as assessed by the worst pain score in the last 24 hours (question 3) of the Brief Pain Inventory – Short Form (BPI), compared to the BPI pain score at baseline.

Or:

2) $\geq 30\%$ reduction in 24-hour opioid dose.

The duration of the pain reduction is measured by weekly BPI pain scores.,

Secondary:

- 1) Incidence and severity of adverse events.
- 2) Effect of Lidocaine infusion on QOL parameters as measured by the Patient Outcome Scale (POS) Questionnaire
- 3) Duration of response to lidocaine infusion.

Notes on Outcome Measures

The BPI refers to “worst pain over the last 24 hours” rated between 0 and 10, and a 2 points difference has been determined in multiple studies to be clinically useful. Based on our experience with lidocaine infusions already we know that a response to lidocaine occurs within the first 3 days (actually usually within the first 24 hours), so the daily BPI for the first 3 days will capture whether or not a clinically significant improvement in pain has been achieved.

Because some patients may accept similar levels of pain but reduce their opioid analgesics significantly, with consequent reduction in side-effects, the 30% reduction in analgesic use is also included as indicative of a positive response, to ensure that clinically meaningful benefits are not missed by relying just on the pain scores.

For this study significant toxicity is considered as any adverse event which either leads to the infusion being terminated, or which leads to medical intervention, such as prescribing of another medication or equivalent treatment.

The Patient Outcome Scale (POS) is a QOL tool used routinely in the BCCA PSMPC clinics that addresses physical, psychological, spiritual, practical, psychosocial and emotional concerns and consists of 12 questions in 9 domains: pain, other symptoms, anxiety, information, support, depression, self-worth, wasted time and personal affairs. It was used in the Subcutaneous Lidocaine Feasibility Study.

The duration of response is a descriptive outcome which will be determined by the time to return of the BPI question #3 worst pain in 24 hours pain rating to the same as at that provided on the morning of the infusion, before the infusion started. The duration of benefit will be reported in descriptive terms only and is not an endpoint which will be subject to statistical analysis. This data will be useful for planning subsequent clinical implementation, if the study shows the treatment to be effective.

Schedule of Assessments:

Baseline:

Age, gender, weight, history and physical, cancer diagnosis, Palliative Performance Scale (PPS), and Edmonton Classification System for Cancer Pain (ECS-CP), physician assessment of cause(s) of pain(s), medication and allergy history, blood pressure, pulse rate and ECG, BPI, POS and blood draw if needed.

Prior to the First Scheduled Treatment:

Medication Use Log use for three days prior to the first treatment visit

Day 1 pre each infusion:

BPI, POS, and Medication Use Log, review of Adverse Events Log, vital signs, attach Holter Monitor. The Holter Monitor will record for the duration of each infusion plus 4 hours subsequently, and will be removed by the patient.

During each infusion:

Vital signs will be measured and the infusor will be inspected every 15 minutes for the 1st hour, halfway through the infusion and on completion; the physician will be contacted ASAP if the pulse drops to less than 60 beats per minute or increases to over 100 beats per minute, or the PaO₂ falls below 90%; systolic BP changes by 25mm from pre-treatment BP. Patients will be given a Medication Log and an Adverse Event Log to keep track of any A/Es they experience.

In the hour prior to completion of each infusion (i.e. 4.5 to 5.5 hours since started: no later than between 2.00 and 3.00pm):

A lidocaine blood level will be drawn at the appropriate BCCA laboratory and the subject's vital signs will be taken. Blood will be analysed at the Provincial Toxicology Lab, Vancouver

At the end of each infusion on Day 1:

BPI, POS, Medication Use Log, assessment of toxicity via Adverse Events Log and vital signs.

At each of the intervals where the vital signs are to be taken, the patient's pain score will be assessed and recorded and the infusion site will be assessed to ensure the medication is infusing properly

Daily During Study:

Medication Use Log

Subjects encouraged to call study physician if any concerns
On day 2 and 3 after each Infusion and at least twice a week
or until pain is back to pre-treatment level

Phone call by physician or study nurse to review opioid dosing, adverse events and subject's perception of pain relief

Once pain returned to baseline, once weekly telephone contact will be done til the 2nd treatment visit to review any condition or medication changes

At 10.00am on Day 2 and Day 3 post each infusion, BPI and POS Questionnaires to be completed.

If there is a response to the treatment, the patient will also complete them on Day, 7, 14 and 21, or until the worst pain score on the BPI #3 has returned to baseline . If there is not a response , the BPI and POS Questionnaires will only be required for Day 2, 3 and 7.

Daily

Medication Use Log to be completed and Adverse Events Log if subject experiences symptoms or side-effects

Final Visit: (post 2nd infusion, once the worst pain score on the BPI (question #3) has returned to baseline by phone assessment and minimum 48 hours and a maximum of three weeks since the return to baseline., At the final visit, the ,BPI, POS, Medication Use Log. Adverse Events Log and PPS will be reviewed

A positive response re: pain relief would be defined as any of the following:

- A 2-point reduction in worst pain intensity (#3 on the BPI) within 48 hours of infusion and lasting a minimum of 7 days
- Reduction in analgesic dose by greater or equal to 30% will also be considered an indicator of positive response.

Statistical Considerations: Objective

To compute the power and sample size calculation for the study

Assumptions

- Probability of response in the placebo group = 30%
- There is no carry-over effect, no period effect and no sequence effect in the study

- 0.01% of the patients who did not respond to the lidocaine will respond to the placebo

Null Hypothesis: There is no difference between a single infusion of subcutaneous lidocaine and the placebo

Alternative Hypothesis: A single infusion of subcutaneous lidocaine can cause a reduction in cancer pain

Sample Size / Interim Analysis

A sample size of 40 patients achieves 84% power to detect a 20% difference at a 2.5% significance level using a one-sided McNemar's Test, under the assumptions that 30% of the patients respond to the placebo and 0.01% of the patients who do not respond to the lidocaine will respond to the placebo. This sample size is increased to 50 patients to account for a 20% drop-out rate. This drop-out rate is based on our experience accruing similar patients to studies. The sample size methodology is based on the methodology described in Lachenbruch 1992.

We have demonstrated in the completed Feasibility Study for a Randomized Double Blind Placebo Controlled Crossover Trial of the Use of Subcutaneous Lidocaine Infusion for Chronic Cancer-related Pain that recruitment to such a study is feasible, and that we should expect this study to take 6 months for accrual.

An interim analysis will be carried out after 20 patients have completed the study to allow the trial to be stopped early for demonstrated efficacy. One-sided McNemar's tests will be carried out to test whether a single infusion of subcutaneous lidocaine will cause a reduction in cancer pain for both the interim and final analyses at the p-values of 0.00153 and 0.02347 respectively.

The assumptions of no carry-over effect, no period effect and no sequence effect are made under this study. To check these assumptions, a repeated measures logistic regression model will be fitted to model the probability of pain reduction by treatment type (placebo versus lidocaine), stratifying by the treatment order (first or second treatment). This model accounts for inter-subject variation and within-subject correlation. Score tests will be used to test whether the treatment order estimate equals to zero at a 5% significance level. Rejection of this null hypothesis implies a carry-over effect, period effect and sequence effect.

Safety Considerations:

Any subject with unrecognized allergy to lidocaine would be expected to react within the first hour, and subjects will be closely observed during that

time. Any later side-effect will be able to be addressed promptly by the patient returning to the Cancer Centre for assessment by the nurse and/or physician. There is an emergency response team in the cancer centre during working hours and the study physician will be available for the duration of all infusions.

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