Background: Understanding analgesic pharmacodynamics (PD) in the elderly is key to optimising pain management. Electrically stimulated pain models (ESPM) permit assessment of pain responses in humans. C and Aδ sensory fibres convey pain and respond to low frequency electrical stimulus (5 and 250 Hz, respectively). Human research suggests pain tolerance threshold (PTT) is similar or decreases with age.

Objectives: To determine whether an ESPM is able to detect a difference in PTT in elderly (≥ 75 years) and young (20-40 years) subjects after single dose administration of a placebo and tramadol, a low potency analgesic.

Study Design: Two-cohort, randomized, placebo-controlled, cross-over study.

Methods: A noncompartmental analysis of data at 17 timepoints on 5 Hz and 250 Hz PTT over 24 h.

Results: Young (16) and elderly (13) patients showed similar baseline (E0) PTT between active and placebo both overall and by age group in both frequencies. Net drug effect took into account negative and positive changes from E0. In the elderly, net peak effect on PTT produced by active treatment was significantly greater for both 5 Hz (34%) and 250 Hz (30%). Net area under the 24-h effect-time curve during active treatment was significantly higher for both 5 Hz (163 %) and 250 Hz (175%) stimulations in the elderly. No clinically significant difference was observed in the young.

Limitations: High variability in young subjects, despite efforts to remove outliers limited our ability to draw conclusions in that age group. Generalizability of results obtained from an experimental pain model in volunteers to treatment of elderly patients may be limited.

Conclusion: ESPM can detect a difference for pain tolerance threshold between placebo and tramadol administration in the elderly. Although both 5 Hz and 250 Hz stimulations can detect a difference, the effect size for 5 Hz is larger and seems more precise and reliable, particularly in the elderly.

Key words: Electrical pain model, elderly, geriatric, tramadol, placebo, opioid, area under the effect curve, noncompartmental analysis
Electrically Stimulated Pain Models (ESPMs) can selectively activate different afferents and nervous structures and thereby evoke various pain sensations (1). The reliability of ESPM to detect differences in current perception threshold has recently been established for potent post-operative analgesia (2). However, differences in pain tolerance threshold (PTT) have not been established for a low potency analgesic such as tramadol and not in an elderly study population.

With age peripheral nerves display structural, functional and biochemical changes that primarily affect Aδ and C-fibres. Electrical current stimulation predominantly stimulates C, Aδ and Aβ fibres (3). C and Aδ fibres are high threshold afferents which convey pain and temperature sensations (4) and which respond to low frequency electrical stimulus (e.g., 5 and 250 Hz, respectively) after several milliseconds of continuous depolarization. Previous work has demonstrated the utility of an ESPM at 5 Hz in determining sensory blockade with ropivacaine, a potent local anesthetic, before and after orthopedic surgery (5,6). Furthermore, ESPMs have been used to study analgesic response in a variety of strong opioids including morphine, alfentanil and remifentanil (7-10).

Tramadol is a centrally acting analgesic which demonstrates weak opioid action and modifies descending pain transmission through inhibition of monoamine reuptake. Its analgesic potency is comparable to codeine and dextropropoxyphene (11,12). Although optimizing pain management in the elderly requires a systematic understanding of the pharmacodynamics (PD) of analgesics in the elderly, few studies have been conducted to assess the efficacy and safety of analgesics in this population (13,14). Pharmacokinetics (PK) have been studied but a quantitative tool that would allow PK/PD studies of analgesics vs. subjective assessment is needed. Data from a study utilizing an ESPM to assess differences between young and elderly patients with regard to pain tolerance of transcutaneous electrical stimuli at 250 Hz and 5 Hz are presented here. The objective of these exploratory analyses is to examine whether the ESPM utilized in the study is able to detect a difference in elderly and young patients at 5 Hz and 250 Hz after a single dose of placebo and tramadol.

**Methods**

**Experimental Design**

Drug effect data from a study conducted between January and February 2007 that was intended to evaluate the PK and PD after a single dose of tramadol Contramid ER tablets in elderly (≥ 75 years) and healthy young (18-40 years) volunteers are analyzed and presented here. This 2-cohort, double-blind, randomized, placebo-controlled, cross-over, study used an ESPM to evaluate PTT. Patients received either a single oral dose of 200 mg tramadol contramid OAD controlled-release tablets or identical placebo with a 7-day washout between each period. The study was conducted at a phase 1 facility (MDS Pharma Services, Montreal, Quebec) where patients were confined for 12 hours prior to dosing and for 48 hours afterwards. The sequence of administration was randomized and double blinded. Each patient was assigned a unique identification number and received the corresponding product according to a randomization scheme taking into account age to ensure an equal number of young and elderly patients in each treatment sequence.

Noncompartmental (NCA) and population PK analyses were reported in an earlier publication (15). Data from this study is used here to assess the ability of 5 Hz and 250 Hz transcutaneous electrical stimuli to detect a difference in PTT response between placebo and active treatment in young and elderly patients. A future publication, will present a PK/PD analysis of 0-desmethyltramadol, tramadol’s active metabolite, in young versus elderly patients(16).

Before initiation of the study, the protocol and informed consent for this study were reviewed and approved by 2 independent ethics committees (Comité d’Ethique de la Recherche des Sciences de la Santé, Université de Montréal; and Investigational Review Board, MDS Pharma Services, Montreal). All patients provided their written informed consent prior to the initiation of any study-related procedures. The study was conducted in accordance with the Declaration of Helsinki as well as the Enonce de politique des trois Conseils. The study is registered and details of the protocol are available at clinicaltrials.gov (NCT02329561).

**Patients**

At screening, patients were determined to be healthy based on medical history, physical examination, and evaluation of vital signs, electrocardiogram (ECG), and clinical laboratory data. Patients with an increased risk of seizures or conditions that would affect sensory nerve conduction were excluded as tramadol lowers the seizure threshold. Patients with bowel disease affecting absorption or previous failure of treatment with tramadol or discontinuation of treatment due
Electrically Stimulated Pain Model in the Young vs. Elderly

to adverse events were also excluded. Female patients of childbearing potential had to have negative pregnancy test results at screening and clinic check-in for each study period. Use of all medication (including over-the-counter products) was prohibited for 7 days prior to dosing and during the time of sample collection with 2 exceptions: elderly patients were permitted to continue taking stable doses of chronic medications, other than strong CYP inhibitors/inducers, and female patients were permitted to continue taking hormonal contraception or replacement therapy. Use of any non-excluded concomitant medications was recorded.

Pharmacodynamic Evaluations

PD data were collected using the Neurometer CPT/C (Neurotron, Inc., Baltimore, MD, USA), a fully automated quantitative neuro-diagnostic device that generates constant alternating current sinusoid waveform stimuli at 3 different calibrated frequencies (2000 Hz, 250 Hz and 5 Hz). The device has a possible range from 0.01 milliAmperes (mA) to 10 mA (with an automatic cut-off at 10mA) (17-19). The Neurometer was used to measure PTT which was defined as the maximum amount in mA of the atraumatic neuroselective electrical stimulus that a volunteer was willing to tolerate. We utilized the 250 Hz and 5 Hz stimulus to selectively target, respectively, Aδ and C fibres which convey pain and temperature sensations (4). We did not use the 2000 Hz frequency which stimulates fibres that convey information about touch and pressure since we are testing a pain model (4).

Prior to administering tramadol, we ensured that the patients were familiar with the electrical stimulus procedure, sensations they might experience and how to stop the test if they wished to. On the evening prior to their first dose, patients received training during which they had at least 2 practice procedures.

In order to administer the painful stimulus, 2 1-cm diameter gold-plated surface electrodes linked to the Neurometer were applied to the non-dominant middle finger of each subject during data collection sessions. If cuts, scrapes, contusions, healing wounds or other signs of recent trauma were present on the non-dominant middle finger, the dominant middle finger or non-dominant index finger were used. Electrical stimulations were conducted at the following times: prior to dosing and at 0.33, 0.75, 1.25, 1.75, 2.5, 3.5, 4.5, 5.5, 7, 9, 11, 14, 20, 24 and 30 hours after dosing. Stimulations occurred at least 5 minutes apart and at each time point, the 250 Hz stimulation was applied first. Since the study also collected PK data, the ESPM ratings were conducted prior to PK sampling to avoid influencing the patients’ pain tolerance. Patients were isolated from each other by means of cardboard dividers during data collection periods; noise and other stimuli were kept to a minimum and patients were asked to remain sitting and minimise physical activity during the first 4 hours after administration of tramadol.

Data

All recorded data from the PD evaluations were entered into Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA) and double verified for accuracy. Initial cleaning of the database to remove duplicates and obvious outliers (20) as well as initial establishment of baseline was conducted prior to unblinding of the data. Initially we intended to utilise the value recorded at Time 0 (t0) for baseline. However, visual inspection of the data demonstrated large variability in PTT for both 5 Hz and 250 Hz in the early sampling times and after 24 hours. Therefore, baseline for each period was estimated from the values at t0 and the last recorded value (21). Data after 24 hours were not used for the noncompartmental analysis to ensure that measurable tramadol concentrations would be observed in all patients in the active period thus providing a meaningful comparison with the placebo period.

Analyses

Demographic Analysis

Descriptive statistics including mean, median, standard deviation (SD) and range were calculated for demographic variables using Sigmaplot 11.0 (Systat Software, San Jose, CA).

Pharmacodynamic Analysis

A noncompartmental analysis was conducted to describe the PTT in young and elderly patients during placebo and active administration phases using model 220 of Phoenix WinNonlin version 6.4 software (Certara USA, Inc., Princeton, NJ). The dependent variable, PTT after 5 Hz and 250 Hz stimulations, were provided at time of observation as well as at dosing time. Determination of baseline response (E0) was carried out as described above for each administration phase (active or placebo). For each patient and administration phase (active or placebo), individual area under the effect-time curve (AUEC) between 0 and 24 h was calculated using the linear trapezoidal rule. Both positive and negative fluctuations from the predetermined baseline
response were taken into account during integration and calculated as AUEC_{above} and AUEC_{below} respectively. Summation of all positive and negative AUEC yielded \( \text{AUEC_{net}} \). Maximum effect (\( E_{\text{max}} \)), Time to maximum effect (\( T_{\text{max}} \)), Time above baseline (\( T_{\text{above}} \)), and percentage change from \( E_0 \) to \( E_{\text{max}} \) (\( \Delta E_{\text{max}} \) (%)) were also analyzed.

A linear mixed effect regression model (LMMEM) (Phoenix WinNonlin version 6.4) was utilized to compare the results amongst the age and administration phases to determine whether the ESPM at each stimulus frequency was able to detect a difference between placebo and active administration phases and between those administration phases in young and elderly patients. Least squares means (LSM) point estimates for each parameter and for the difference between the parameters overall, by age and by administration phase were calculated along with standard error of the means, 95% confidence intervals (CI) and \( P \)-values (significant < 0.05). To compare our data with the literature on placebo effect, Cohen’s \( d \) for \( E_{\text{max}} \) was calculated as follows: \( \text{mean } E_{\text{max}} \text{ for active (A) - mean } E_{\text{max}} \text{ for placebo (P)} / \text{Standard Deviation (SD) for pooled; SD pooled was calculated as } \sqrt{\text{SD}_A + \text{SD}_P}/2 \) (22).

Results

Demographics

A total of 20 young and 15 elderly patients were recruited between December 2006 and February 2007 and enrolled in the study. One subject from the elderly group discontinued early in the first period due to personal reasons and was excluded from the analyses. Five patients, 4 from the young group and 1 from the elderly group, were excluded from analyses due to a food effect as described in detail in Skinner Robertson et al’s previous report (15). The analyses presented here included 29 healthy young and elderly patients (Table 1) most of whom were male. In the first cohort of patients, a concealed electrical panel at the research clinic interfered with the functioning of one of the neurostimulation devices by spontaneously shutting it down at times before PTT was reached and thereby delaying data acquisition (less than 10 min). The issue was resolved by the time the second cohort was brought to the clinic for testing. Despite this, there was no statistically significant cohort effect. Patients were followed for safety for 30 days following their last dose in the study.

Comparison of Active and Placebo Period in Patients Regardless of Age Group

Table 2 presents the data observed for effect at \( E_0 \) and \( E_{\text{max}} \) and \( \Delta E_{\text{max}} \) (%). The data are presented for all patients and by age group for active and placebo as the LSM point estimate (mean) and difference of the means with the 95% confidence interval. All point estimates and all differences in the means were within the 95% CI.

Adverse events reported by at least 10% of patients are presented in Table 3.

Both when all patients were considered and when the age groups were compared, there were no differences by administration phase (placebo vs. active) at baseline (\( E_0 \)) for PTT under 5 Hz or 250 Hz stimulation.

Maximum effect and \( \Delta E_{\text{max}} \) (%) were significantly greater in the active versus placebo administration phases for both 5 Hz and 250 Hz stimulations when patients were compared regardless of age group (Table 2).

The results of the noncompartmental analysis of the data by treatment regardless of age group are presented as Whisker plots in Fig. 1. For both 5 Hz and 250 Hz stimulations, the point estimate for the difference between active and placebo means was statistically higher for AUEC_{above} after 5 Hz (511, 95% CI [152-871]; 54% relative increase) and 250 Hz (566, 95% CI [141-
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991); 58% relative increase); for AUECnet after 5 Hz (612, 95% CI [223-1002]; 75% relative increase) and 250 Hz (625, 95% CI [183-1068]; 57% relative increase); and, Timeabove after 5 Hz (4.14 h, 95% CI [1.38-6.90 h]; 22% relative increase) and 250 Hz (3.37 h 95% CI [0.79-5.95h]; 18% relative increase). AUECbelow was significantly lower only for stimulation with 5 Hz.

Comparison of Active and Placebo Phase by Age Group

Mean results by stimulation frequency, administration phase and age group are presented in Table 2. All point estimates and means were within the 95% CI. The SE is lower in the 5 Hz group consistently.

For $E_0$, no differences were observed between placebo and active administration phase in the young and elderly groups under either 5 Hz or 250 Hz stimulation (Table 2). In elderly patients, there was a significantly higher $E_{\text{max}}$ and $\Delta E_{\text{max}}$ during the active administration phase after both 5 Hz and 250 Hz stimulations while a higher $\Delta E_{\text{max}}$ (but not $E_{\text{max}}$) was observed during active administration phase in young patients only after 250 Hz stimulation (Table 2).

Table 3. Most commonly reported adverse events* by age group and active or placebo treatment (15).

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Young (n = 20)</th>
<th>Elderly (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active</td>
<td>Placebo</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (45)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (35)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (25)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2 (10)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

*Adverse events reported by 10% or more of patients

Number and percentage of subjects experiencing the adverse event at least once

Whisker plots of the results of the NCA by stimulation frequency, administration phase and age group are presented in Fig. 2. For the 5 Hz stimulation, the interquartile range (IQR) was greater in young patients, particularly during placebo administration, with the exception of AUECbelow*. For the 250 Hz stimulation, the IQR was greater in young patients than elderly patients, with the exception of AUECnet*.

In young patients, difference in the point estimate between the means for active versus placebo adminis-
Fig. 1. Noncompartmental analysis of PTT response after 5 Hz and 250 Hz stimulations during placebo and active phases in all patients.

PTT: pain tolerance threshold; Hz: hertz; AUEC: area under the effect-time curve; AUEC_{above}; AUEC_{below}; AUEC_{net}; AUEC_{baseline}; AUEC_{net}; Difference between AUEC_{above} and AUEC_{below}.

Note: 25th percentile: boundary of the box closest to zero; mean: dashed line within the box; median: solid line within the box; 75th percentile: boundary of the box farthest from zero; Whiskers (error bars) above and below the box indicate the 90th and 10th percentiles. * Difference of the means statistically significant at P < 0.05

In elderly patients, the point estimate for the difference between the means showed a significantly higher AUEC_{above} (5 Hz: 906 mA, 95% CI [355-1457] relative difference: 118% higher; 250 Hz: 695, 95% CI [44-1347] relative difference: 116% higher or two-fold difference), and AUEC_{net} (5 Hz: 1009 mA, 95% CI [412-1606] relative difference: 163 % higher or almost 3-fold difference; 250 Hz: 734 Hz, 95%
Fig. 2. Noncompartmental analysis of PTT response after 5 Hz and 250 Hz stimulations during placebo and active administration phases in young and elderly patients.

PTT: pain tolerance threshold; Hz: hertz; AUEC: area under the effect-time curve; AUEC\textsubscript{above}: AUEC above baseline value; AUEC\textsubscript{below}: AUEC below baseline value; AUEC\textsubscript{net}: difference between AUEC\textsubscript{above} and AUEC\textsubscript{below}.

Note: 25th percentile: boundary of the box closest to zero; mean: dashed line within the box; median: solid line within the box; 75th percentile: boundary of the box farthest from zero; Whiskers (error bars) above and below the box indicate the 90th and 10th percentiles. * Difference of the means statistically significant at $P < 0.05$.

CI [56-1412] relative difference: 175% higher or almost 3-fold difference) during active administration for both 5 Hz and 250 Hz stimulation. Time\textsubscript{above} was significantly longer only for the 5 Hz stimulation in elderly patients (5 Hz: 5.02 h, 95% CI [0.80-9.26] relative increase: 35% higher).
**Discussion**

The objective of this analysis was to determine whether the ESPM, using the 5 or 250 Hz frequency, was able to capture changes in tolerance to pain intensity using PTT after the administration of a weak opioid in healthy volunteers. During analysis, we also explored whether an age-related difference in response existed between elderly and young patients. This study demonstrated that in elderly patients an ESPM is able to detect a difference in pain tolerance between placebo and active administration phases. Although the difference can be detected for both 5 Hz and 250 Hz, the effect size for 5 Hz is larger and seems more precise and reliable particularly in the elderly.

Although currently open to debate, placebo control in clinical studies is traditionally accepted by the scientific community as the best way to determine the true effect of a medication, based on the premise that there is an underlying effect of placebo and that true medication effect is additive to that of the placebo effect (23). Placebo response is highly variable and depends on many contextual factors (22), this is particularly true in analgesic studies and therefore our study had a placebo control arm.

To ensure that the ESPM was able to detect a difference between active and placebo administration phases, we first examined the data by administration phase (placebo vs. active) without taking into consideration age group and found no significant differences at baseline in PTT between the active and placebo groups with either frequency. In our study, when patients were administered placebo the maximum value for PTT over baseline (ΔE\text{max}) was increased by 81%. Vase et al (22), in their meta-analysis of 21 articles published between 2002 and 2007, found a highly variable magnitude of placebo analgesia with effect size calculated using Cohen’s D ranging from 0.12 to 2.51. The average effect size in studies where placebo is used as a control for medication effect is additive to that of the placebo effect (23). Placebo response is highly variable and depends on many contextual factors (22), this is particularly true in analgesic studies and therefore our study had a placebo control arm.

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When analyses were conducted to take into account the age-related differences in pain tolerance, there were no significant differences in E\text{max} between the age groups with 5 Hz or 250 Hz stimulation. Studies in humans, in general, have drawn inconsistent conclusions with regard to the purported increase in pain perception and the decrease in pain tolerance in the elderly (27). In experimental studies the modality of the painful stimulus seems to play a key role. Pain perception has been shown to decrease with thermally induced pain (28-31) and increase with mechanically induced pain (32,33). Results of published studies of age related changes in pain tolerance using electrical nociceptive stimuli are less clear with one demonstrating a no change (34), 2 demonstrating reduced pain perception. Our exploratory results for pain tolerance showed baseline PTT in elderly showing a trend to be lower than in the young.

Data in the young group failed to demonstrate significance against placebo in any of the analyses except for ΔE\text{max} after 250 Hz stimulation. The clinical significance of this observation is debatable as no difference was observed between active and placebo AUECs in young patients. In our opinion, AUEC is a more robust indicator of the persistence of effect. The point estimates for the mean AUEC\text{above} and AUEC\text{net} were consistently higher in the elderly during active administration phase for both 5 Hz and 250 Hz stimulations. A plausible reason for the fact that only elderly patients showed a consistent and sustained increase in PTT during the active phase was identified in our previous noncompartmental PK analysis where a 30% higher exposure to (+)-0-Desmethyltramadol (+-ODM) was observed in elderly patients (15). As this metabolite is associated with much of the opioid analgesic effect of tramadol, this would roughly correspond to the 30% higher AUEC\text{above} and AUEC\text{net} observed in the elderly compared to young during the active period.
Within the elderly age group, the analyses showed that while both the 5 Hz and 250 Hz ESPM were able to reliably detect a difference between active and placebo administration phases, variability was smaller in the 5 Hz results for the elderly. The greater reliability of the 5 Hz versus the 250 Hz frequency could be particularly relevant in the elderly age group due to changes in the detection, processing and modulation of pain signals related to age. Age related structural and functional impairment in peripheral nerves is most notable in A-δ fibres which are selectively stimulated by the 250 Hz frequency of the Neurometer (19,27,35). Therefore, the 5 Hz data will form the basis for future PK/PD modeling of the data.

Limitations
For most measures, variability is higher in the young group with both the IQR (25% and 75%) and the 10th and 90th percentile error bars usually being greater. This is evident despite efforts to remove outliers during early visual inspection of the data. We speculate that the greater variability is a result of a desire of some of the younger patients to test whether their pain tolerance would be higher than the cut-off limit of the Neurometer apparatus. Including an older young group, such as 30-50 year olds may have reduced the attempts to test the limits of the machine and reduced variability. Since the objective of the ESPM is to demonstrate changes in pain tolerance and not the maximum tolerance of a given individual, anchoring the rating to a visual analog scale to help the patients more consistently determine their PTT could have further reduced variability. Also, elderly patients are more experienced in gauging their pain tolerance.

Finally, one may also question the generalizability of the results obtained from an experimental pain model conducted in volunteers to treatment of elderly patients. However, Olesen et al suggest that experimental pain models offer the opportunity to study pain responses when they are not blurred by other symptoms and where confounding environmental circumstances are as controlled as possible (1). Development of a population PK/PD model that links the ESPM to the concentrations of O-desmethyltramadol will be important future work to determine how age related factors affect the pain response of elderly patients administered tramadol.

Conclusions
After single dose administration to healthy young and elderly patients, ESPM is able to detect a difference between placebo and active administration phases for pain tolerance threshold in the elderly. Although both 5 Hz and 250 Hz can detect a difference, the effect size for 5 Hz is larger and seems more precise and reliable particularly in the elderly.

References
11. Lehmann KA, Kratzenberg U, Schroeder-Bark H, Horrichs-Haermeyer G. Postoperative patient-controlled analgesia with tramadol: Analgesic efficacy and