A PILOT STUDY ASSESSING FENTANYL DOSE REQUIREMENTS IN OPIOID-MAINTAINED INDIVIDUALS

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ABSTRACT

Pain is poorly managed in the opioid-maintained population. This study aimed to find safe and efficacious doses of fentanyl for acute pain management in the opioid-tolerant using experimental pain models and link that with the baseline morphine equivalent daily dose that the patients were taking. 9 patients were enrolled in the study from the Pain Management Unit at the Royal Adelaide Hospital. The study was an open label study using an infusion pump and STANPUMP software to rapidly achieve constant estimated effect compartment fentanyl concentrations. Fentanyl effect site concentrations of 2, 4, 6 and 8 ng/ml were targeted for the first visit and 4, 8, 12 and 16 ng/ml were targeted for patients on the second visit. The infusion involved four infusion steps lasting for 30 minutes each and during each step pharmacodynamic measures were taken that consisted of electroencephalography (EEG), saccadic eye movement test (SEM), pupillometry, morphine-benzedrine group scale (MBG) and cold pain test. The subjective opioid withdrawal scale tests (SOWS) were conducted once the infusion was stopped. Using PK/PD modelling techniques within R, the concentration-effect relationships were described using zero slope, linear, $E_{max}$ and Sigmoid $E_{max}$ models. Our study was not able to demonstrate that the baseline morphine equivalent daily dose predicted suitable doses of fentanyl in acute pain management of the opioid-tolerant. This was probably due to the fact that the study was of insufficient sample size to detect the effect of the covariate. However, we have demonstrated that the study design was safe, informative and suitable for it to be replicated with a larger number of subjects in the future.
DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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3 March 2014
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ABBREVIATIONS

µ  mu
µV microvolt
δ  delta
κ  kappa
5-HT serotonin
AC adenylyl cyclase
AIC Akaike information criteria
Arr3 arrestin 3
BID twice a day
cAMP cyclic adenosine monophosphate
CCK cholecystokinin
CGRP calcitonin gene-related peptide
CIP Compact Integrated Pupillograph
COX cyclooxygenase
CREB cyclic adenosine monophosphate response element-binding protein
C<target> target effect site concentration
CV coefficient of variation
ECG electrocardiogram
EC50 concentration at which half the maximum effect was achieved
EEG electroencephalography
E<max> maximum effect
ERK extracellular signal-regulated kinases
Fz frontal
Cz central
GABA gamma-aminobutyric acid
GCP Good Clinical Practice
GDP: guanosine diphosphate
GPCR: G protein-coupled receptors
GRK: G protein-coupled receptor kinase
GTP: guanosine triphosphate
Ht: height
ICH: International Conference on Harmonisation
IL-1β: interleukin-1β
IL-6: interleukin-6
MBG: Morphine-Benzedrine Group scale
MEDD: morphine-equivalent daily dose
min: minute
mm: millimetre
MOR: μ-opioid receptor
ng/ml: nanograms per millilitre
NK-1: neurokinin-1
NMDA: N-methyl-D-aspartate
NOP: nociceptin/orphanin FQ peptide receptor
OIH: opioid-induced hyperalgesia
Oz: occipital
PARC: Pain and Anaesthesia Research Clinic
PD: pharmacodynamics
PK: pharmacokinetics
Pz: parietal
QD: once a day
RVM: rostral ventral medulla
SEM: saccadic eye movement test
SOWS: subjective opioid withdrawal scale
SSRI: selective serotonin reuptake inhibitor
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<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>TID</td>
<td>three times a day</td>
</tr>
<tr>
<td>TLR</td>
<td>toll-like receptor</td>
</tr>
<tr>
<td>TRPV1</td>
<td>transient receptor potential vanilloid-1</td>
</tr>
<tr>
<td>VPC</td>
<td>visual predictive check</td>
</tr>
<tr>
<td>VLow</td>
<td>very low</td>
</tr>
<tr>
<td>Wt</td>
<td>weight</td>
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