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

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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
EC_{50}	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

TID	three times a day
TLR	toll-like receptor
TRPV1	transient receptor potential vanilloid-1
VPC	visual predictive check
VLow	very low
Wt	weight

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