Transdermal Fentanyl for Pain Management in Cancer Patients

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'The woods are lovely, dark and deep.
But I have promises to keep, and miles to go before I sleep'

Robert Frost (1874-1963)

ॐ भूभुः तत्सवितुर्वरणं भगवादेवस्य धीमहि धीयो यो न प्रचोदयात् ।।
Gayatri Mantra; Rig Veda (10:16:3)

(O thou existence absolute, creator of the three dimensions, we contemplate upon thy
divine light. May he stimulate our intellect and bestow upon us true knowledge)
Abstract

Moderate to severe pain is common among cancer patients and affects 70–80% of patients with advanced cancer. We have the means and the knowledge to relieve pain in many patients, but evidence from surveys and observational studies shows that many patients have troublesome or severe pain and do not get adequate relief. Although opioids remain the only class of drug with the ability to ameliorate severe pain, even in developed countries with access to a range of opioids, opioid formulations and adjuvant therapies, pain management is still a major problem in cancer care. As there is a narrow therapeutic window between pain control and toxicity, there is also substantial potential for side-effects, and, therefore, current practice when starting patients on fentanyl (an opioid class of drug) is to begin with a low dose and titrate the dose up slowly according to pain response and adverse events. As a consequence, it is often several days before a patient’s pain is controlled. Little is known about how factors such as patient demographics, organ function, effect of enzyme inhibitor/inducer, or the drug delivery system itself influence the pharmacokinetics (PK) of fentanyl in cancer patients. Better methods are required to monitor, individualise and improve opioid dosing.

Patients with advanced malignant disease are by definition frail and have poor performance status. There is considerable reluctance on the part of health professionals to subject these individuals to non-essential tests and investigations, including the repeated venepuncture that has been necessary in PK studies to date. The use of saliva rather than plasma has been shown to be an attractive alternative for therapeutic drug monitoring (TDM) because the collection is painless, simple and cheaper than venesection. Relatively little is known about the PK profile of fentanyl in cancer patients. If the PK profile of fentanyl could be studied in a heterogeneous group of cancer patients, this could help in optimising fentanyl dosing through population PK analysis. It would further enhance the safety and efficacy of fentanyl in clinical practice. This study has examined various factors and variables that influence the PK of fentanyl, thus potentially improving the effective management of pain in cancer patients. Additionally, this study has measured drug concentrations in saliva to investigate its potential as a substitute for plasma analysis, for use in future monitoring of therapeutic drug concentrations and in PK studies.
This study was conducted using both analytical and observational methods. Paired saliva and blood samples were taken from in-patients and out-patients with malignant disease at an oncology/palliative care service at the Mater Adults Hospital, Brisbane, Australia. A visual and descriptive scale of 0–4 (0: perfectly adhered to; 4: completely peeled off the skin) developed by the Food and Drug Administration (FDA) for pharmaceutical manufacturing purposes, was used to grade the degree of fentanyl patch adhesion at the time of sampling. A study was conducted to validate this scoring tool for use in clinical practice. At the time of sampling, participants were also asked to identify their pain score on a numerical rating scale of 0–10 (0: no pain; 10: worst pain). Wherever possible, samples were taken at the same time as routine pathology testing.

A sensitive, accurate and precise method of quantifying fentanyl and nor-fentanyl in plasma and saliva samples was developed and validated using high performance liquid chromatography coupled to tandem mass spectrometry (HPLC-MS/MS). Total and free fentanyl and nor-fentanyl concentrations were quantified using the method developed. A protein binding study was also performed, which demonstrated that fentanyl was bound extensively to albumin (ALB) rather than α-1 acid glycoprotein (AAG). The protein binding study determined the free fraction of fentanyl available for the pharmacodynamic (PD) effect. Almost 96% of fentanyl was bound to plasma protein. This study found saliva drug concentrations to far exceed plasma concentrations, suggesting the possibility of a mechanism of active transport into saliva for fentanyl. No correlation between plasma and saliva concentration was observed, and no correlation was found between the concentration of fentanyl and its metabolite, nor-fentanyl, in either of the matrices. However both plasma and saliva mean concentrations of fentanyl were well correlated with dose, with considerable inter-patient variation at each dose. Pain score data revealed that the majority of patients had adequate pain control. A preliminary study to examine several polymorphisms in the ARRB2, BDNF and KCNJ6 genes to determine any association with fentanyl dosing showed no association with any of the genotypes investigated in our population. Population PK analysis was performed using non-linear mixed effects modelling (NONMEM) software. Various cofactors such as pain score, effect of enzyme inhibitor/inducer, liver function, renal clearance and patch adhesion were included in the modelling. Besides a priori included weight, no other patient characteristic could be identified that significantly influenced fentanyl pharmacokinetics in a predictive manner. Patch adhesion, while not identified as a significant covariate is likely to influence fentanyl exposure and should be monitored in
clinical practice. The overall degree of patch adhesion within the study cohort was high (>90% patients scored 0) and potentially the reason why incomplete patch adherence did not significantly impact on overall bioavailability in PK studies.

This study investigated many aspects of the use of transdermal fentanyl in cancer patients. Though no significant factors were found that could change the current dosing practices of fentanyl for pain management in cancer patients, various crucial findings were demonstrated. Data on protein binding, novel extraction methods and adsorption minimizing techniques in analysis should assist, and have an impact on, future clinical research and trials. A useful tool for scoring patch adhesion has been validated and deemed reliable to use in clinical practice. Detection of higher fentanyl concentrations in saliva than plasma, with a good correlation to dose, may allow saliva to be used as an alternative to plasma in PK/PD studies of fentanyl in cancer patients.
Statement of Originality

This work has not previously been submitted for a degree or diploma in any university. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

_____________________________
Sudeep Raj Bista
Acknowledgements

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<tbody>
<tr>
<td>AAG</td>
<td>α-1 acid glycoprotein</td>
</tr>
<tr>
<td>ABC</td>
<td>ATP binding cascade</td>
</tr>
<tr>
<td>ABCB1</td>
<td>ATP-binding cassette B1 gene</td>
</tr>
<tr>
<td>ADME</td>
<td>absorption, distribution, metabolism, excretion</td>
</tr>
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<td>ALB</td>
<td>albumin</td>
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<td>alanine aminotransferase</td>
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<td>APCI</td>
<td>atmospheric pressure chemical ionisation</td>
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<tr>
<td>BBB</td>
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<td>brain-derived neurotrophic factor</td>
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<td>BOV</td>
<td>between occasion variability</td>
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<td>BPI</td>
<td>brief pain inventory</td>
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<td>BSA</td>
<td>body surface area</td>
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<td>between subject variability</td>
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<td>CDB</td>
<td>cotton dental bud</td>
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<td>CE</td>
<td>collision energy</td>
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<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
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<td>clearance</td>
</tr>
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<td>creatinine clearance</td>
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<tr>
<td>CRF</td>
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<tr>
<td>CTCAE</td>
<td>common terminology criteria for adverse events</td>
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<tr>
<td>CV</td>
<td>coefficient of variation</td>
</tr>
<tr>
<td>CXP</td>
<td>collision cell exit potential</td>
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<td>deoxyribonucleic acid</td>
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<td>declustering potential</td>
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<tr>
<td>DRD2</td>
<td>dopamine receptor D2 gene</td>
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<tr>
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<td>dialysis tubing</td>
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<tr>
<td>EDTA</td>
<td>ethylene diamine tetra acetic acid</td>
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<td>Abbreviation</td>
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<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
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<tr>
<td>EP</td>
<td>entrance potential</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionisation</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FOCE</td>
<td>first order conditional estimation</td>
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<td>GC-MS</td>
<td>gas chromatography mass spectrometry</td>
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<tr>
<td>GIRK</td>
<td>G protein-activated inward rectifier potassium channel</td>
</tr>
<tr>
<td>HC</td>
<td>high control</td>
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<td>HPLC-MS/MS</td>
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<td>HREC</td>
<td>human research ethics committee</td>
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<tr>
<td>IS</td>
<td>internal standard</td>
</tr>
<tr>
<td>ka</td>
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</tr>
<tr>
<td>KCNJ6</td>
<td>G protein-activated inward rectifier potassium channel 2 gene</td>
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<tr>
<td>LC</td>
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<tr>
<td>LLOQ</td>
<td>lower limit of quantification</td>
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<tr>
<td>LOQ</td>
<td>limit of quantification</td>
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<td>MAF</td>
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<td>mass balance approach</td>
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<td>MF</td>
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<td>MΩ</td>
<td>megaohm</td>
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<td>MOR</td>
<td>μ opioid receptor</td>
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<td>mobile phase a</td>
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<tr>
<td>MP-B</td>
<td>mobile phase b</td>
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<tr>
<td>MR</td>
<td>metabolic ratio</td>
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<td>multiple reaction monitoring</td>
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<td>MWCO</td>
<td>molecular weight cut off</td>
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<tr>
<td>m/z</td>
<td>mass/charge</td>
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<td>NCBI</td>
<td>National Centre for Biotechnology Information</td>
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<tr>
<td>NONMEM</td>
<td>non-linear mixed effects modelling</td>
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<tr>
<td>OFV</td>
<td>objective function value</td>
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<tr>
<td>OPRM1</td>
<td>opioid receptor, mu 1 gene</td>
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<td>PBS</td>
<td>phosphate buffer solution</td>
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<tr>
<td>PCI</td>
<td>post column infusion</td>
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<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
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<td>p-glycoprotein</td>
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<td>POMC</td>
<td>pro-opiomelanocortin</td>
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<td>QC</td>
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<tr>
<td>SNP</td>
<td>single nucleotide polymorphism</td>
</tr>
<tr>
<td>TDDS</td>
<td>transdermal drug delivery system</td>
</tr>
<tr>
<td>TDM</td>
<td>therapeutic drug monitoring</td>
</tr>
<tr>
<td>UF</td>
<td>ultrafiltration</td>
</tr>
<tr>
<td>ULOQ</td>
<td>upper limit of quantification</td>
</tr>
<tr>
<td>Vd</td>
<td>volume of distribution</td>
</tr>
<tr>
<td>VPC</td>
<td>visual predictive check</td>
</tr>
<tr>
<td>WT</td>
<td>weight</td>
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\[ Cn = \frac{(Cu \times Ws)}{Wu} \quad \text{Eq- 2. 1} \] \hspace{1cm} 22

\[ \% \text{ Loss} = \frac{Ccs - Cds}{Ccs} \times 100 \quad \text{Eq- 3.2} \] \hspace{1cm} 47

\[ \% \text{ Recovery} = 100 - \% \text{ Loss} \quad \text{Eq- 3.3} \] \hspace{1cm} 47

\[ F_b = F_t - F_f \quad \text{Eq- 3.4} \] \hspace{1cm} 48

\[ \% \text{ bound} = \frac{(F_b)}{(F_t)} \times 100 \quad \text{Eq-3.5} \] \hspace{1cm} 48

\[ \% \text{ PPB} = \frac{(C2 - C3) \times V2C2 \times V2 + (C3 \times V3) \times 100}{C3 \times V1} \quad \text{Eq- 3.6} \] \hspace{1cm} 49

\[ \% \text{ Recovery} = \frac{C2 \times V2 + (C3 \times V3)(C1 \times V1) \times 100}{C1 \times V1} \quad \text{Eq- 3.7} \] \hspace{1cm} 49

Unbound fraction \((F_u) = \frac{F_f}{F_t} \quad \text{Eq- 3.8}\) \hspace{1cm} 50

Bound fraction = 1 – \(F_u\) \quad \text{Eq- 3.9} \hspace{1cm} 50

\[ S/P = 1 + 10(pKa - pHs) \times fp/1 + 10(pKa - pHp) \times fs \quad \text{Eq- 5.10} \] \hspace{1cm} 71

\[ c(t) = \frac{\text{Dose}}{V} \times \exp\left(\frac{CL}{V} \times t \right) \quad \text{Eq- 7.1} \] \hspace{1cm} 109

\[ C_{ij} = C_{\text{pred,ij}} + \varepsilon_{ij} \quad \text{Eq- 7.2} \] \hspace{1cm} 110

\[ C_{ij} = C_{\text{pred,ij}} \times \exp^{\varepsilon_{ij}} \quad \text{Eq- 7.3} \] \hspace{1cm} 110

\[ C_{ij} = C_{\text{pred,ij}} \times \exp^{\varepsilon_{ij}} + \varepsilon_{ij} \quad \text{Eq- 7.4} \] \hspace{1cm} 110

\[ \Theta_i = \Theta_{\text{pop}} \times e^{\eta_i} \quad \text{Eq- 7.5} \] \hspace{1cm} 111

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Conferences


Queensland Translating Research into Practice (TRIP) symposium, 25 July, Brisbane, Australia.


**Grants**

