Plasma concentrations of fentanyl with subcutaneous infusion in palliative care patients

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1 Plasma concentrations of fentanyl were measured by g.c. in 20 patients (median age: 75 years and range: 54–86 years; eight females) in palliative care receiving the drug by continuous s.c. infusion (median rate: 1200 µg day⁻¹ and range: 100–5000 µg day⁻¹).

2 The infusion rate was significantly related to the duration of therapy (Spearman ρ = 0.56, P < 0.05). The total steady-state plasma concentrations of fentanyl ranged between 0.1 and 9 ng ml⁻¹, with a median of 1 ng ml⁻¹. The unbound fraction of fentanyl in the plasma ranged from 17.8 to 44.4%, with a median value of 33.6%. Infusion rates and both total and unbound plasma concentrations of fentanyl were correlated (Spearman ρ = 0.92, P < 0.05 in each case). Even with standardization for dosage, there was an eightfold variation in total plasma concentrations and 3.5-fold variation in unbound plasma concentrations of fentanyl.

3 There is considerable inter-patient variability in the pharmacokinetics of fentanyl with s.c. infusion in the palliative care setting, which necessitates careful titration of dosage according to individual clinical response.

Keywords: fentanyl, subcutaneous infusion, plasma concentrations, cancer pharmacokinetics

Introduction

The administration of fluids and drugs by subcutaneous (s.c.) infusion is now commonplace in palliative care [1–3]. This route is particularly useful for analgesics, where constant plasma concentrations of drug and continuous pain relief can be achieved in patients unable to take, or not responding to, oral therapy. Morphine is generally regarded as the opioid of choice for the treatment of cancer pain [4,5], and is frequently administered by the s.c. route. Fentanyl is also now being used in palliative care units, especially when morphine causes persistent distressing adverse effects such as hallucinations, nightmares, nausea and sedation [2,5]. Apart from the s.c. route, the recent introduction of a transdermal formulation for fentanyl has also allowed it to be delivered continuously for up to 72 h in patients with stable pain and with only low to medium opioid requirements [6–8].

While there have been many pharmacokinetic studies of fentanyl following intravenous administration [9,10] and some with transdermal delivery [6–8], there are no published data on plasma concentrations of fentanyl during s.c. therapy in palliative care patients.

Methods

Patient sample and blood collection

In-patients of the Palliative Care Unit, Repatriation General Hospital, Daw Park, Adelaide, who were receiving continuous fentanyl therapy administered as a s.c. infusion, generally through a needle inserted into the chest wall (via a Graseby® portable syringe pump), were recruited consecutively into the study. The study protocol had been approved by the Research and Ethics Committee at Repatriation General Hospital, Daw Park, Adelaide.

Patients in the unit are routinely assessed for pain at least four times daily using visual analogue scales and,

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if necessary, changes to the infusion rate and/or the administration of further bolus doses of fentanyl are made. A venous blood sample (5 to 10 ml) was drawn after at least 24 h of therapy at a constant infusion rate with no bolus doses. Plasma was separated by centrifugation and frozen at -18°C until determination of the fentanyl concentration. Pain control was assessed at the time of blood sampling using a visual analogue scale (a 10 cm line with extremes marked 'no pain' and 'worst possible pain').

The sample of 20 patients consisted of 12 males and 8 females, ranging in age from 54 to 86 years, with a median age of 75 years. The patients had various forms of cancer: genitourinary (7 patients), lung (6), gastrointestinal (4), breast (2) and skin (1). Nine patients had biochemical evidence of hepatic disease (defined as the presence of a serum albumin below 35 g l⁻¹ with abnormal serum concentrations of at least two of: bilirubin, alanine aminotransferase, alkaline phosphatase, or gammaglutamyl transpeptidase). The patients were receiving other drugs in addition to fentanyl (median: 8 drugs; range: 3–15), including antiemetics (18 patients), laxatives (18), corticosteroids (13), benzodiazepines (14), antifungals (6), tricyclic antidepressants (5) and non-steroidal anti-inflammatory agents (5).

**Assay for total and unbound plasma concentrations of fentanyl**

The materials used included pure fentanyl citrate (Janssen-Cilag Pty Ltd; Lane Cove, NSW, Australia), tritiated fentanyl (372 GBq/mmol) with a radiochemical purity of 99.6% (Janssen Research Foundation, Beerse, Belgium) and imipramine hydrochloride (Ciba-Geigy Ltd; Pendle Hill, NSW, Australia). All solvents were of analytical grade.

The method for drug extraction from plasma was very similar to that described by Kowalski et al. [11] with imipramine, rather than dextromoramide, as the internal standard and hexane, rather than heptane, as the extracting solvent. An aliquot (1 µl) of the final organic phase was injected into the gas chromatograph, a Varian 3300 (Varian Pty Ltd; Melbourne, Australia) equipped with a thermionic specific detector. The column used was an 11 m x 0.32 mm internal diameter cross-linked fused-silica ultraperformance capillary column coated with silicone gum (0.52 µm film thickness, HP-1; Hewlett-Packard, Melbourne, Australia) and fitted to a Varian model 1093 septum-equipped programmable injector containing a glass wool packed insert.

The column temperature was held at 80°C for 1 min and then increased at 30°C per min to 300°C. The injector temperature began at 60°C and was increased at 200°C per min to 300°C. The detector was maintained at 300°C. Ultra high-purity helium (Commonwealth Industrial Gases Ltd; Hobart, Australia) was used as the carrier gas to produce a head pressure of 8 p.s.i., nitrogen (Commonwealth Industrial Gases Ltd, Hobart, Australia) as the makeup gas, and air and hydrogen (4.5 ml min⁻¹; Commonwealth

Industrial Gases Ltd, Hobart, Australia) as the detector gases.

Fentanyl and the internal standard (imipramine) were completely separated and had retention times of 7.3 and 5.9 min, respectively. The relationship between the plasma concentration of fentanyl and the peak area ratio (fentanyl/imipramine) was linear (r = 1.0) over the concentration range of 0.1–10 ng ml⁻¹. Using tritiated fentanyl, the analytical recovery was found to be 81.5 ± 3.7% (n = 5) at a plasma concentration of 2.5 ng ml⁻¹. The intra- and inter-day coefficients of variation for the determination of fentanyl at 2.5 ng ml⁻¹ were 5.7% (n = 5) and 4.9% (n = 3), respectively. The sensitivity limit of the assay for measuring fentanyl in plasma was 0.1 ng ml⁻¹ when 2 ml of plasma was used.

Fentanyl binding to plasma proteins was measured by ultrafiltration at 37°C using tritiated fentanyl and the Amicon MPS-1 microparticulation system with YMT membranes (Amicon Division, W. R. Grace & Co.; Danvers, Ma, USA) [12]. The unbound fentanyl concentration was calculated as the product of the total concentration and unbound fraction. Preliminary experiments showed that there was only minimal loss of fentanyl (3.2 ± 2.8%, n = 5 at a concentration of 2.5 ng ml⁻¹) through adsorption to the membrane or to the ultrafiltration device, and that the protein binding of fentanyl was not affected by prior freezing of plasma samples.

**Statistical analyses**

All data were stored and statistically analysed (Statview SE + Graphics®, Abacus Concepts; Palo Alto, CA, USA) on a Macintosh® computer. Relationships between the plasma concentrations of fentanyl and s.c. dosage, and factors such as age, sex, the presence of hepatic dysfunction and pain control were investigated using appropriate non-parametric statistical procedures (Spearman rank correlations and Mann–Whitney U-tests). A P value below 0.05 was considered statistically significant.

**Results**

The total duration of s.c. fentanyl therapy at the time of blood sampling ranged from 1 to 157 days, with a median of 7 days. The median dosage of fentanyl by continuous s.c. infusion was 1200 µg day⁻¹, with a range of 100 to 5000 µg day⁻¹. There were no significant associations between either the sex or age of the patient and the fentanyl dosage. The dosage of fentanyl was significantly related to the duration of s.c. fentanyl therapy (Spearman ρ = 0.56, P < 0.05). The patients with biochemical evidence of liver disease tended to be receiving lower dosages of fentanyl than the other patients (medians: 800 and 1600 µg day⁻¹; Mann–Whitney U = 24.5, z = −1.67, P = 0.09).

The plasma concentrations (assumed steady-state) of fentanyl displayed a marked inter-patient variability.
The median total concentration was 1 ng ml\(^{-1}\), with a range of 0.1–9.0 ng ml\(^{-1}\). The unbound fraction of fentanyl in the plasma ranged from 17.8 to 44.4%, with a median value of 33.6% (n=14). The unbound fraction was not measured in all patients because some plasma volumes were insufficient. The unbound fraction and plasma albumin concentration were moderately related (Spearman \(\rho = -0.50, P=0.07\)). The unbound fentanyl concentration ranged from 0.1 ng ml\(^{-1}\) to 1.9 ng ml\(^{-1}\), with a median value of 0.35 ng ml\(^{-1}\) (n=14). The total and unbound plasma concentrations of fentanyl were strongly correlated (Spearman \(\rho = 0.98, P<0.001\)).

There was also considerable variation in the ratio of total and unbound plasma concentrations of fentanyl divided by the daily dosage; the ratio varied eightfold for the total plasma concentrations and 3.5-fold for the unbound plasma concentrations. A significant correlation existed between fentanyl dosage and both the total plasma concentration and unbound plasma concentration (Spearman \(\rho = 0.92, P<0.05\) in each case; Figure 1).

Modest correlations existed between the duration of fentanyl therapy and the total and unbound fentanyl plasma concentrations (Spearman \(\rho = 0.67, P<0.01, n=19\) and Spearman \(\rho = 0.55, P=0.06, n=13\), respectively).

Visual analogue pain scores ranged from zero to 5.8, with a median score of zero indicating good pain control in the study patients. Significant correlations did not exist between pain control and either the fentanyl dosage, the total plasma concentration or the unbound plasma concentration of fentanyl. Total and unbound plasma concentrations of fentanyl in patients experiencing some degree of pain (n=9) were not significantly different from those in patients free from pain.

Discussion

There was considerable inter-patient variability in s.c. dosage requirements and resulting plasma concentrations of fentanyl in this sample of patients. This variability is not unexpected in the palliative care setting and would reflect differences in factors including the clearance of fentanyl, severity of pain and pharmacodynamic sensitivity to fentanyl.

The s.c. dosages of fentanyl varied 50-fold but were similar to those studied elsewhere for transdermal administration [6–8]. The total fentanyl plasma concentrations also varied greatly (90-fold) and were again similar to those reported with transdermal delivery [6–8].

There was a significant correlation between the s.c. fentanyl dosage and the resulting plasma concentration. The fentanyl dosage and plasma concentration were significantly related to the duration of s.c. fentanyl therapy, reflecting tolerance to the analgesic effect or, perhaps more likely, worsening pain with progress of the disease.

Values for unbound fractions of fentanyl in plasma have been reported to be between 13 and 21% [9]. The unbound fraction of fentanyl in the plasma in this study was consistently higher, ranging from 17.8 to 44.4%. This difference may be explained by the high incidence of hypoalbuminaemia among these palliative care patients (18 of the 20 patients).

Examination of possible relationships between the dose and plasma concentration of fentanyl and the analgesic effect was limited by the finding that pain control was generally excellent, with more than half the patients being pain-free. By waiting for at least 24 h of therapy at a constant infusion rate with no bolus doses, it is not surprising that good pain relief had been attained. Patients still in pain would most likely be having infusion rate changes and/or receiving bolus doses.

The variability in both dosage and plasma concentrations of fentanyl highlights the need for careful dosage individualization and titration based on clinical response.

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References


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