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Research Paper

Prolonged therapy with the anticonvulsant carbamazepine leads to increased plasma clearance of fentanyl

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Abstract

Objectives Fentanyl is a potent analgesic that accounts for an increasing number of overdose deaths in the United States. This study tested whether altered pharmacokinetics plays a pivotal role in the increased fentanyl dose requirements in patients receiving the enzyme-inducing anticonvulsant, carbamazepine.

Methods Neurosurgical patients receiving carbamazepine for >6 weeks ($N = 11$) or no carbamazepine ($N = 6$, controls) received a single bolus dose of fentanyl (200 μg) intravenously. Plasma was collected before and for up to 9 h after the bolus. Fentanyl concentrations were measured using liquid chromatography–mass spectrometry. Pharmacokinetic variables were derived from plasma concentration–time curves best fitted to a two-compartment model.

Key findings Fentanyl clearance was significantly higher in the carbamazepine group compared to controls (mean ± SD: 20.1 ± 6.8 vs 13.2 ± 4.8 ml/min per kg, $P < 0.05$), and area under the plasma concentration curve (AUC) was significantly lower (150 ± 65 vs 233 ± 70 ng/ml × min, $P < 0.02$). Volume of distribution was larger in the carbamazepine group, but the difference was not statistically significant (5.4 ± 3.1 vs 3.6 ± 1.2 l/kg, $P > 0.15$). The terminal elimination half-life did not differ between the two groups.

Conclusions Chronic carbamazepine therapy leads to increased fentanyl clearance and decreased AUC, which may result in decreased duration of therapeutic plasma concentrations of fentanyl and an increased dose requirement. Assuming that carbamazepine does not change fentanyl pharmacodynamics, patients on chronic carbamazepine therapy may require more frequent or higher fentanyl doses to maintain therapeutic plasma concentrations.

Introduction

Fentanyl is a potent opioid agonist with well-established analgesic efficacy and minimal cardiovascular side effects, and is among the more common opioid analgesic drugs administered during the perioperative period.[1] Fentanyl use is also increasing in the palliative care of patients with chronic pain since the introduction of its oral transmucosal (Actiq lollipop and Fentora buccal tablet) and conventional or iontophoretic transdermal preparations (Duragesic or fentanyl patch). However, there is concern that the rapid and unpredictable respiratory depressant effects of fentanyl have contributed to its role as a principal cause of morbidity and mortality in the current opioid overdose epidemic in the United States.[2]

Patients treated chronically with certain antiepileptic drugs (AEDs) such as carbamazepine have been noted to require higher fentanyl doses to achieve adequate analgesic efficacy.[3] The mechanism of the higher dose requirements in these patients has not been fully established, but may result from increased hepatic clearance due to induction of the enzymes responsible for fentanyl clearance.[4] Better understanding of the pharmacokinetics of fentanyl during AED therapy should provide a basis to guide clinicians in predicting dose adjustments to avoid supratherapeutic or suboptimal dosing, and the

associated respiratory depressant effects or inadequate analgesia. This study tested the hypothesis that carbamazepine-induced alterations in fentanyl pharmacokinetics may result in subtherapeutic plasma concentrations, and play a pivotal role in its increased dose requirements. The study evaluated neurosurgical patients on chronic carbamazepine therapy, along with control patients who were not taking carbamazepine or other known enzyme inducers or inhibitors.

Methods

The study was reviewed and approved by the Institutional Review Board of the Massachusetts General Hospital. Written informed consent was obtained from all study participants after explanation of the study design in lay terms. Subjects were patients scheduled to undergo elective craniotomy that required placement of an arterial and peripheral venous catheter for perioperative care, which could be used for blood sample collection. Nineteen adult subjects with American Society of Anesthesiologists (ASA) physical status classification 1–3 were enrolled. Using the fentanyl exposure data reported for the interaction between ketoconazole and fentanyl,[5] it was estimated that a 35% difference of carbamazepine on fentanyl exposure could be shown with 10 subjects with an α-error of 5% and a power of 80%. Nineteen patients were enrolled, 11 of whom were receiving chronic treatment with carbamazepine for greater than 6 weeks duration (the AED or carbamazepine group). The remainder eight patients served as controls. Exclusion criteria included age younger than 18 years, ASA physical status 4 or greater, chronic opioid treatment, history of hepatic or renal dysfunction (laboratory values >2 times normal limits), treatment with other medications that induce or inhibit drug-metabolizing enzymes (e.g. cimetidine, azole antifungals, antiretroviral agents and rifampin), a me dical contraindication to administration of fentanyl, or pregnancy.

All patients received a single intravenous bolus dose of 200 μg of fentanyl by their anaesthetist at induction of anaesthesia, after which no additional doses of fentanyl were given during or after surgery. Alternative analgesics other than fentanyl were used, and included morphine, hydromorphone, remifentanil or sufentanil, administered, as indicated, at the discretion of the primary anaesthetic or surgical teams. Induction and maintenance of anaesthesia were conducted according to the standard routine for all craniotomies at the institution. Induction of anaesthesia was with propofol, followed by the use of a nondepolarizing neuromuscular blocking drug to facilitate endotracheal intubation. Anaesthesia was maintained with either total intravenous or volatile anaesthetics, as determined by the primary anaesthesia team.

A baseline blood sample was obtained before fentanyl administration, and subsequent blood samples were collected at 1, 5, 15, 30 and 60 min, and then hourly for up to 9 h after the fentanyl bolus dose. Blood samples were collected in EDTA tubes, centrifuged within 30 min of sampling, and the plasma was stored in aliquots at −70° until later assay.

Analysis of fentanyl in plasma

Plasma fentanyl concentrations were determined by liquid chromatography–tandem mass spectrometry (LC-MS/MS). To each (0.2 ml) plasma sample and appropriate calibration standards, fentanyl-D5 was added as internal standard. Samples were extracted with methyl-*t*-butyl ether. The extract was separated, evaporated to dryness, and reconstituted with mobile phase for analysis. The analytic instrument was an AB Sciex API 5000 triple quadrupole mass spectrometer equipped with a QJet ion guide and accelerated by a LINAC collision cell (AB Sciex, Foster City, CA, USA) with an atmospheric pressure chemical ionization probe in a Turbo Vion source, interfaced with a Waters Corporation (Milford, MA, USA) Acquity ultra pressure liquid chromatograph. Analyst software 1.6.2 (AB Sciex, Foster City, CA, USA) was used for system control and data processing. The LC system was equipped with an Acquity UPLC HSS T3 1.8 μm, 2.1 × 50 mm HPLC column, and an Acquity UPLC HSS T3 1.8 μm VanGuard precolumn (Milford, MA, USA). The mobile phase consisted of a mixture of 0.1% formic acid in water (solvent A) and 0.1% formic acid in acetonitrile (solvent B), with a flow rate of 0.5 ml/min and run time of 2 min. Solvents A and B were combined in a gradient: 0–1 min: 85% A; 1–1.5 min: 50% A; 1.6–2 min: return to initial conditions and hold for 3 min. The electrospray source was operated in the positive ionization mode, using collision gas (CAD) 12, curtain gas (CUR) 20, ion source gas 40, and ion spray voltage 5500 V with temperature 500 °C. The instrument was operated in the multiple reaction monitoring (MRM) mode. The following MRM transitions of precursor ions to product ions were selected: fentanyl, m/z 337.2 → 188.2 (collision energy, CE 24 V); fentanyl-D5, m/z 342.2 → 188.2 (collision energy, CE 35 V). The scan time was 100 ms for all analyses. The concentration range in calibration standards was 0.01–20 ng/ml of fentanyl. The limit of sensitivity was 0.05 ng/ml of plasma using a 0.2-ml sample. The within- and between-day variability did not exceed 10%.

Pharmacokinetic and statistical analyses

A linear sum of either two or three exponential terms, consistent with a two- or three-compartment model,[6,7] was fitted to data points by nonlinear regression using

GraphPad Prism 7. Residual errors were weighted by the reciprocal of the measured concentration. Coefficients and exponents from the fitted functions were used to calculate the following kinetic variables for fentanyl: volume of the central compartment (V1), total volume of distribution using the area method (V_d), elimination half-life in the terminal 'beta' phase ($T_{1/2}$), total area under the plasma concentration curve (AUC), and total clearance.

Differences between control and carbamazepine groups in patient characteristics and fentanyl kinetic variables were compared statistically using Student's *t*-test for independent groups, or by an analogous nonparametric test.

Results

Two subjects in the control group had a sampling duration of only 3 h, and could not be included in the pharmacokinetic analysis due to the short sampling duration. Consequently, the final sample sizes were $N = 6$ in the control group and $N = 11$ in the carbamazepine group.

The control and carbamazepine groups were comparable in demographic characteristics and baseline laboratory values (Table 1). The mean duration of surgery was longer in the control patients. Both groups received other opioids intraoperatively.

Figure 1 shows mean plasma fentanyl concentrations in the two groups, along with pharmacokinetic functions consistent with the aggregated data points. An extensive phase of drug distribution is evident during the first 30 min after the fentanyl injection. At 5 and 15 min after injection, generally corresponding to the time of maximum analgesic effect, concentrations were lower in the carbamazepine recipients than in the control patients.

Kinetic parameters are provided in Table 2. Central compartment volumes and total volumes of distribution, with or without normalization for body weight, were larger in carbamazepine-treated patients than in controls, though the differences were not statistically significant. Total area under the plasma concentration curve was significantly lower in the carbamazepine group than in controls, and total clearance of fentanyl was correspondingly increased (Table 2). Elimination half-life of fentanyl did not differ between groups.

Table 1 Patient characteristics, surgery type and other intraoperative opioids[a]

	Carbamazepine ($N = 11$)	Control ($N = 6$)	*P* value
Characteristics			
Female, *n* (%)	5 (45)	3 (50)	0.72
Age (years)	49.5 ± 16.5	53 ± 17.6	0.67
Weight (kg)	72.6 ± 12.1	80.1 ± 4.2	0.43
Height (cm)	170 ± 9	172 ± 12	0.63
BMI (kg/m^2)	24.7 ± 2.7	27.2 ± 8.1	0.41
Creatinine (mg/100 ml)	0.87 ± 0.11	0.73 ± 0.20	0.10
eGFR (ml/min)	107 ± 23	94 ± 15	0.57
Albumin (g/100 ml)	4.4 ± 0.2	4.3 ± 0.2	0.36
Surgery type			
Craniotomy for tumour		4 (50)	
Acoustic neuroma resection		2 (25)	
Microvascular decompression	10 (91)		
Other neurosurgical procedures	1 (9)	2 (25)	
Duration of surgery (min)	257 ± 58	407 ± 163	0.01
Intraoperative opioids			
Alfentanil (mg)	0.13		
Hydromorphone (mg)	0.09 ± 0.3	0.26 ± 0.39	
Meperidine (mg)	2.27		
Morphine (mg)	1.54 ± 3.5	1.25 ± 3.5	
Remifentanil (mg)	0.51 ± 0.87	0.36 ± 0.51	
Sufentanil (mcg)	17.5 ± 27.6	68.1 ± 57.2	

P values are from Student's *t*-test for independent groups. [a]Values are mean ± standard deviation, or number and per cent of total, as appropriate.

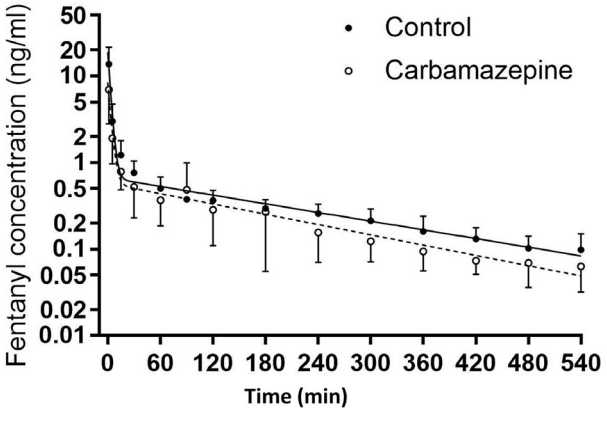

Figure 1 Mean (±standard error) plasma fentanyl concentrations at corresponding times in the control patients and in the carbamazepine-treated patients. Lines represent the pharmacokinetic functions determined by nonlinear regression analysis.

Discussion

This study demonstrates that chronic carbamazepine therapy significantly influences the pharmacokinetics of an intravenously-administered single bolus dose of fentanyl, increasing its plasma clearance and reducing the total AUC. The trend for larger total V_d of fentanyl among carbamazepine recipients did not reach statistical significance. It is notable, however, that during the distribution phase, mean concentrations of fentanyl were lower at those times when the peak analgesic effect of fentanyl is anticipated (5–15 min after injection). Despite the enhanced clearance

Table 2 Pharmacokinetic variables for fentanyl

	Mean (±SD) value for		
	Control (N = 6)	With carbamazepine (N = 11)	P value[a]
Central compartment volume			
Litres	35 (±33)	42 (±42)	>0.5
Litres/kg	0.49 (±0.47)	0.51 (±0.40)	>0.5
Total volume of distribution			
Litres	258 (±91)	422 (±270)	>0.15
Litres/kg	3.6 (±1.2)	5.4 (±3.1)	>0.15
Total AUC (ng/ml × min)	233 (±70)	150 (±65)	**<0.02**
Clearance			
ml/min	919 (±242)	1554 (±624)	**<0.02**
ml/min per kg	13.2 (±4.8)	20.1 (±6.8)	**<0.05**
Elimination half-life (h)	3.28 (±0.89)	3.09 (±1.34)	>0.5
Distribution half-life (min)	6.6 (±5.1)	2.7 (±1.4)	**<0.03**

Bold numbers indicate statistically significant differences ($P < 0.05$)
[a]Based on parametric or nonparametric test.

observed with concomitant carbamazepine therapy, the elimination half-life was not different between groups. The relationship between $T_{1/2}$, V_d and clearance is given by the following equation[8,9]:

$$T_{1/2} = (\ln 2) \times V_d/(\text{clearance})$$

We observed that carbamazepine treatment was associated with an increase in both V_d and clearance. As such, $T_{1/2}$ was not different between groups. Nonetheless, the increased CL and V_d were associated with lower mean concentrations of fentanyl at the clinically important time of its peak analgesic onset, that is at 5 and 15 min after administration. These findings might explain the increased dose requirement of fentanyl reported in patients receiving carbamazepine therapy for prolonged periods. This is a novel finding with important perioperative implications. Fentanyl is the most common intraoperative opioid, used globally for many types of surgeries including neurological surgery and craniotomies. Carbamazepine, on the other hand, is an important antiepileptic agent and is also commonly administered for other conditions such as trigeminal neuralgia. Co-administration of these agents is hence a common clinical scenario, yet the absence of pharmacokinetic data had limited the clinician's ability to optimize the perioperative pain control. An insufficient dose of fentanyl in this scenario can lead to significant pain upon emergence from anaesthesia, while a larger than required dose can lead to excessive respiratory depression and delayed extubation. The current study elucidates the altered plasma fentanyl concentration in patients with this AED, guiding the clinician to optimize its dose and frequency for effective pain control without excessive respiratory suppression.

It should be noted, however, that the pharmacodynamic consequences of the pharmacokinetic changes were not directly assessed in this study. The therapeutic window for fentanyl is defined as the range between the minimally effective analgesic dose and that associated with respiratory depression. A concentration of 0.6 ng/ml results in slight but measurable analgesia.[10,11] At a serum concentration of 1.4 ng/ml, a 50% decrease in pain intensity is reported with 12% reduction in minute ventilation, and at 3 ng/ml a 23% reduction. Thus, the therapeutic window for fentanyl providing analgesia without clinically significant respiratory depression in awake patients is reported between 0.6 and 2 ng/ml. During the intraoperative period, however, the pharmacodynamic effects of opioids need to be considered in conjunction with other analgesic and anaesthetic agents, as well as the significance and magnitude of the surgical stimuli, the need for airway control (e.g. intubation of the patient), and mechanical ventilation.

Carbamazepine itself has no opioid receptor activity.[12] However, AED drugs, including carbamazepine, are commonly used for treating neuropathic pain conditions and to potentiate opioid analgesic effects.[13] Although AEDs have no direct interaction with opioid receptor activity, carbamazepine has inhibitory actions on the sodium channel, explaining the opioid potentiation in neuropathic conditions. Whether chronic carbamazepine actions are different from acute effects remains unclear. However, the pharmacodynamic effects and pharmacological interactions of these drugs can be different when administered acutely as compared to chronic and long-term administration. This feature is well exemplified by many drugs including opioids and other centrally acting agents. For example, while opioids have profound analgesic effects when administered for short periods, their prolonged administration can lead to increased nociceptive behaviours (opioid-induced hyperalgesia). Similarly, it is well established that midazolam acutely potentiates opioid effects. However, prolonged co-administration of midazolam with morphine induces greater opioid tolerance than morphine alone.[14] Experimental studies suggest that this phenomenon is not explained by a pharmacokinetic interaction.[15] Whether chronic carbamazepine can similarly have divergently opposite effects on analgesia during acute vs chronic administration needs further study. It is notable, however, that in another study of AED interaction with a different type of analgesic, dexmedetomidine, no changes in pharmacodynamics or other definitive interactions were observed.[16]

The mechanism of enhanced clearance of fentanyl in carbamazepine-treated patients is not established. Fentanyl is a high-clearance drug after intravenous administration, with mean total clearance values among control patients in the range of 900 to 1000 ml/min. This is approximately

two-thirds of estimated hepatic blood flow (HBF) in healthy individuals (about 1500 ml/min), and as such clearance of intravenous fentanyl is partly dependent on HBF, and can be influenced by changes in HBF.[17,18] We previously reported significant increases in fentanyl clearance among patients under treatment following burn injury, presumably due to the high cardiac output and increased HBF in patients with burn injury.[7] The burned patients also had an increase in fentanyl V_d compared to nonburned controls.

The remaining component of fentanyl clearance is explained by hepatic metabolism, with the principal pathway being transformation by cytochrome P450-3A (CYP3A) enzymes[5,19,20] to norfentanyl, hydroxypropionyl-fentanyl and hydroxyproprionyl-norfentanyl, all with minimal pharmacological activity.[21] Clearance of intravenous fentanyl is impaired by co-administration of the CYP3A inhibitor ketoconazole,[5] and transmucosal fentanyl clearance is similarly impaired by the CYP3A inhibitor troleandomycin.[22] Enzyme-inducing agents have the opposite effect on fentanyl clearance. Reduced analgesic efficacy of fentanyl is reported in patients receiving the inducer rifampin.[23,24] In a pharmacokinetic study, co-administration of rifampin greatly reduced AUC and increased clearance of oral transmucosal fentanyl.[22] The increased clearance of fentanyl in this study is likely explained by some combination of increased liver size or HBF associated with the inducer carbamazepine, together with the well-established capacity of carbamazepine to induce CYP3A metabolic activity. It is unlikely that fentanyl clearance was significantly influenced by differences in renal excretion of the intact drug, as there were no differences in the renal function (creatinine levels and estimated glomerular filtration rates) between carbamazepine and control groups. In addition, renal clearance is minimal for fentanyl, with less than 10% of the intact drug excreted by the kidneys.[25]

In addition to the above drug–drug interaction and the increased fentanyl clearance, patients with chronic carbamazepine treatment are also reported to be resistant to other important drugs that are commonly used during the intraoperative period or in the intensive care setting. These medications include a common neuromuscular blocking agent vecuronium,[26] as well as the α-2 agonist dexmedetomidine.[16] The suggested mechanism is similar to that of fentanyl, and appears to include the enzyme induction by this anticonvulsant. It is of great importance that the clinicians consider these interactions in all patients on chronic carbamazepine treatment.

The relatively small sample size is a limitation of this study. However, this limitation needs to be considered in the context of the difficulty to enroll patients with significant pain or seizure disorders requiring surgery under general anaesthesia with an arterial catheter, for whom the needs of a research protocol cannot override the many clinical perioperative considerations. We believe, nevertheless, that the availability of a dense sampling scheme for each subject is a strong point of the design, enabling full characterization of the pharmacokinetics in each subject individually. Also, the current study was not designed to elucidate the pharmacodynamic consequences of the reported pharmacokinetic changes. Hence, despite clear differences in fentanyl clearance, the exact analgesic differences and other hemodynamic and respiratory consequences of these changes are not explored. Acute administration of carbamazepine is commonly a part of the therapeutic regimen of multimodal analgesia to potentiate opioid drugs.[27] As discussed above, whether chronic carbamazepine, similar to chronic opioids, antagonizes opioid effects needs further study.

In conclusion, chronic treatment with carbamazepine results in decreased fentanyl plasma concentrations after a single intravenous dose, due to increased fentanyl clearance. This effect may contribute to the decreased sensitivity to the analgesic effects of fentanyl and to the increased perioperative or nonoperative dose requirements.

Declaration

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