Title

Safe prognostication following cardiac arrest: the role of the pharmacokinetics of fentanyl in patients treated with targeted-temperature management

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Conflicts of interest

None

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Keywords

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Abstract

Background

Neurological prognostication following cardiac arrest (CA) is complex and sedative agents may significantly impair responses to clinical examination. This study investigates the elimination of fentanyl in patients treated with targeted temperature management (TTM).

Methods

We measured the blood concentration of fentanyl in 23 post-cardiac arrest patients treated with TTM following discontinuation of continuous infusion. Fentanyl was discontinued when the patients were rewarmed to a temperature of 36-36.5°C and a blood sample taken 12 h later. Measured concentrations were compared with predicted concentrations using population pharmacokinetic parameters. Variables likely to prolong half-life were analysed using a multivariate regression model.

Results

We found a statistically significant difference between median measured and predicted concentrations (measured 0.93 μg/L [range 0.11-8.29 μg/L] vs. predicted 0.30 μg/L [range 0.16-0.59 μg/L]; $p<0.05$). Univariate analysis identified a significant relationship between estimated fentanyl half-life and serum lactate concentrations ($r=0.45$, $p<0.05$. Multivariate linear regression identified two variables (SAPS score, and genotype), which together were able to explain approximately 30% of the variation in the population (adjusted $R^2=0.3177$, $p=0.0194$). No significant

relationships were found between fentanyl half-life and patients' clinical or biochemical variables or co-administration of drugs metabolised by cytochrome p450.

Conclusions

There is marked variation in the clearance of fentanyl following continuous infusion during TTM after CA which correlates with illness severity, lactate concentration and genetic polymorphisms of the cytochrome p450 liver enzymes. Sustained presence of fentanyl may influence response to neurological examination at 12 hours post discontinuation in patients receiving the drug as an infusion as part of TTM.

Introduction

Neurological prognostication following cardiac arrest (CA) is complex, and sedative agents may significantly impair responses elicited during clinical examination as part of multifactor assessment of patients [1]. The European Resuscitation Council recommends waiting 12 hours from stopping sedative infusions before prognostication, accepting the limited evidence for this recommendation [1]. In patients who have received sedatives less than 12 hours before neurological assessment the reliability of clinical examination may be reduced, but a 12 hour delay in prognostication may be insufficient in patients treated with targeted-temperature management (TTM) [2, 3]. Whilst the recommendation is to wait for longer than 12 hours before prognostication following TTM, the pharmacokinetics and potential accumulation of drugs infused during this period is unknown and as

71 the infusions may be continued into the normothermic period, of clinical
72 significance.

73 There is a recognised subset of patients with delayed awakening and good outcome
74 following CA who may have unfavourable neurological signs at 48 hours following
75 discontinuation of TTM and sedation [3-5]. Both animal and human research
76 demonstrates that hypothermia delays the clearance of opioid drugs [6-10]. The
77 clearance of fentanyl is significantly lower in hypothermic patients, being reduced by
78 as much as 45% in some cases [7, 11]. There is evidence that concomitant
79 administration of CYP3A substrates/inhibitor drugs commonly used on the ICU also
80 reduces metabolism of fentanyl [12]. Polymorphisms in the gene coding for CYP3A5
81 liver enzymes can also potentially influence fentanyl plasma levels [13]. It is not
82 known how these multiple factors may influence the elimination of fentanyl in
83 patients treated with TTM after a CA.

84 We hypothesised that in patients receiving TTM following CA, concentrations of
85 fentanyl will be significantly higher than would be expected based upon their dose
86 rate, and population estimates of volume of distribution (V) and half-life ($t_{1/2}$) under
87 normal conditions (i.e. the absence of TTM). A secondary consideration is that there
88 may be certain clinical factors, including organ perfusion, genotype, and patient
89 characteristics that can be used to predict patients with residual plasma fentanyl at
90 12 hours post-infusion.

91

92 **Materials and methods**

The Health Research Authority approved our protocol in June 2016 (IRAS 178665).

Participants

Adult patients admitted to the ICU following CA and treated with our institutional protocol for TTM from January 2017 to May 2018 were eligible for the study. Patients were screened daily and considered for enrolment if they received a fentanyl infusion as part of on-going post resuscitation care. Patients were recruited to the study if it was predicted that their clinical condition meant it was likely the fentanyl infusion could be stopped following rewarming. Assent was obtained from the patients' next of kin or legal surrogate. Exclusion criteria were: patients whose advocates refused assent, patients requiring on-going sedative infusions for analgesia or agitation, pregnant women or patients in whom sedatives were not stopped because they are not expected to survive.

As this was an observational study, fentanyl and all other medications were administered solely at the discretion of the treating physician.

Targeted temperature management

TTM followed our institution's protocol. Patients suffering an out of hospital CA with a primary rhythm of ventricular fibrillation or pulseless ventricular tachycardia were cooled at the discretion of the attending team if they had a Glasgow Coma Score <7, and there were no contraindications such as cardiovascular instability. Patients were cooled to 33-36°C using external cooling or the Thermogard XP system (Zoll Medical Corporation) for a period of between 12 and 24 hours. They were then slowly

rewarmed over 2-4 hours. At this point the fentanyl infusion was discontinued, and the total dose infused recorded.

Fentanyl assay

A single blood sample was collected in an EDTA tube at 12 hours from discontinuation of the fentanyl infusion and immediately transferred for temporary storage in a fridge at 4 °C (less than 5 days). It was then stored at -80 °C for up to one month. Previous studies have confirmed stability of fentanyl at 4^{o}C for up to 3 months [14]. Analysis of the blood levels of fentanyl was conducted within one month of sample collection using a commercial ELISA kit (Neogen Corporation). For the assay of fentanyl, 0.5 ml of the blood sample was diluted 1:50 and 1:10 and measured.

Genotyping

DNA was extracted from thawed whole blood samples using DNeasy extraction columns (Qiagen). The CYP3A4 and ABCB1 genes were amplified by polymerase chain reaction (PCR) with HotstarTaq polymerase (Qaigen) using standard primers (supplementary appendix). PCR conditions were as follows: initial denaturation step at 95°C, followed by 35 cycles of the denaturation step at 95°C, then annealing at 56°C, then finally extension at 72°C. PCR products were then sequenced by Sangar sequencing (Source Bioscience), and electropherograms visually inspected to determine genotype (supplementary appendix).

Demographic and Clinical Variables

136 Demographic and clinical variables were collected including age, gender, body mass
137 index (BMI), and Illness severity as calculated by SAPS ll score. Renal function was
138 assessed by calculated creatinine clearance on admission using the Cockcroft and
139 Gault formula [15]. Ischaemic hepatitis was crudely assessed using baseline Alanine
140 Aminotransferase (ALT) and lactate. The co-administration of CYP3A
141 substrates/inhibitor drugs was also recorded.
142
143 *Sample size*
144
145 Reports in the literature suggest the minimum effective concentration of fentanyl for
146 analgesia in critical care patients is between 1 and 3 μg/L [16]. Our hypothesis is
147 therefore that: twelve hours following cessation of a fentanyl infusion in TTM
148 treated patients the plasma concentration of fentanyl (C_{t12}) will be above 1 μg/L, i.e.
149 within the therapeutic range. In order to determine the sample size, we assumed
150 that a value around 1 μg/L was still therapeutic. Therefore a value of 0.6 μg/L was
151 adopted and considered to be outside the therapeutic range. This requires a sample
152 size of 23, and provides a power of 95%, with alpha set at 5% when tested against a
153 sample mean of 1 μg/L with a standard deviation of 0.5 μg/L (Cohens's *d*, 0.7,
154 supplementary appendix).
155

156 *Statistical analysis*

157 Statistical tests (Student's one-sample t-test, Wilcoxon Signed Rank test, simple
158 correlations, and Friedman tests) were performed in GraphPad Prism v6.0 (GraphPad
159 Software, La Jolla California USA, www.graphpad.com). Data plots were also
160 compiled in Graphpad Prism. A generalised multiple regression model was built in R
161 v3.5.1 (R Core team, 2018), using a minimum effective model approach to establish
162 the simplest, statistically significant model. Data are presented as mean ± standard
163 deviation unless otherwise stated.

164

165 *Pharmacokinetic calculations*

166 Two predicted plasma concentrations at 12 hours post-infusion (C_{t12}) were
167 calculated for each patient using Equation 1, where *R* is the dose rate of fentanyl, $t_{1/2}$
168 is the half-life, *V* is the volume of distribution, and *t* is the time since the infusion
169 stopped (i.e. 12 hr).

170

171

$$C_{t12} = \frac{R t_{1/2}}{0.693 \times V} e^{-\frac{0.693}{t_{1/2}} t}$$

172

173 **Equation 1.**

174

175 Equation 1 describes a single exponential process, where in fact fentanyl can be
176 described in terms of a two-compartment model with an alpha-distribution phase.
177 However, by 12 h (our plasma sampling time), full distribution can be assumed. At
178 that point, fentanyl elimination kinetics takes the appropriate form of a single
179 exponential.
180
181 The first predicted plasma concentrations at 12 h post-infusion were calculated
182 using values for $t_{1/2}$ and V obtained from population pharmacokinetic studies on
183 healthy volunteers (where $t_{1/2}$ = 4.35 ± 1.18 h and V = 4.07 L/kg) [17]. The second
184 predicted C_{t12} was calculated using values for $t_{1/2}$ and V obtained from a published
185 pharmacokinetic investigating fentanyl kinetics in critically ill patients [18].
186 Differences between the actual C_{t12} values obtained from our patient sample, and
187 the two predicted values using population kinetics were tested using a Friedman test
188 with post-hoc analysis.
189
190 Using the single plasma sample taken at 12 hr, we also estimated the $t_{1/2}$ for each
191 patient according to the methodology outlined by Scutt *et al.* [19], assuming that
192 steady state fentanyl concentrations had *not* been reached. Briefly, the elimination
193 rate constant for each patient was estimated using the single plasma fentanyl
194 concentration obtained at 12 hrs, along with the known rate of fentanyl
195 administration, combined with a population estimate of the V for fentanyl in critical
196 care patients [18]. The elimination rate constant was converted to half-life by
197 dividing it by the natural logarithm of 2 (approximate value 0.693).

Results

Recruitment and patient demographics

Seventy-two patients were initially considered for recruitment. 23 of these were excluded, as they did not receive TTM. 25 patients were withdrawn from the study as their clinical condition prevented discontinuation of fentanyl on rewarming. One patient had a blood sample taken for fentanyl analysis at an incorrect time. Twenty-three patients completed the study, two of which were re-warmed prior to fentanyl being stopped (Figure 1). All patients were sedated with propofol, which was stopped with fentanyl in all but 2 of the patients (median cumulative dose 4660 mg (range 2590-10920mg)).

The median age of patients who completed the study was 66.0 years, with the majority of subjects being male (22/23); Table 1. The two patients who were rewarmed prior to the fentanyl infusion being stopped were younger (67.0 [24.0-89.0] vs. 50.5 [36.0-65.0]), and had better renal function than the rest of the study sample (CrCl=64.67 ±24.86 vs. 91.5 ±20.5 mLs/min; Table 2). They were also administered more fentanyl, over a longer duration (Table 2).

222 *Fentanyl pharmacokinetics*

223

224 The mean and median measured C_{t12} values for fentanyl were 1.83 ±1.99 μg/L and
225 0.93 μg/L (range 0.11-8.29 μg/L) respectively. There was no direct correlation
226 between total dose of fentanyl and blood concentration level at 12 hours (Pearson's
227 r = 0.0027, p>0.05). Measured C_{t12} values for fentanyl were significantly different
228 from a hypothetical value 0f 0.6 μg/L (p<0.05, Wilcoxon Signed Rank Test). Based on
229 the fentanyl doses administered and population averages for V and $t_{1/2}$ in healthy,
230 and critically ill patients, we were able to predict C_{t12} fentanyl plasma for individuals
231 in our sample [17, 18] and compare these to the measured concentrations. We
232 found a statistically significant difference between our measured concentrations and
233 predicted concentrations at 12 h (using population pharmacokinetic values for V and
234 $t_{1/2}$ from healthy patients). However, we did not find a significant difference
235 between our median measured concentration and median predicted concentrations
236 at 12 h when using population pharmacokinetic values based on critically ill patients
237 (0.82 [0.07-8.29] vs. 0.30 [0.16-0.59] vs. 1.20 [0.75-2.10] in sample population,
238 healthy, and critically ill populations respectively; p<0.0001 sample population vs.
239 healthy population, Friedman test with Dunn's post hoc multiple comparisons;
240 Figure 2A). The spread of measured C_{t12} values was over a larger range than our
241 predicted C_{t12} values in critically ill patients. When comparing the cumulative
242 distribution of C_{t12} of these two datasets (measured and predicted) we find a
243 significant difference (p<0.01, Kolmogorov-Smirnov test) suggesting different
244 distributions.

245

246 By applying the mathematical method outlined by Scutt et al. [19], we estimated the
247 half-life of fentanyl for each participant from the single plasma concentration
248 obtained at 12 hours, and their individual fentanyl dose administration rates, and
249 infusion durations. In 1/23 patients, the estimated $t_{1/2}$ was approximately 5 times
250 the standard deviation of the population and was identified as an outlier by
251 application of Grubb's method (alpha=0.0001) and excluded from the subsequent
252 analysis. This patient was an opioid user. Most of the estimated fentanyl half-lives in
253 the remaining patients (18/22) were greater than the half-life for fentanyl quoted in
254 the literature for healthy individuals [17]. In most patients (15/22), based on their
255 prolonged estimated half-life, it would have taken more than 24 h for the fentanyl
256 concentration to have declined by 95% (i.e. 4.3 x $t_{1/2}$) and be considered to have
257 been cleared from the body. In five patients, based on the large estimated half-life,
258 it would take in excess of 48 h to clear fentanyl from the plasma (i.e. decline to 95 %
259 of its initial value). Figure 2B shows calculated half-life of fentanyl and clearance for
260 individual patients.
261
262 *Predictors of prolonged half-life*
263
264 Univariate analysis identified a significant relationship between estimated fentanyl
265 half-life and serum lactate concentrations (Pearson's r=0.45, p<0.05; Figure 3A). We
266 were unable to find a relationship between estimated fentanyl half-life and any
267 other clinical or biochemical predictor, including CKD categories using KDIGO scoring
268 [20]. Multivariate linear regression identified two variables (SAPS score, and
269 genotype) which together were able to explain approximately 30% of the variation in

the population (adjusted R^2=0.3177, p=0.0194). Predictor variables included in the model are outlined in Table 1 (indicated with an *). It should be noted, that the half-life for fentanyl in the two patients who were rewarmed was significantly shorter than patients who remained cooled through the period of fentanyl administration (p<0.01 Figure 3C).

Discussion

Pharmacokinetics of Fentanyl

The American College of Critical Care Medicine practice guidelines consider fentanyl by infusion in ICU patients to have a context-sensitive half-life of 300 minutes after 12 hours [21]. During prolonged infusion there is an increased volume of distribution presumably due to equilibration between plasma and deep tissues [22], which may also effect the alpha-distribution phase. Patients may have a terminal half-life of fentanyl of greater than 12 hours even with normal organ function if they received a continuous infusion over a number of days [23]. Other authors have demonstrated wide variability in fentanyl concentrations in ICU patients receiving routine infusions [24]. The wide variation in fentanyl concentrations we have found is not therefore unexpected in this population group.

Factors known to influence fentanyl clearance

There is limited data in the ICU population on the pharmacokinetics of fentanyl, the largest study is from Choi et al., who studied fentanyl pharmacokinetics in 337 critically ill patients as part of the BRAIN-ICU study [18]. They concluded that fentanyl clearance was reduced in patients with severe liver disease, congestive heart failure, and most markedly those with a lower BMI. As fentanyl is extensively (99%) metabolized via CYP3A4 to norfentanyl, which is an inactive metabolite, it is generally considered safe in renal impairment [25, 26]. Choi found no association

between chronic kidney disease, age, illness severity, CYP3A inhibitor/inducer use and fentanyl clearance [18]. Our data, although with much smaller numbers, demonstrates a potential association with SAPS score and CYP3A4 polymorphism status and lactate levels. .

Delayed Awakening post CA

The role of sedation in delayed awakening is speculative, but analysis of awakening in the TTM trial demonstrated that although 496 patients had registered the day of awakening in the ICU, another 43 awoke after ICU discharge; so late awakening is common enough to merit further investigation [27]. Lybeck et al also concluded that time to awakening was longer in patients cooled to 33 degrees compared with 36, but this difference could not be attributed to differences in ***dosing*** of sedative drugs administered during the first 48h. The known reduction in drug metabolism with hypothermia may have a role in this context.

Hypothermia may decrease hepatic enzyme function, decreasing drug metabolism for hepatically cleared drugs and that this may influence the pharmacokinetics of fentanyl in the critically ill [28].

The addition of mild to moderate hypothermia decreases the clearance of cytochrome P450 metabolized drugs between 7% and 22% per degree Celsius below 37°C during cooling. [29].

Study strengths and limitations

The questions addressed in this study are clinically important, as neurological prognostication in CA patients is vital for determining subsequent care and treatment targets. We specifically sampled the patients at the time recommended it was safe to prognosticate in current recommendations. We have demonstrated that a substantial proportion of patients (68%) would not have cleared fentanyl from their plasma by 24 hours, and may still have fentanyl levels in the analgesic range. To our knowledge, this is the first study looking at blood fentanyl concentrations after discontinuation of fentanyl infusion in patients treated with hypothermia.

The obvious limitation of our study is that we did not use a matched control group of normothermic critically ill patients receiving fentanyl infusions for comparison. However, the study was already logistically challenging and attempts to find a matched group of patients would have made it extremely difficult to complete. We also noted a move towards maintaining hypothermia at 36 °C rather than at lower temperatures as a result of the TTM trial [5]. This may have meant that any effects on fentanyl kinetics were less marked than expected compared with more profound levels of hypothermia. Recent work by Lascarrou *et al* may provoke a change practice back to lower targeted temperatures making this more relevant [30]. It took longer to complete the study than anticipated due to a combination of continuation of sedation due to concerns around post-anoxic seizure activity after rewarming and an exacerbation of a cultural shift away from managing patients with TTM [31, 32].

Although we aimed to stop sedation at exactly 36°C, this proved challenging as the sedation was weaned over the course of the 1-2 hours, which lead to some of the patients having higher recorded temperatures at the point at which the fentanyl was stopped. We excluded several patients in whom the sedation had been continued greater than 2 hours after patients had been rewarmed to 36.5°C. This in itself inadvertently yielded some interesting data.

Alternative analgesics

Concerns around delayed awakening have led to suggestions that moderate rather than deep sedation may be beneficial in patients post TTM. In one review of 166 patients, the median time to following commands was 3 hours after rewarming [33]. Paul et al recently reported that sedation with propofol-remifentanil was associated with significantly earlier awakening, compared with midazolam-fentanyl [34], but a greater proportion of patients will require cardiovascular support if sedated with this method [35]. However, surveys looking at use of analgesics in cardiac arrest patients suggest fentanyl is still the most commonly used opioid [36].

Conclusion

There is marked variation in the clearance of fentanyl by continuous infusion following TTM after CA. This correlates with illness severity, lactate concentration and genetic polymorphisms of the cytochrome p450 liver enzymes but not age, BMI, renal dysfunction or drug administration.. Great care should be taken when assessing neurological function in patients sedated with fentanyl and receiving TTM

as the half-life of fentanyl might be increased to a clinically relevant degree. Further work needs to be undertaken to investigate other sedative regimens.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Health Research Authority IRAS 178665) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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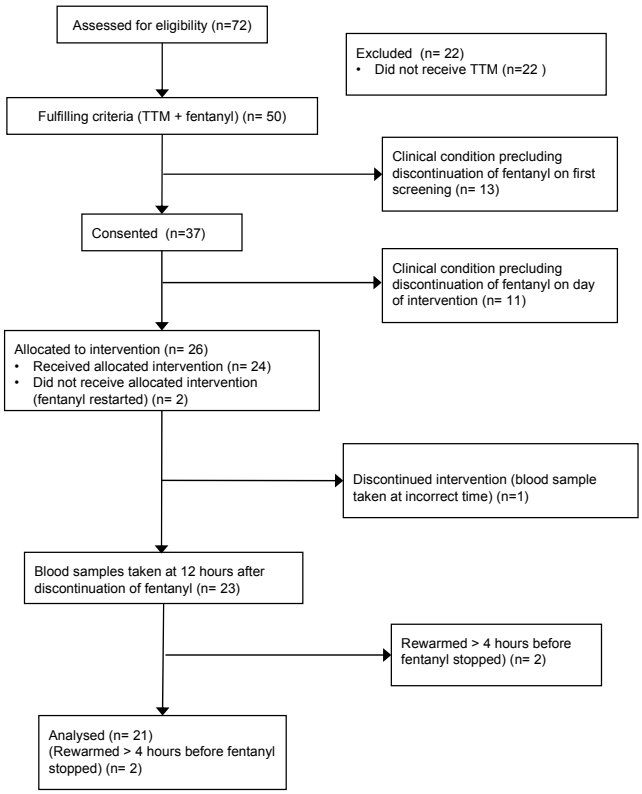
	All (n=23)	Cold (n=21)	Warmed (n=2)
Temp (^{o}C)*	36.2 (±0.5)	36.2 (±0.5)	37.2 (±0.14)
Amount of fentanyl administered (μg)	4346 (±2363)	4178(±2161)	8900(±522)
Duration (hrs)	35 (13-81)	35 (13-61)	71(61-81)
Halflife (hrs)	7.7 (3.3-366.7)	7.7(3.3-366.7)	5.4(5.1-5.8)
C_{pt} (μg/L)	0.93 (0.11-8.29)	0.93(0.11-8.29)	0.55(0.41-0.68)
Age (years)*	66 (24.0-89.0)	67.0(24.0-89.0)	50.5(36.0-65.0)
Height (cm)*	171.6(±8.8)	171.1(±8.6)	179.0(±1.4)
Weight (kg)*	74.3((±11.7)	74.2(±12.3)	75.0(±0.0)
BMI (kg/m^2)*	24.0 (20.0-53.0)	25.6(20.0-53.0)	23.0(23.0-23.0)
Lactate (mmol/L)*	2.0(±1.0)	2.1(±1.0)	1.9(±1.3)
ALT (IU/L)*	106.5(±78.1)	113.1(±78.6)	142.5(±156.3)
Creatinine (μmol/L)*	118.9(±58.4)	117.3(±56.9)	95.0(±42.3)
CrCl (mL/min)*	67.0(±25.3)	66.6(±24.2)	91.5(±20.5)
SAPS*	48.4(±7.9)	48.8(±8.0)	38.5(±2.1)
Gene (CYP3A4*1G)*	15/20	15/19	1/2

Table 1. Demographic and physiological characteristics



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507 **Figure 1. Recruitment Flow Diagram**

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510

511 **Figure 2. Fentanyl pharmacokinetics. A Measured fentanyl C_{t12} vs. Predicted**

512 **fentanyl C_{t12} (based on population pharmacokinetic data using Eq. (1) in healthy**

513 **(middle bar) and critically ill patients († end bar). B Estimated half lives for**

514 **patients enrolled in the study. The arrows indicate the fentanyl half lives for two**

515 **patients who were rewarmed during the infusion of fentanyl. ****p<0.0001**

516 **(Friedman Test), §p<0.05 actual vs hypothetical C_{t12} of 0.6 μg/L (Wilcoxon Signed**

517 **Rank Test).**

Figure 3. Predicting altered fentanyl pharmacokinetics. A Relationship between serum lactate and estimated fentanyl half-life. B Relationship between CKD categories and estimated fentanyl half-life. C Estimated fentanyl half-life in cooled patients vs. rewarmed. **p<0.05

Figure 2
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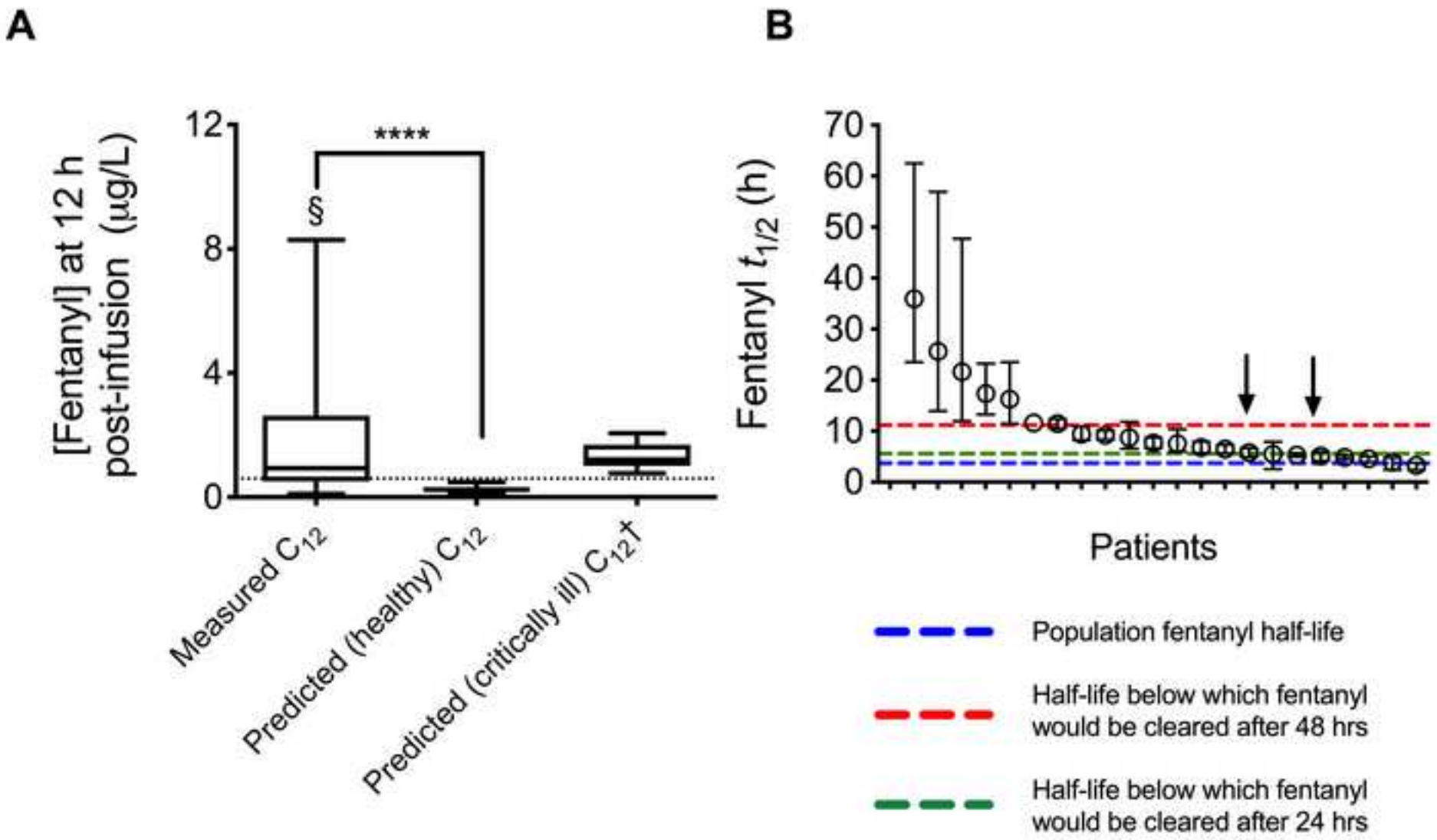

Figure 3

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