The pharmacokinetics and pharmacodynamics of cisatracurium in critically ill patients with severe sepsis

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Cisatracurium is a non-depolarizing neuromuscular blocking drug used in anaesthesia and intensive care.
- Cisatracurium degrades at physiological pH via Hofmann elimination. Therefore, the elimination of cisatracurium may be from both plasma and tissues.
- Critically ill patients may have or develop resistance to non-depolarizing neuromuscular blocking drugs.
- Pathophysiological changes in critically ill patients with sepsis can cause changes in both pharmacokinetics (PK) and pharmacodynamics (PD).

WHAT THIS STUDY ADDS

- This is the first study to characterize PK and PD of cisatracurium in intensive care patients with severe sepsis following a single bolus dose.
- This study suggests that standard dosing of cisatracurium in patients with severe sepsis results in a slower patient response with a reduced effect.
- The resistance to cisatracurium in these patients is more attributed to altered PD as pharmacokinetic parameters were similar to those described in other patient populations.

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AIM

To characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of cisatracurium in critically ill patients with severe sepsis.

METHODS

Blood samples were collected before and over 8 h after a single bolus dose of cisatracurium 0.1 mg kg⁻¹. Neuromuscular block was assessed by accelerometric peripheral nerve stimulation (TOF Watch). Plasma concentration and neuromuscular block data were fitted using population analysis.

RESULTS

Steady-state volume of distribution was determined to be 111 ± 71 ml kg⁻¹ and plasma clearance was 5.2 ± 1.8 ml min⁻¹ kg⁻¹ in these patients with greater inter-patient variability compared with other populations. The time to maximum block (8.3 ± 2.9 min) and delay time of transferring from central to effect compartment (17.2 min) was much longer, while the maximum block (95.0 ± 6.3%) was less compared with those in other patient populations. The effect compartment concentration resulting in 50% of maximum effect (128 ± 58 ng ml⁻¹) was larger than previously described.

CONCLUSIONS

This study suggests that standard dosing of cisatracurium in patients with severe sepsis results in a slower patient response with a reduced effect. Use of a larger dose may overcome this reduced delayed response.

Introduction

The pharmacokinetics (PK) and pharmacodynamics (PD) of the neuromuscular blocking drug cisatracurium are well described in a variety of patient populations [1–5], but not specifically in critically ill patients with severe sepsis. Most recommendations for the current use of neuromuscular blocking drugs in patients with sepsis, either in the operating theatre or the intensive care unit (ICU), are extrapolated from studies performed in other patient populations [6]. It has been reported that ICU patients may have or develop resistance to non-depolarizing neuromuscular blocking drugs [7]. It is not known whether this relates to alterations in drug PK, PD or both. Patients with severe sepsis have alterations to both body fluid distribution and organ function which can have a significant impact on drug behaviour [8–10]. Neuromuscular blocking drugs generally have a volume of distribution that is restricted to the extracellular fluid space and alterations in the distribution volumes for other polar molecules such as antibiotics has been described in patients with sepsis [11, 12]. Cisatracurium has an organ independent elimination. Hence, alteration in its pharmacokinetics will arise from any potential changes in volume of distribution ($V_{d,ss}$). Pathophysiological changes may also affect neural transmission and the subsequent dose response. The aim of this study was to describe the PK and PD of cisatracurium in patients with severe sepsis following a single dose.

Methods

Subjects

This was a clinical study that had approval from the Princess Alexandra Hospital Research Ethics Committee (ethics number PAH REC 176/02), The Guardianship and Administration Tribunal and each patient's statutory health attorney. Eligible patients were those critically ill patients with severe sepsis whom the treating clinician deemed to require paralysis with a neuromuscular blocking agent as part of their clinical care. Severe sepsis was defined as sepsis (two or more Systemic Inflammatory Response Syndrome criteria in the setting of presumed or proven infection) with organ dysfunction [13]. Patients who were pregnant, had pre-existing neuromuscular disease, burn injuries or required renal replacement therapy were excluded from the study as these are factors known to impact on the pharmacology of neuromuscular blocking drugs. Patients with a known allergy to non-depolarizing neuromuscular blocking drugs were also excluded. Each patient could be studied on more than one occasion (with at least 48 h washout period between occasions) during an episode of sepsis.

Experimental design

Basic demographic data were collected for each patient on each study day, including age, gender, source of sepsis and

positive microbiological isolates. All drugs administered were recorded and the physiological observations, including both core and peripheral body temperature, were noted. The results of routine laboratory tests for electrolytes, urea, creatinine, bilirubin, liver enzymes, albumin, total protein, haemoglobin, haematocrit and white blood cell count were recorded.

An Acute Physiology and Chronic Health Evaluation (APACHE II) score for the 24 h period around the first bolus dose assessment of cisatracurium was calculated together with a Sepsis-related Organ Failure Assessment (SOFA) score for each study day [14, 15]. It was noted if patients continued to fulfil the criteria for severe sepsis on the subsequent occasions they were assessed.

Neuromuscular monitoring

The pharmacodynamic response to cisatracurium was assessed by accelerometric peripheral nerve stimulation (TOF Watch, Organon Teknika). The skin over the ulnar nerve at the wrist was gently abraded and then cleaned with an alcohol wipe. Electrocardiographic electrodes were applied to allow stimulation using the train of four (TOF) twitch technique with assessment of the adductor pollicis twitch response at 1 min intervals. The degree of neuromuscular block was described as a percentage of the height of T1 before dosing and the T4:T1 ratio was also recorded. The maximum suppression (peak effect), the time to maximum suppression after the dose (onset) and recovery parameters were recorded [16].

Blood sampling

Arterial blood was sampled before and on 16 occasions post dose (at 1, 3, 5, 8, 10, 12, 15, 20, 25, 30, 45, 60, 90, 120, 240 and 480 min) after administering a single bolus of 0.1 mg kg⁻¹ cisatracurium. Blood was collected into an EDTA collection tube, mixed gently and then immediately transferred to a 1.5 ml tube and centrifuged promptly at the bedside using a Beckman Microfuge (15 000 rev min⁻¹, 13 000 g) for 1 min. The plasma was decanted to another 1.5 ml tube containing 25 µl of 2.0 mol l⁻¹ sulphuric acid to prevent degradation of the cisatracurium (this process was completed within 3 min of collection). The specimens were stored frozen at –20°C prior to analysis.

Cisatracurium plasma concentration was determined by high performance liquid chromatography, using a Luna® C₈ reverse phase column (150 mm × 4.6 mm, 5 µm; Phenomenex, Torrance, CA, US) coupled with fluorescence detection. This method was adapted from that previously described [17] and the assay proved to be sensitive and linear over the range of 20 to 1000 ng ml⁻¹ with precision and accuracy within ± 15%.

PK/PD modelling

PK and PK/PD analyses were performed with a nonlinear mixed-effects population modelling approach as implemented in NONMEM software version VI (ICON Develop-

ment Solutions, Ellicott City, MD, USA). Only the first assessments for all the subjects were used for PK/PD analysis. Population means and inter-subject variability of PK/PD parameters were determined. The first order conditional estimation with interaction option was used for all analyses. Model evaluation was based on graphical inspection of basic goodness-of-fit plots, the objective function value (OFV) and the precision of parameter estimates. A two-compartment model was applied to describe PK data (plasma concentration – time profile). The model was parameterized in terms of the clearance (CL), the central (V_1) and peripheral (V_2) volumes of distribution and the intercompartmental clearance (Q). The volume of distribution at steady-state (V_{dss}) was determined as the sum of V_1 and V_2 . PD data (T1 suppression data) were described by a sigmoid E_{max} model. PK and PD were linked via an ‘effect compartment’ modelling approach [18] (Figure 1). Delay time of transferring cisatracurium from plasma to effect compartment (neuromuscular junction) (t_{delay}), the effect compartment concentration required to produce 50% T1 suppression (EC_{50}), which is an index of patient sensitivity, and the slope factor (γ) were also determined.

Inter-subject variability was modelled using an exponential model. This imposes a log-normal distribution on

the parameters and the result is expressed as a coefficient of variation. Residual unexplained variability was modelled as a combination of exponential and additive error models for PK data whereas an additive error model was used in fitting the PD data.

Results

Eight critically ill patients with sepsis were studied on a total of 17 separate occasions during their ICU admission. The basic demographic details and clinical diagnosis are provided in Table 1. The cohort had a mean age of 55.3 years and a mean APACHE II score of 11.9 on the first day of study assessment. The single dose pharmacokinetic parameters and neuromuscular response data for the first assessment of all patients are presented in Table 2. From the measured plasma concentrations the mean $\pm$ SD steady-state volume of distribution ($V_{d,ss}$) was $111 \pm 71 \text{ ml kg}^{-1}$ and the mean $\pm$ SD plasma clearance (CL) was $5.23 \pm 1.8 \text{ ml min}^{-1} \text{ kg}^{-1}$. The elimination half-life was 14.8 min calculated from the CL and V_d . The time to maximum block was 8.3 ± 2.9 min and twitch height failed to return to baseline levels on nine occasions. The maximum block achieved was $95 \pm 6.3\%$ of baseline. Unreliable peripheral nerve stimulation readings (PD data) were noted on two patients during the study. The delay time of transferring cisatracurium from the central compartment (plasma) to the effect compartment (t_{delay}) was 17.2 min from model fitting and an effect compartment concentration resulting in 50% effect (EC_{50}) was 128 ng ml^{-1} .

Figure 2 shows plasma concentration – time profile of each patient obtained on different occasions and the fitting curve for the first assessment. It is obvious that the first assessment data are well described by the current model. However, the concentration – time profile of the repeated assessment (second or third run) of some patients (patients 2, 4, and 8) is not predicted by the first assessment.

Figure 1
Schematic of PK/PD link model showing the link between the three compartment PK model and sigmoid E_{max} PD model

Table 1
Demographic characteristics and clinical diagnosis of patients

Patient	Diagnosis	Age (years)	Gender	Apache II	Initial SOFA score	Weight (kg)	Height (cm)	Times assessed
1	Biliary sepsis	49	F	15	7	86	150	3
2	Pneumonia	63	M	9	4	71	168	2
3	Cholangitis	70	M	15	12	104	172	2
4	Infected pancreatitis	31	M	10	5	93	185	2
5	Pneumonia	45	M	16	8	62	164	3
6	Intraabdominal sepsis	60	M	15	6	105	170	2
7	Pneumonia	51	M	8	10	92	181	1
8	Oesophageal perforation	73	M	7	5	109	179	2
Mean		55.3	1/7 (F/M)	11.9	7.1	88.6	169	
SD		14.0		3.7	2.7	16.6	11	

Table 2
Basic parameters of illness severity, pharmacokinetics and pharmacodynamic response

Illness severity			Pharmacokinetics			Pharmacodynamics			Recovery Time to maximum recovery baseline (%)	Recovery Time to maximum recovery (min)	EC ₅₀ (ng ml ⁻¹)	t _{delay} (min)
Patient	Days in ICU	Number of SIRS	Vasoactive agents	Clearance (ml min ⁻¹ kg ⁻¹)	V _{d,ss} (ml kg ⁻¹)	Onset Maximum effect (% of baseline)	Onset Time to maximum effect (min)					
1	3	4	Yes	4.68	101	94	11.5	89	68.5	234	14.2	
2	5	3	No	7.45	139	100	8	70	72	80.0	13.2	
3	1	2	No	6.49	130	100	6	60	121	61.6	41.3	
4	2	4	Yes	9.28	149	84	9	100	75	129	19.0	
5	5	3	Yes	4.89	116	92	11	100	63	238	9.48	
6	3	3	Yes	3.62	98.5	NR	NR	NR	NR	NR	NR	
7	3	3	Yes	5.56	134	NR	NR	NR	NR	NR	NR	
8	4	3	Yes	2.73	67.2	100	4	NR	NR	128	17.1	
Mean	5.4	3		5.23*	111*	85.6	8.7	86.1	59.8	128*	17.2*	

*Population estimation from NONMEM analysis. NR, No result obtained. SIRS, Systemic Inflammatory Response Syndrome. V_{dss}, volume of distribution at steady-state.

The PD profile of each patient is shown in Figure 3. The data are only available for six patients. As observed in the PK profile, the model could well describe the first assessment data, while fail to predict the repeated assessment for all patients.

The PK/PD parameters obtained in the current study in critically ill patients with sepsis were compared with published data from other patient populations as shown in Table 3. These sepsis patients had a relatively longer time to a less profound maximum block compared with all patients groups. In keeping with this finding the delay time of transferring cisatracurium from the central compartment to the effect compartment was also longer than that described previously and the effect compartment concentration resulting in 50% effect was larger.

Discussion

This is the first study to model systematically single dose PK and PD data for cisatracurium in intensive care patients with severe sepsis. It confirms that critically ill patients with sepsis are resistant to neuromuscular blockade following a single bolus dose of 0.1 mg kg⁻¹ (2 × ED₉₅) cisatracurium. This resistance is probably more attributed to altered PD as the PK parameters were similar to those described in some other patient populations.

Pathophysiological changes seen in critically ill patients can impact on both PK and PD responses. Alterations may be seen in pH, protein binding, cardiac output as well as fluid shift and hepatic or renal dysfunction. Drug interactions are numerous and other therapeutic interventions, such as renal replacement therapy or vasopressor use, may also result in significant changes in drug behaviour [9]. The larger than expected V_d predicted in patients with severe sepsis was not seen in this study. This may reflect the local practice in fluid resuscitation or a reduced severity of illness when compared with previous studies that have noted greatly expanded distribution volumes [11, 12]. While all patients had severe sepsis, as defined by the presence of organ failure, the APACHE II and SOFA scores suggest they were at the less severe end of the spectrum of life threatening sepsis. This is in part due to the deliberate exclusion of those patients requiring renal replacement therapy.

In this study, it was found that the PK and PD profile of critically ill patients obtained from the initial assessment seemed to predict inappropriately the consequent assessment when the patients were examined repeatedly especially for the PD profile. The changes of patients' disease status and the treatment received might contribute to it. However no covariates were noted during the study to predict these changes, which would support the need for increased neuromuscular monitoring in these patients.

The analysis of the PK data and subsequent modelling for cisatracurium is complex. Because of the organ inde-

Figure 2

Plasma concentration – time profile of each patient after a single bolus injection of cisatracurium. The solid line represents the fitting curve for the data obtained from first assessment. Δ measured data from first assessment, ■ measured data from second assessment, ○ measured data from third assessment

pendent elimination of the drug some authors believe any model must consider elimination from more than just the central compartment and failure to do so underestimates the V_d [19]. Cisatracurium elimination may be from tissues as well as plasma and this would magnify any changes if the V_d is increased. Previous work has estimated cisatracurium PK parameters using a one compartment model after infusion [1] and a two compartment model (with elimination from the central compartment or from both the central and peripheral compartment) [2, 3, 5, 20–22]. In this study, we found that a two compartment model with elimination from the central compartment could well describe the plasma concentration–time profile as assessed by visual evaluation of fitting curve.

Our results suggest a slow onset for a block that is not complete, does not last as long as may be expected and does not return to baseline. It is possible that the PD response to neuromuscular blocking drugs is altered on

multiple levels in patients with sepsis [7]. Changes in tissue blood flow may impair drug distribution to the neuromuscular junction in this patient population, resulting in a delay in observed onset time. Altered acetylcholine receptors and altered drug response are possible and have been described in other clinical settings [23]. However, previous animal studies have reported that an alteration in drug binding to plasma proteins rather than changes in the acetylcholine receptor is the more likely reason for an altered drug response in systemic inflammation [24]. Proving alterations in protein binding for cisatracurium is difficult as the acidification of samples to inhibit metabolism also results in protein precipitation and so prevent evaluation of protein binding [25].

The majority of prior studies on other patient groups have used the standard dose of $2 \times ED_{95}$ (0.1 mg kg^{-1}) as used in this study [1, 3, 22, 26]. To overcome the slow onset of an incomplete block, the results of this study support

Figure 2

Continued

the routine use of larger dose (at least $3 \times ED_{95}$) to achieve an adequate block in a clinically appropriate time frame.

It is unclear if the observed failure of the assessed neuromuscular function to return to baseline in many patients represents a real phenomenon or is a measurement artifact. It must be acknowledged that although peripheral nerve stimulation is the common technique used to guide clinical therapy, it has limitations in this patient cohort [27]. The presence of tissue oedema or profuse sweating can limit recordings and were the likely explanation on the occasions when no reliable recordings could be obtained in this study. It would seem less likely that these factors could account for a failure to return to baseline strength when good ongoing recordings were possible. We believe that the observed delay in response and faster recovery in some patients reflects a degree of abnormal response in the neuromuscular junction in patients with sepsis. Cer-

tainly the use of neuromuscular blocking drugs has been associated with a prolonged weakness in critically ill patients [28, 29].

This study suggests that standard dosing of cisatracurium in patients with severe sepsis results in a slower patient response with a reduced effect. Use of a larger dose may overcome this reduced delayed response. Further studies are indicated to define the impact of increased dosing of cisatracurium in patients with severe sepsis, particularly to evaluate the speed of onset, degree of block, recovery of neuromuscular function and ICU length of stay.

Competing Interests

There are no competing interests to declare.

Figure 3

Pharmacodynamic profile [T1 suppression (%) vs. time] of each patient after a single bolus injection of cisatracurium. The solid line represents the fitting curve for the data obtained from first assessment. Δ measured data from first assessment, $\blacksquare$ measured data from second assessment, $\circ$ measured data from third assessment

Table 3

Comparison of pharmacokinetic and pharmacodynamic parameters of cisatracurium after an i.v. bolus of 0.1 mg kg⁻¹ in different patients population [mean (SD)]

Parameter	Critically ill patients with sepsis (n = 8)*	Critically ill patients with mechanical ventilation [1] (n = 6)†	Healthy patients [4] (n = 10)‡	Children [5] (n = 9)§	Surgical patients¶ [2] Liver transplantation (n = 12)	Control (n = 11)	Geriatric surgical patients†† [3] Elderly (n = 12)	Young (n = 12)
CL (ml min ⁻¹ kg ⁻¹)	5.2 (1.8)	7.9 (2.7)	6.4 (0.9)	6.8 (0.7)	6.6 (1.1)	5.7 (0.8)	5.0 (0.9)	4.6 (0.8)
V _{d,ss} (ml kg ⁻¹)	111 (71)	317 (14.7)	207 (25)	207 (31)	195 (38)	161 (23)	126 (18)	108 (13)
EC ₅₀ (ng ml ⁻¹)	128 (58)‡‡			129 (27)	79 (33)	98 (34)		
Maximum block (%)	95.0 (6.3)‡‡		100 (0.0)		99.5 (1.4)	99.8 (0.6)	99.0 (1.8)	99.5 (1.0)
Time to maximum block (min)	8.3 (2.9)‡‡		3.6 (0.9)		2.4 (0.8)	3.3 (1.0)	5.2 (1.3)	4.2 (1.9)
T25 (min)	44.3 (24.3)‡‡			37.6 (10.2)	53.5 (11.9)	46.9 (6.9)	61.1 (13.8)	55.6 (9.2)

*Data defined for patients in this study. †CL, V_{d,ss} was normalized to mean bodyweight of the population (69 kg). ‡CL, V_{d,ss} was normalized to mean bodyweight of the population (66 kg). The population was healthy patients scheduled for elective operations in general surgery, ophthalmology and major otorhinolaryngology. §Children were aged from 1–6 years and undergoing dental surgery. ¶‘Control’ were patients without known hepatic or renal disease and ‘Liver transplant’ were patients with end-stage liver disease and undergoing liver transplantation. ††Elderly patients were aged 65–82 years and young patients were aged 30–49 years. ‡‡n = 6.

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