OPIS PRZYPADKU/CASE REPORT
Otrzymano /Submitted: 18.06.2009 • Poprawiono/Corrected: 30.09.2009 • Zaakceptowano/Accepted: 01.10.2009

Pharmacokinetics and pharmacodynamics of cisatracurium in a patient with Steinert's myotonic dystrophy

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Summary

Case report. A patient with myothonic dystrophy (MD), who received 0.2 mg.kg-1 cisatracurium during a propofol-fentanyl-O2:air anaesthesia, was monitored by Datex electromyography. The cisatracurium resulted in a rapid onset of complete (100%) neuromuscular block, in 2.8 min, a clinical duration (time from injection of cisatracurium to 25% ratio of the first twitch of the train-of-four to the control twitch (T1/C ratio) of 84 min, a recovery index (25% to 75% T1/C ratio) of 17 min, and recovery TOF-ratios (ratio of the fourth to the first evoked response) of 0.75, 0.90, 0.95 and 1 in 142, 146.2, 147.9 and 150.9 min respectively. ***Conclusion.*** This case demonstrates that cisatracurium behaves in Curschmann- Steinert's disease just as other neuromuscular blocking agents (NMBAs), with the possibility of increased sensitivity to cisatracurium, although the magnitude of these changes is variable and depends on numerous factors. For this reason careful quantitative monitoring of neuromuscular transmission is mandatory. *Anestezjologia i Ratownictwo 2009; 3: 400-405.*

Keywords: cisatracurium, myothonic dystrophy, neuromuscular blockade

Introduction

Myothonic dystrophy (MD), was first diagnosed by Steinert in 1909. It is also known as myotonia dystrophica, Steinert's syndrome or Curschmann- Steinert's disease. MD is a severe dominant autosomic multisystemic disorder, and the most common and serious form of myotonic dystrophy afflicting adults. MD has an incidence of 1/8000 newborns and a prevalence of 2.1-14.3/100000 habitants [1-4].

The clinical manifestations of MD can range from a late onset presented after 50 years of cataracts, to an extremely severe, often fatal congenital myopathy. DM's heredity is characterised by the existence of anticipation, so that successive generations show the earliest and severest appearances of the illness [5]. Usually, MD becomes evident between the second and fourth decades of life. The clinical picture consists of myotonia, progressive weakness and wasting of facial, respiratory, laryngeal, axial and distal limbs' muscles.

MD is a multisystemic disorder, and can be associated with cardiomyopathies, cardiac conduction disturbances, chronic pulmonary obstructive disease and peripheral airway obstruction related to alterations in the elastic properties of the lung [6], obstructive sleep apnoea syndrome, microatelectasis, chest wall deformity, pathognomonic respiratory patterns (rapid shallow breathing) due to progressive reduction of the tidal volume, and decreased afferent inputs from the periphery to the supraspinal centres, increased respiratory work (inability to use the expiratory abdominal muscles efficiently), delayed gastric emptying, cognitive

disorders (mental deficiency, attention disorders), diabetes mellitus, hypogonadism, hypothyroidism, cataracts, infertility and diabetes mellitus [7].

Myotonia (slow relaxation after contraction) is present in almost every patient with symptomatic MD. The neuromuscular function may exhibit hyperexcitability secondary to chloride and sodium channels alterations, which condition repetitive potentials of action. Myotonia is especially observed in masticator, neck, pharynx and distal limbs' musculatures.

MD is associated with hypersensitivity to some anaesthetics, such as hypnotics, neuromuscular blocking agents (NMBAs) (both depolarising and non depolarising), neostigmine (cholinesterase inhibitors) and opioids. This hypersensitivity could result in postoperative complications due to muscular weakness and central hypoventilation with diminished response to carbon dioxide. Other factors related to the triggering of a myotonic crisis are hypothermia, shivering and mechanical or electrical stimulation.

To date, there are few references concerning the clinical use of NMBAs and only one of cisatracurium in DM [5]. In this clinical case though, we contribute something to our knowledge of the subject with the pharmacodynamic profile and the pharmacokinetics, analysing the possible factors that could modify the effect of cisatracurium in DM.

Clinical features

After approval from the local ethics committee and written informed consent was obtained, a 54 year-old man, 165 cm tall, weighing 71 kg, was programmed for a thoracotomy due to a lung nodule compatible with bronchogenic carcinoma.

The patient was previously diagnosed with penicillin allergy, familial Steinert's myothonic dystrophy (all his brothers were also affected), active tobacco consumption, anxiety, depressive syndrome, and oesophageal reflux with hiatal hernia.

He was previously operated on with a regional anaesthesia, and had never received general anaesthesia before. Pre-operatively, the only remarkable item was the existence of a first degree auriculoventricular heart blockade (with normal echocardiography). The results of laboratory tests (hemogram, biochemical and coagulation), were all within normal limits.

After continuous electrocardiography, non-invasive arterial blood pressure, pulsoximetry and neuromuscular blockade (Relaxograph Datex®) at the *adductor pollicis* muscle, according to the recommendations of the GCPR [8], were all monitored, and a thoracic epidural catheter was emplaced (D3-D4). Anaesthesia was then induced with fentanyl and propofol. The patient was intubated easily, using the Sellick manoeuvre without NMBAs. Immediately after, a nasogastric tube was placed to favour drainage of the gastric dilation. Once intubated the patient was monitored with capnography and invasive arterial pressure, central venous pressure, diuresis and esophageal temperature. Hypothermia was prevented with fluid therapy warming and a hot air blanket. Anaesthesia was maintained with O_2-air, continuous infusion of propofol and supplemental doses of fentanyl. A continuous epidural infusion of bupivacaine with fentanyl was also used. Once the Relaxograph was calibrated, after electromyographic signal stabilisation, 14 mg of cisatracurium (4 x ED_{95}) was injected to obtain an adequate surgical neuromuscular blockade. The patient was then moved to the left decubitus position for the surgery. Fibreoptic bronchoscopy was performed to assess correct placement of the orotracheal tube. The procedure lasted for 3 hours (about 2 hours of left single lung ventilation). Hemodynamics were stable and normal during the procedure. The patient was extubated in the surgical room and transferred to the Critical Care Unit, where he was kept under strict observation during the immediate post-operative period, without complications.

Concerning the PK-PD study, after stabilisation of anaesthesia and train of four (TOF) response, a blank sample was drawn before the bolus dose of cisatracurium was administered. Blood sampling was performed at minutes 0 (blank sample), 2.5 , 7.5 , 10, 15, 20, 40, 75 and 120 min and also at determined moments of spontaneous neuromuscular recovery: recovery of first twitch from the TOF response to (duration of action, DA) 5, 10, 25, 50, 75, 90, 95 and 100%, recovery index 25%-75% (RI_{25-75} , time between 25 and 75% recovery of first twitch) and TOF-ratios of 50, 70, 75, 80, 85, 90, 95 and 100%.

To minimise the in vitro degradation of cisatracurium, samples were kept in pre-acidified tubes in an ice water bath and centrifuged, then frozen immediately on dry ice. Samples were stored at -70°C until high performance liquid chromatography analysis coupled with fluorescence detection could determine the plasmatic concentrations of the single bolus of cisatracurium,

after which a pharmacokinetic/pharmacodynamic (PK/PD) analysis was completed, using a bicompartmental model with beta phase with the program WinNonlin Professional (Pharsight Corp.®).

Discussion

Anaesthesia in patients with DM can result in life-threatening complications, such as malignant hyperthermia (we applied the specific protocol to avoid it), dysrhythmias such as atrial fibrillation or flutter, ventricular tachycardia, ventricular fibrillation or cardiac arrest. Degeneration of cardiac muscle invariably accompanies DM, and endomyocardial fibrosis, fatty degeneration and hypertrophy of myocardial cells could lead to conduction abnormalities. A pacemaker is sometimes necessary in DM, and one should be available during surgery.

The oesophageal reflux with active hiatus hernia, in a patient who shows great anxiety, increases the risk of pulmonary aspiration, and so he should be intubated quickly with great caution. Our patient was uncooperative, and considered an inappropriate candidate for awake fibreoptic intubation as no sedative drugs could be administered, in order to avoid the possibility of apnoea or respiratory depression due to hypersensitivity. Therefore, intubation was performed without NMBAs for many reasons. First, succinylcholine can trigger myotonic crisis causing difficulties in orotracheal intubation and ventilation. Second, the relationship between DM and malignant hyperthermia is unclear, and finally, the patient presented symptomatic oesophageal reflux, so a non-depolarising agent should be used in higher doses than normal to reduce the onset, especially in a patient with possible sensitivity to these drugs. Some authors also claim that non-depolarising NMBAs are not mandatory for intubation [9].

Propofol was used as an anaesthetic inductor because a total intravenous anaesthesia (TIVA) was selected as the most appropriate anaesthetic technique for this patient. We avoided halogenated agents to prevent malignant hyperthermia and myocardial depression [10]. There is disagreement regarding the use of propofol in DM, as some authors reported respiratory depression or even prolonged apnoea [11] while others have not observed problems [12]. The same is applicable to thiopental and etomidate, and both drugs have been used in DM [13]. However these anaesthetic inductors are not suitable for use in continuous infusion in a TIVA. So, propofol was used despite the reported complications (prolonged apnoeas, one episode of myasthenic crisis and excessive arterial hypotension when associated with isoflurane) [3,14].

Concerning the discussion of whether or not to use NMBAs, although surgery (and intubation) without these drugs has been postulated previously [3,10,15], we preferred to use cisatracurium to obtain an adequate surgical exposure.

Clinical experiences had been reported anecdotally, with vecuronium [16,17] (different sensitivity was observed in various muscles) [18], mivacurium, with normal [19] and increased sensitivity ($RI_{25\%-75\%}$ of 10 min and a $RI_{5\%-95\%}$ of 30 min) [20] and atracurium [21,22], where sensitivity was not seen. There are no reported data about the effects of cisatracurium in DM. In our patient, we observed (table 1) a normal onset value and prolonged DA_{25} (84 min) and RI_{25-75} (17 min) compared with DA_{25} of 24-38 min and RI_{25-75} of 12-14 min respectively [23]. The increase of the RI_{25-75} is especially significant, as this value usually remains fairly constant despite differences in the dosages of cisatracurium, with values of 12,6 min (2 ED_{95}), 13,8 min (3 ED_{95}), 19 min (4 ED_{95}), 14.5 min (6 ED_{95}) and 14.3 min (8 ED_{95}) [23].

Table 1. PD parameters of cisatracurium (4 x ED_{95}) in Steinert's myotonic dystrophy

Parameter (min)	Time (min)
Maximum blockade	2.8
Duration of action 5%	67.1
Duration of action 10%	77.3
Duration of action 25%	84.0
Duration of action 50%	92.7
Duration of action 75%	101.0
Duration of action 90%	104.3
Duration of action 95%	104.9
Duration of action 100%	105.3
Recovery index 25%-75%	17.0
TOF-ratio 50%	134.9
TOF-ratio 70%	140.6
TOF-ratio 75%	142.0
TOF-ratio 80%	143.0
TOF-ratio 90%	146.2
TOF-ratio 95%	147.9
TOF-ratio 100%	150.9

Table 2. Plasmatic concentrations of cisatracurium (venous samples and times of extraction)

Time (min)	Concentration (μg.ml^{-1})
0	0,000
2,5	2,941
7,5	1,658
10	1,224
15	0,840
20	0,755
40	0,352
75	0,122
120	0,062

A kinetic analysis was made to compare with healthy patients (table 3) with liquid chromatography and spectrometry of masses of high resolution. The PK parameters of cisatracurium at doses from 1.5 to 6 ED_{95} are: k_{e0} of 0.050 min^{-1}, $t_{1/2}\beta$ from 22.6 to 26.5 min, Clp from 3.6 to 4.6 ml. min^{-1}.kg^{-1}, V_{dss} from 0.07 to 0.12 l.kg^{-1}, V_1 of 0.05 l.kg^{-1} and MRT of 30.6 min.

Factors that may cause PK differences in DM with regard to healthy patients are not well established. On the one hand, pharmacokinetic/pharmacodynamic (PK/PD) parameters of NMBAs are generally assumed to be dose-independent. Over the range of doses used in clinical practice, the equilibration rate constant between plasma and effect compartment concentrations (ke_0) is believed to be concentration independent for most drugs [24]. However, this may not be the case after high bolus doses of drugs that reach maximum effect within the first 2 min of i.v. administration, such as NMBAs [25].

On the other hand, the form of administration of cisatracurium can influence the diffusion of the drug into the synaptic cleft, because there is a limited space (30-50 nm) available for diffusion of NMBAs within the synaptic cleft itself. After a high bolus dose, a transient increase in the unbound concentration of cisatracurium may occur as nicotinic receptors and non-specific sites become suddenly occupied, thus reducing the concentration gradient of unbound cisatracurium between the interstitial fluid and the synaptic cleft. Owing to the very high density of nicotinic receptors, a slower diffusion of NMBAs into this restricted space may ensue. The nerve terminal would also represent a physical barrier to the diffusion of NMBAs out of the cleft, thus enhancing repetitive binding to acetylcholine receptors [25].

Table 3. PK parameters of cisatracurium (4 x ED_{95}) in Steinert's myotonic dystrophy

	Unit	Value	Error	VC %
A	mg.L^{-1}	3.142	0.193	6.17
B	mg.L^{-1}	1.107	0.238	21.57
Alpha	min^{-1}	0.198	0.030	15.47
Beta	min^{-1}	0.027	0.006	22.39
AUC	mg.min.L^{-1}	55.455	4.020	7.25
K10 Half Life	min	9.043	0.831	9.19
Alpha Half Life	min	3.492	0.539	15.45
Beta Half Life	min	24.793	5.546	22.37
K10	min^{-1}	0.076	0.007	9.20
K12	min^{-1}	0.077	0.013	17.92
K21	min^{-1}	0.072	0.019	27.41
Cmax	mg.L^{-1}	4.250	0.197	4.64
V1	L.kg^{-1}	0.047	0.002	4.64
CL	L.kg^{-1}.min^{-1}	0.003	0.0002	7.27
AUMC	mg.min.L^{-1}	1497.043	389.840	26.04
MRT	min	26.995	5.173	19.16
Vss	L.kg^{-1}	0.097	0.012	12.67
V2	L.kg^{-1}	0.050	0.011	22.78
CLD2	L.kg^{-1}.min^{-1}	0.003	0.0005	14.26

PK parameters for a bicompartimental model with beta phase calculated with WinNonlin Professional (Pharsight Corp.®). There are a good adjustment and small coefficients of change (VC %). AUC = area under the concentration - time curve, Cmax = maximum concentration, CL = plasmatic clearance, AUMC = area under the moment curve, MRT = mean residence time, Vss = volume in steady state and CLD2 = intercompartmental clearance.

The exact reason for the altered response in DM patients to NMBAs is still unclear and remains speculative. In principle, two possibilities must be considered: (1) changes in pharmacokinetics; and/or (2) changes in pharmacodynamics, such as alterations in the neuromuscular junction due to the underlying disease.

In conclusion, this case demonstrates that cisatracurium behaves in Curschmann- Steinert's disease just as other NMBAs, with the possibility of increased sensitivity to cisatracurium, although the magnitude of these changes is variable and depends on numerous factors, including the extension of the disease and the type and dosage of NMBAs. For this reason it is necessary to include anaesthetic measurements adapted to anticipate the possible complications that can appear in DM, and from the point of view of the handling of NMBAs, careful quantitative monitoring of neuromuscular transmission is mandatory.

Acknowledgments

We would like to thank Rosario Calvo, Antonio Carcas, Luciano Aguilera, Belén Sádaba and Miguel A. Campanero for their technical support.

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