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Pharmacokinetics and pharmacodynamics of cisatracurium in a patient with Duchenne muscular dystrophy

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Summary

Case report. We describe the effect of 2 x ED_{95} of cisatracurium on a 10 year old boy diagnosed with DMD: slow onset with maximum block in 10.5 minutes and a prolonged effect, with duration of action of 25% (DA_{25}) of 56.2 min and RI_{25-75} of 80.4 min (up to 5 times the normal values). A kinetic analysis was made to compare this result with healthy patients, with liquid chromatography and spectrometry of masses of high resolution. The PK parameters of cisatracurium in the case reported were: $t_{1/2}\beta$ 16.2 min, Clp 4,833 ml. $kg^{-1}.min^{-1}$, V_{dss} 0,078 $l.kg^{-1}$, V_1 of 0,05 $l.kg^{-1}$ and MRT of 16.152 min. ***In conclusion***, this case demonstrates that cisatracurium behaves in DMD just as other neuromuscular blocking agents (NMBAs), with increased onset and recovery, although the magnitude of these changes is variable and depends on numerous factors, including the extension of the illness and the type and dose of the NMBAs. *Anestezjologia i Ratownictwo 2009; 3: 406-411.*

Keywords: anaesthesia, cisatracurium, Duchenne's muscular dystrophy

Introduction

The pseudohypertrophic muscular dystrophy, also known as Duchenne muscular dystrophy (DMD) is the most common (3 per 10,000 births) and most severe form of progressive muscular dystrophy. DMD is an inherited, X linked disease caused by mutations in the dystrophin gene, resulting in complete loss of the muscular protein dystrophin, leading to a weakened sarcolemma [1]. The etiology of DMD is genetic, however the specific pathophysiological mechanism remains obscure. Three major theories to explain manifestations of the disease are neuronal malfunction, microinfarcts due to circulatory disorder, and genetic malfunction of the surface membranes of muscle cells and perhaps other cells as well.

DMD is characterised by severe proximal muscle weakness, progressive degeneration, and fatty infiltration of muscles. The progressive nature of the disorder results in restrictive pulmonary disease, multiple contractures and kyphoscoliosis, becoming apparent in males aged 2 to 5 years. There is steady deterioration in skeletal muscle strength, resulting in confinement to a wheelchair by 8 to 11 years. Death usually occurs at 15 to 25 years of age due to congestive heart failure, pneumonia, or both. Until treatment of the basic genetic defect is available, medical, surgical, and rehabilitative approaches can be used to maintain patient function and comfort.

One concern for the anaesthetist when managing DMD patients is the use of depolarising neuromuscular blocking agents, because of the risk of hyperkalemia,

rhabdomyolysis or even cardiac arrest. The effect of non-depolarising muscle relaxants, however, remains to be elucidated in these patients.

To date, there are no references on the use of cisatracurium in DMD. In this clinical case though, we contribute something to our knowledge of the subject with, in addition to the pharmacodynamic profile and the pharmacokinetics, analysis of the possible factors that could modify the effect of cisatracurium in these patients.

Clinical features

After approval from the local ethics committee and written informed consent from his parents, a 10 year-old boy, 137 cm tall, weighing 40 kg, with progressive kyphoscoliosis caused by DMD diagnosed by histological examination, was programmed for thoracolumbosacral vertebral arthrodesis surgery. Pre-operatively, he showed a moderate pulmonary restrictive pattern and right bundle heart blockade. The results of laboratory tests (hemogram, biochemical and coagulation) were all within normal limits. Physical examination showed the characteristic signs of his disorder, resulting in confinement to a wheelchair. His medical history indicated one episode of general anesthesia (muscle biopsy) without information or clinical report about incidences.

Continuous electrocardiography, invasive arterial blood pressure, pulsoximetry, capnography, esophageal temperature, central venous pressure, diuresis and neuromuscular blockade (Relaxograph Datex®) of the *adductor pollicis* muscle according to the recommendations of the GCPR [2], were all monitored. Cefazoline (1 g) was administered as antibiotic prophylaxis. Anesthesia was induced with fentanyl (0.1 mg) and propofol (150 mg), after which the patient was intubated easily using the Sellick manoeuvre without neuromuscular blocking agents (NMBAs). Immediately after, a nasogastric tube was placed to favour drainage of the gastric dilation. Anesthesia was maintained with O_2-air, a continuous infusion of propofol and repeated doses of fentanyl.

Cisatracurium besylate (Nimbex®) (4 mg, 2 ED_{95}) was administered to obtain an adequate surgical neuromuscular blockade after electromyographic signal stabilisation, and the patient was then moved to the prone position for surgery, which ultimately lasted 7.5 hours. Blood loss was corrected by transfusion of crystalloids, colloids and packed red blood cells. At the end of surgery, the patient was transferred to the Intensive Care Unit, where he was extubated two hours later. There were no complications within the post-operative period.

After stabilisation of anaesthesia and TOF response, a blank sample was drawn before the first bolus dose of cisatracurium was administered. Blood sampling was performed at minutes 0 (blank sample), 1, 3, 5, 10, 15, 30, 45, 60, 90, 120, 150, 180, 240, 292 and also at determined moments of spontaneous neuromuscular recovery: recovery of first twitch from the TOF response to (duration of action) 5, 10, 25, 50, 75%, 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 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

Anesthesia in patients with DMD can result in life threatening complications, such as malignant hyperthermia [3] (we applied the specific protocol to avoid it), rhabdomyolysis [4], myoglobinuria, respiratory acidosis, massive potassium release leading to dysrhythmias such as ventricular fibrillation or cardiac arrest [5-7] and acute heart failure [8]. Patients with DMD are considered to be at high risk of perioperative complications. Heart failure and respiratory insufficiency often remain covert in the early stages of the disease. Degeneration of cardiac muscle invariably accompanies DMD, so hemodynamic monitoring is necessary, and not only because it is major surgery but also due to the frequent presentation of arrhythmias (especially sinus tachycardia and sinus extrasistolia), mitral regurgitation (due to papillary muscle dysfunction and to decreased myocardial contractility), cardiac failure and complete heart block (a pacemaker should

be available). We had no hemodynamic complications during the perioperative period.

Chronic weakness of inspiratory respiratory muscles and a decreased ability to cough can result in loss of pulmonary reserve, and an accumulation of secretions that predisposes to recurrent pneumonia. Kyphoscoliosis can contribute further to a restrictive pattern of lung disease. Hypomotility of the gastrointestinal tract may delay gastric emptying, which in the presence of weak laryngeal reflexes will increase the risk of pulmonary aspiration. So, these patients must be intubated quickly with great caution [9]. Non depolarising neuromuscular blockers are usually needed, but an increase of dosage to reduce the onset is followed by an undesirable, over-prolonged effect. Rapacuronium is no longer available [10], and the response to rocuronium [9,11] is not as satisfactory as we previously described for 0.6 $mg.kg^{-1}$: maximum block (100%) in 4 min and 40 s, with clinical duration of 74 min, TOF ratio 75% in 134 min and recovery index 25% - 75% (RI_{25-75}) of 101 min [9]. Clinical experiences with vecuronium [12,13], atracurium [14] and mivacurium [15,16] have been reported anecdotally, always with similar findings: greater initial blockade, prolonged RI_{25-75} and lower doses of drug needed to maintain the same effect when compared with healthy children. There do not exist up-to-date references to the employment of cisatracurium in DMD. In this case, (table 1) we observed a slow initial response to cisatracurium with maximum block in 10.5 minutes and prolonged effect, with duration of action of 25% (DA_{25}) of 56.2 min, RI_{25-75} of 80,4 min (table 1) compared with maximum block of 1.7-3.3 min, DA_{25} of 24-38 min and RI_{25-75} of 12-14 min in healthy children respectively [17]. The increase of RI_{25-75} in DMD (up to 5 times normal values) is especially significant, since this value usually remains fairly constant in spite of the differences in 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}) [17].

A kinetic analysis (table 2) was made to compare with healthy patients with liquid chromatography and spectrometry of masses of high resolution. The PK parameters of cisatracurium at doses from 1.5 and 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.

Table 1. PD parameters of cisatracurium (2 ED_{95}) in DMD

Parameter (min)	Time (min)
Maximum blockade	10,5
Duration of action 5%	14,5
Duration of action 10%	25,2
Duration of action 25%	56,2
Duration of action 50%	85,8
Duration of action 75%	136,6
Recovery index 25%-75%	80,4
TOF ratio 50%	56,2
TOF ratio 70%	80,2
TOF ratio 75%	85,8
TOF ratio 80%	96,5
TOF ratio 85%	110
TOF ratio 90%	116,6
TOF ratio 95%	136,6
TOF ratio 100%	219,5

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

Time (min)	Concentration ($\mu g.ml^{-1}$)
0	0,000
1	2,772
3	1,248
5	0,709
10	0,393
15	0,321
30	0,167
45	0,080
60	0,042
90	0,009
120	0,000
150	0,000
180	0,000
240	0,000
292	0,000

Factors that cause PK differences in DMD with regard to healthy patients are multiple, and are not well established. On the one hand, the 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 [18]. 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 [19].

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 the repetitive binding to acetylcholine receptors [19].

The exact reason for the altered response of DMD 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.

(1) DMD patients have a lower percentage of total body water and a higher extracellular water to intracellular water (ECW/ICW) ratio compared with normal subjects. However, it is not known whether this is due to increased fat mass or a decreased amount of ICW in muscle cells in DMD patients. DMD patients have elevated ECW/ICW ratios compared with obese subjects and non-obese controls. However, obese subjects and non-obese controls have similar ECW/ICW ratios, despite the increased fat tissue mass in obese subjects. This suggests that the elevated ECW/ICW ratios in DMD subjects are not due to increased fat mass but rather some other mechanism, likely impaired cellular homeostasis due to muscle membrane instability [20].

(2) There are two seemingly contradictory PD findings (prolonged onset and prolonged recovery) in DMD. The reason for the prolonged duration is easily understood, because it could be due to the known degradation of muscle fibres and their replacement with fatty and fibrous tissue with progression of DMD, decreasing the total number of neuromuscular junctions and receptors. However, patients with DMD, as a result of muscle regeneration, may also have upregulation of nicotinic acetylcholine receptors (AChRs) [21].

Table 3. PK parameters of cisatracurium (2 ED_{95}) in DMD

	Unit	Value	Error	VC %
A	$mg.L^{-1}$	3,85	0,022	0,58
B	$mg.L^{-1}$	0,58	0,014	2,5
Alpha	min^{-1}	0,55	0,007	1,29
Beta	min^{-1}	0,04	0,001	3,33
AUC	$mg.min.L^{-1}$	20,69	0,258	1,25
K10 Half Life	min	3,22	0,047	1,46
Alpha Half Life	min	1,24	0,016	1,28
Beta Half Life	min	16,20	0,539	3,33
K10	min^{-1}	0,21	0,003	1,46
K12	min^{-1}	0,27	0,004	1,63
K21	min^{-1}	0,11	0,003	3,04
Cmax	$mg.L^{-1}$	4,44	0,026	0,6
V1	$L.kg^{-1}$	0,02	0,0001	0,6
CL	$L.kg^{-1}.min^{-1}$	0,004	6E-005	1,25
AUMC	$mg.min.L^{-1}$	334,20	15,194	4,55
MRT	min	16,15	0,544	3,37
Vss	$L.kg^{-1}$	0,07	0,001	2,27
V2	$L.kg^{-1}$	0,05	0,001	3,11
CLD2	$L.kg^{-1}.min^{-1}$	0,006	7,8E-005	1,26

PK parameters for a bicompartmental model with beta phase calculated with WinNonlin Professional (Pharsight Corp.®). These show 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.

This involves an increase in the number of AChRs spreading throughout the muscle membrane. There is now evidence that an isoform of AChR, neuronal (nicotinic) a7AChR, is expressed and upregulated in muscle with these conditions. These a7AChRs are more sensitive to succinylcholine than normal AChRs, but have a lower affinity for non-depolarising neuromuscular blocking drugs, and higher doses are required [22] (shift of the dose response curve of non-depolarising NMBAs to the right). This could be one of the causes of the prolonged onset of these drugs in DMD. Another cause of the altered behaviour of the DMD muscle against NMBAs could be the structural changes in the neuromuscular junction, such as possible changes of dystrophin and its related protein complex in the microstructure of the subsynaptic membrane at the neuromuscular junction (dystrophin is necessary for normal acetylcholine receptor–cytoskeleton interaction). Such a concept could also explain the reported normal response to NMBAs in early stages and the prolonged recovery in later stages of the disease.

In conclusion, this case demonstrates that cisatracurium behaves in Duchenne muscular dystrophy just as other NMBAs, with increased onset and recovery, although the magnitude of these changes is variable and depends on numerous factors, including the extension of the illness and the type and dosage of NMBAs. For this reason it is necessary to adopt anaesthetic measurements adapted to anticipate the possible complications that can appear in DMD, and from the point of view of the handling of NMBAs, careful quantitative monitoring of neuromuscular transmission is mandatory.

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