The King-Denborough syndrome in the paediatric patient.

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ABSTRACT

King Denborough syndrome is a rare myopathy with characteristic skeletal and craniofacial abnormalities and a susceptibility to malignant hyperthermia (MH). We describe the management of two children with a diagnosis of King Denborough syndrome.

The first case is that of a 23-month-old term male infant requiring repair of a cleft palate. After flushing the anaesthetic machine, infusions of remifentanil at 0.25 μ/kg/min and propofol at 12 mg/kg/hr were commenced. These were subsequently changed to 0.40 μ/kg/min and 10 mg/kg/hour followed by 8 mg/kg/hour respectively. The case proceeded uneventfully and the patient was managed in the ward postoperatively. The second case was a three-year-old, 5.7kg, former 34-week premature male infant with a dysplastic kidney and hydronephrosis, and recurrent urinary tract infections requiring ureteric re-implantation and repair of the hypospadias. Cardiac echocardiography confirmed the atrial septal defect (ASD: secundum type). Remifentanil and propofol were also used for this case. The patient was fully awake within 10 minutes and managed in the ward postoperatively.

These case reports describe the successful use of total intravenous anaesthesia with propofol and remifentanil in paediatric patients who are susceptible to MH.

Introduction

The King-Denborough syndrome (KDS) is a rare congenital myopathy that was first described in 1970. It is associated with craniofacial and skeletal abnormalities as well as a susceptibility to malignant hyperthermia (MH).[1] The mortality from anaesthesia-related MH has fallen from 70% when it was first recognised, to less than 5% currently.[2] We report the anaesthetic management of two cases of KDS presenting for surgery.

Case 1

A 23- month-old (9.4 kg) full-term male infant was referred from a peripheral hospital for repair of a cleft palate. The child had two brothers and a sister, all of whom were well. On clinical examination he was found to have an unusual facial expression with low-slung ears, a small chin and ptosis. Motor development was delayed. He was unable to stand and appeared to have diffuse muscular hypotonia. A diagnosis of KDS was made.

On the morning of surgery, EMLA® was applied to the dorsum of the child's hand. A MH emergency kit was immediately available. The anaesthetic machine was flushed with 100% oxygen at 10 l/min for 30 minutes. Once intravenous access was established, infusions of remifentanil at 0.25 μ/kg/min and propofol at 12 mg/kg/hr were commenced. We elected not to use a muscle relaxant. After 2 minutes, the trachea was intubated with a size 4.5mm ID preformed RAE® endotracheal tube. Electrocardiography, pulse-oximetry, non-invasive blood pressure, temperature and end-tidal carbon dioxide were monitored. After ten minutes the propofol infusion was reduced to 10 mg/kg/hour and to 8 mg/kg/hour after a further 10 minutes. The remifentanil infusion was maintained at 0.40 μg/kg/min after surgery commenced. The palate was injected with vasoconstrictor and the repair proceeded uneventfully. There were no haemodynamic changes during the surgery. Approximately twenty minutes before the expected end of surgery, 1 mg of morphine was given intravenously. At the conclusion of surgery, the infusions of remifentanil and propofol were discontinued. A nasopharyngeal tube was inserted. The child was suctioned under direct vision then extubated when awake and spontaneous ventilation had returned.

Postoperatively the patient was managed in the ward with routine postoperative monitoring, including temperature.

Case 2

A 3-year-old, 5.7kg, former premature male infant born at 34-weeks with a dysplastic kidney and hydronephrosis presented for ureteric re-implantation and repair of the hypospadias. He had recurrent urinary tract infections for which he was on antibiotic therapy. The child was known to have KDS and had had a trigger-free repair of a cleft palate a year previously. He had delayed motor milestones, and was unable to sit up. In addition, the child had generalised seizures and an atrial septal defect (ASD). The child's older sibling was well. At preoperative evaluation, we encountered a child with an elongated face with micrognathia, hyperteliorism, low-set ears, ptosis and pectus carinatum. The neurological examination showed marked muscular hypotonia. Cardiovascular evaluation revealed a fixed split second heart sound and an ejection systolic murmur in the pulmonary area. Cardiac echocardiography confirmed the ASD (secundum type). There was no pulmonary hypertension or any other associated anomalies. Laboratory results showed a urea level of 13.6 mmol/L, a creatinine level of 251 μmol/L and a haemoglobin of 11.5 g/dL. Ultrasound of the kidneys showed marked bilateral

hydronephrosis and hydroureter to the level of the bladder. A DMSA scan calculated relative renal function to be 48% on the right-hand-side and 52% on the left.

Sedative pre-medication was omitted. EMLA® was applied to the dorsum of the child's hand. An MH emergency kit was available. The Siemens KION® anaesthetic machine was flushed with 100% oxygen at 10 l/min for 30 minutes. Once intravenous access was established, prophylactic antibiotics were administered for subacute bacterial endocarditis. A bubble trap was used and we paid meticulous attention to prevent paradoxical air embolism Electrocardiography, pulse oximetry, non-invasive blood pressure, temperature and end-tidal carbon dioxide were monitored. Infusions of remifentanil at 0.25 µ/kg/min and propofol at 12 mg/kg/hr were then commenced. The trachea was intubated with a size 4.5mm ID endotracheal tube. After ten minutes the propofol infusion was reduced to 10 mg/kg/hour and to 8 mg/kg/hour after a further 10 minutes. The remifentanil infusion was maintained at 0.30 µg/kg/min after surgery commenced. Surgery proceeded uneventfully, there were no haemodynamic changes and the temperature remained normal, during surgery. Approximately thirty minutes before the expected end of surgery, 1 mg of morphine (175 µg/kg) was given intravenously. At the completion of surgery, the infusions of remifentanil and propofol were discontinued. The child was awake within 10 minutes and the trachea was extubated without incident.

Postoperatively, the child was cared for in the paediatric urology ward and his temperature was monitored. The child had an uneventful postoperative course and was discharged from hospital four days later.

Discussion

In this paper we report on the successful outcome of two patients with the KDS. This rare syndrome was identified by King and Denborough in Australia and New Zealand in 1970.[1,2] It is found in children, with a male preponderance. The boys have cryptorchidism, short stature, lumbar lordosis, thoracic kyphosis and pectus carinatum. These children also have a typical facial appearance with low-set ears, ptosis, micrognathia, crowded teeth, anti-Mongoloid palpebral fissures and a protuberant nose. Many of the features of KDS such as delayed motor development, diminished tendon reflexes, scapular winging and joint hyper extensibility may be explained by the myopathy.[3] Cleft palate and a high-arched palate have been described in several patients.[4-6] The myopathy is usually progressive. In their review of 14 patients with KDS, Graham et al suggest that the syndrome represents a phenotype that is common to several different slowly progressive congenital myopathies.[3] This group of investigators also suggest that there is considerable overlap with the Noonan syndrome, however no KDS patient had been reported with the Noonan combination of hyperteliorism, epicanthic folds, lymphoedema and bleeding diathesis.[3] Cardiac anomalies are not usually associated with KDS.[3]

The identification of KDS is challenging and there are no specific diagnostic criteria. There appears to be no characteristic abnormality on muscle biopsy except for smaller type 1 fibres.[7] It has been suggested that creatinine phosphokinase may be elevated, but the predictive value of this in uncertain.[8] There are two standardized protocols involving *in vitro* muscle contracture tests (IVCTs) that are widely practiced in identifying the MH susceptible patient. These are the European Malignant Hyperthermia Group (EMHG) protocol and the North American Malignant Hyperthermia Group (NAMHG) protocol.[9-12] These protocols are summarized in table1.[9-15] The EMHG protocol has a false positive rate of approximately 6% compared with the 9% false positive rate of the NAMHG protocol.[10-15]

The inheritability of this syndrome is unclear. Originally this syndrome was thought to occur sporadically but there have been several reports of relatives of patients with KDS having musculoskeletal abnormalities, suggesting an autosomal dominant myopathy with variable expressivity.[4,16] In both cases the patients were the only members of their families with craniofacial and musculoskeletal abnormalities. Inherited abnormalities in patients that are MH-susceptible lie in the regulation of myoplasmic calcium.[2] Mutations of the ryanodine receptor gene (RyR1) (chromosome 19q 13.l) may be responsible for conferring MH susceptibility in some patients.[17] Currently it is estimated that up to 25% of MH cases studied may have some form of RyR1 receptor mutation.[2,17,18] Overall genetic testing for MH-susceptibility is limited by being expensive, time consuming, not widely available, has a low sensitivity (25%) and there is significant inter- and intra-individual variability in phenotype expression in patients known to be MH susceptible.[18,19]

The perioperative issues of major concern were the MH susceptibility, and the potential airway problems. We elected not to use Dantrolene prophylaxis. In the past experts have recommended oral Dantrolene. A regimen starting 1-2 days before surgery of 4-8 mg/kg/day[20,21] has been proposed. There are significant variations in the plasma levels achieved

Table 1: Comparison of European Malignant Hyperthermia Group (EMHG) and the North American Malignant Hyperthermia Group (NAMHG) protocols for IVCTs[9-15]

Protocol	EMHG	NAMHG
Halothane administration	Incremental administration of halothane 0.5%, 1%, 2%	Single bolus administration of halothane 3%
Caffeine administration	Incremental administration of caffeine 0.5, 1, 1.5, 2, 3, 4, 32 mM	Incremental administration of caffeine 0.5, 1, 2, 4, 32 mM
Muscle strips in each test	Duplicate	Triplicate
Accepted muscles	M. vastus	M vastus, M. rectus abdominis
Diagnostic criteria	Contracture halothane ≥0.2 g Contracture caffeine ≥0.2 g	Contracture halothane ≥0.7 g (≥0.5-<0.7 g equivocal) Contracture caffeine ≥0.3 g (≥0.2- <0.3 g equivocal)
Estimated false positive rate	6%	9%
Estimated Sensitivity	99%	97%
Estimated Specificity	94%	22%

from oral therapy. Side effects include muscle weakness (22%), phlebitis (10%), respiratory failure (3%) and gastrointestinal discomfort (3%) as well as drug interactions such as prolonging the effect of non-depolarizing muscle relaxants. Several studies have shown that MH is unlikely to occur during or after a trigger free anaesthesia.[22-23] Furthermore, MH has invariably responded to Dantrolene provided the diagnosis is early and the drug promptly administered.[24] In light of the questionable benefits of Dantrolene prophylaxis, the various adverse effects mitigate against its prophylactic use. Both oral and intravenous prophylaxis is now thought to be unhelpful, and Dantrolene prophylaxis is not recommended.[25]

Preparation of the anaesthetic machine requires the use of a disposable circuit, flushing the machine, removal of the vaporizers, changing the soda lime or using a non-rebreathing circuit, and replacement of the breathing circuit.[26] It is not necessary to flush the anaesthetic machine with oxygen for several hours. The 10-minute flush at a fresh gas flow of 10 L/min was derived from the Ohmeda Excel 210 (GE Healthcare, Helsinki, Finland).[27] The new anaesthetic machines contain significantly more parts composed of plastic and rubber that may absorb and subsequently release volatile anaesthetic agents.[28-33] Guidelines specific to anaesthetic machines and manufacturers have been suggested. Preparation of the KION® for MH susceptible patients requires that the machine, without the carbon dioxide absorber, be flushed with 10 l/min fresh gas flows for at least 25 minutes to achieve 10 ppm anesthetic concentration.[31] This fresh gas flow should be maintained throughout the anaesthetic to avoid increases in anaesthetic concentration in the fresh gas flow. Recommendations regarding the Datex-Ohmeda® workstation advise flushing with oxygen at 10 l/min for ten minutes.[32] All machines used in this study achieved less than 1 ppm in 10 minutes. If the ventilator is required then ventilating an artificial lung for 30 minutes with a fresh gas flow rate of 10 l/min should be performed.[32] The Drager Primus® machine must be flushed for at least 70 minutes to decrease the anesthetic concentration to 5 ppm when using a FGF of 10 L/min.[33]. A fresh gas flow of 10 L/min should be maintained for the duration of anaesthesia to prevent the rebound increase in anesthetic concentration in the fresh gas flow.[33]

There is no single clinical feature that is specific for MH. Often, the earliest feature of MH is a rise in the end-tidal carbon dioxide. Desflurane anaesthesia causes a slower onset of MH than that associated with halothane or sevoflurane use.[34,35]. The presentation of this group of patients may be delayed, deviating from classical descriptions of MH and may make the diagnosis more difficult.[34,35] In both of our cases the temperature, end-tidal carbon dioxide and haemodynamics remained within normal limits. Historically, the use of vasopressors agents was considered to be a MH trigger. However, this group of drugs has been reportedly used safely in MH susceptible patients and we elected to permit the use of vasoconstrictors to assist homeostasis.[36,37] The review by Hopkins provides a comprehensive list of pharmacological triggers.[13]

Both patients were managed in the routine postoperative ward. Temperature measurement, in addition to the standard postoperative monitoring, was continued. Given the uneventful intra-operative and immediate post-operative course, the utilisation of intensive care or high care resources was thought to be inappropriate. A recent report by Pollock *et al* advised that a 1-hour stay in the post anaesthesia care unit and a further 1.5 hours in a step-down unit would be acceptable.[38] No cases of MH were missed by the reduced monitoring period. Post-operative pyrexia in the absence of other features of hypermetabolism such as tachypnoea, tachycardia and hypercarbia is not indicative of MH.[39] MH susceptibility is not a contraindication to the safe performance of day-stay anaesthesia.[40]

Both children had significant craniofacial anomalies, making tracheal intubation potentially difficult. Laryngeal mask airway and fibre-optic equipment were readily available. An approach to the paediatric patient with a potentially difficult airway and in particular reports of successful use of these tools in the paediatric patient with congenital anomalies of the upper airway has been advanced in recent reviews.[41-47] These publications provide invaluable general advice about airway assessment, organization and planning as well as specific strategies about devices and instruments, airway maneuvers and maintaining spontaneous ventilation. Preoperative assessment to predict the difficulty in intubation is not always practicable in these patients and we have often employed 3-dimensional spiral computed tomography reconstruction studies. An important clinical clue is that patients with severe airway problems tend to have a history of significant feeding problems.[48,49] The laryngeal mask airway has been recommended as a guide for fibre-optic intubation in children with congenital craniofacial abnormalities.[48-51] Many techniques for intubation without the use of neuromuscular blockers have been described.[52] We elected to use a combination of remifentanil and propofol. The use of a bolus of remifentanil between 1 μ/kg to 5 μ/kg prior to intubation in adult patients is widely cited.[52-56] A bolus of 2 μg/kg or more is associated with an increased risk of bradycardia, hypotension and chest wall rigidity.[57] We omitted the bolus dose of remifentanil and still achieved ideal intubating conditions. There had been a case report of the successful use of remifentanil in a rapid sequence induction in a child with a family history of MH and a potentially difficult airway.[58]

Remifentanil has many features of an ideal anaesthetic drug. It is a potent analgesic and has a short half-life that facilitates the quick return of respiratory and central neurological function. Elimination is independent of organ function and this is ideal for children that may have immature hepatic and renal function. The pharmacokinetics of remifentanil appears to be the same in children and adults.[59-61] Remifentanil is a unique drug and has a useful role to play in anaesthesia for children.

Propofol provides superior intubating conditions to thiopental, achieves greater jaw relaxation and is more effective in attenuating the laryngeal reflexes.[62,63] In most studies citing the use of remifentanil without neuromuscular blockade to achieve tracheal intubation, induction was performed with propofol. It is unlikely that the adequacy of intubating conditions would be the same if either thiopentone or etomidate was employed instead of propofol.[63] When used as a solitary agent, a dose of 2.5 mg/kg propofol may provide satisfactory intubating conditions in up to 96% of patients.[64]

It would be sensible to delay extubation until the patient is fully awake. Regional anaesthesia and nerve blocks are useful alternatives to opioid analgesia in the selected patient. The infra-orbital nerve block has been employed following repair of cleft lip and the caudal block is widely practiced in genitourinary surgery.[65,66]

In conclusion we describe the management of two MH-susceptible paediatric patients with remifentanil and propofol. A high index of sus-

picion, awareness for the need to modify anaesthetic technique as well as the collaboration of the various disciplines with meticulous planning, is key to a successful outcome. **SAJAA**

Author disclosure

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