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Curare and Alloferin in Paediatrics

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The increasing development of paediatric anaesthesia as a specialised entity, which has arisen as a necessity because of the rapid advances in the field of paediatric surgery, has resulted in the gradual application of techniques that have been proven in other branches of anaesthetic practice. This adaptation is particularly evident in the use of muscle relaxants in paediatric anaesthesia, and these drugs, which were originally considered to be contraindicated in children, are now being increasingly employed. Providing the administrator is experienced in the use of these agents, and that there are no specific contraindications to a particular muscle relaxant, age per se is no contraindication and all the relaxant drugs may be safely and successfully used in children of all ages including even the most premature baby.

A number of dose schedules have been recommended and the wide variation in suggested doses may be explained by the different roles to be played by the relaxant drug in the anaesthetic technique. Any dose, therefore, must be considered in the context of the purpose of its administration and the circumstances of the particular anaesthetic technique selected. The use of antidepolarising relaxant drugs in paediatric anaesthesia may be arbitrarily divided into two groups. In the first instance these drugs are used to potentiate the degree of muscle relaxation produced by other anaesthetic agents. Used in this manner only relatively small doses are required and by this means the side effects are claimed to be reduced and the hazards of reversing the myoneural blocking action at the end of the operation are eliminated, since it is believed that at this stage their effects will be minimal. No satisfactory dose schedule can be recommended if antidepolarising relaxants are used in this way since the many variables such as depth of anaesthesia, the particular primary agent being used, the degree of respiratory depression already present and the duration and nature of the operative procedures must all be taken into consideration.

An alternative method is to use large doses of antidepolarising relaxants so as to produce almost complete muscular paralysis thus facilitating the surgical procedure, assisting in the control of pulmonary ventilation and abolishing the unwanted reflex responses to the operative stimuli. Under these circumstances, using only nitrous oxide/oxygen anaesthesia, little

systemic disturbances are produced, excellent operating conditions are guaranteed, and there is a rapid return of protective reflexes and consciousness without restlessness postoperatively. This routine technique is applicable in almost all surgical procedures, whether they are superficial, intra-abdominal or intrathoracic, in which the expected duration exceeds 20–30 min. Standardisation of premedication and induction enables a dose schedule based on body weight to be defined that will produce ideal conditions for intubation and surgery with control of pulmonary ventilation. This method has been used for the last ten years in both Liverpool children's hospitals involving approximately 100,000 children.

The initial intravenous dose of tubocurarine that has been found to be most satisfactory in practice is 0.7 mg/kg body weight with incremental doses of 0.1–0.2 mg/kg body weight. In the case of alloferin the initial dose is 0.32 mg/kg body weight with increments of 0.04–0.08 mg/kg body weight. Using a standard premedication and an induction dose of 4 mg/kg body weight of thiopentone, excellent conditions for intubation can be produced only 1 min after the intravenous administration of the relaxant drug in 90% of cases (Bush 1965). In certain circumstances this dose schedule requires modification. Because of the resistance to antidepolarising relaxants found in patients with burns (Bush 1964) and in those patients with a raised basal metabolic rate, such as produced in infective processes, the initial dose of relaxant requires to be considerably increased. On the other hand, following the prior administration of suxamethonium, following induction of anaesthesia with halothane or ether, or in the presence of muscle wasting diseases, the initial dose should be considerably reduced. Similarly in the case of newborn infants the suggested doses of these relaxants requires alteration because of the reduced requirements of the neonate for the antidepolarising relaxants (Bush and Stead 1962). In these infants it is wise to establish a secure airway by endotracheal intubation prior to the induction of anaesthesia not only because of the relative atraumatic ease of this procedure in the newborn, but also because of the occasional presence of an associated congenital deformity of the upper airway rendering intubation extremely difficult or indeed impossible. However, once intubation has been performed, tubocurarine or alloferin may be administered in incremental doses to produce the desired degree of muscle relaxation and facilitation of the control of pulmonary ventilation. In full-term babies the initial dose of tubocurarine should be 0.5 mg and of alloferin 0.2 mg and 0.25 mg of tubocurarine or 0.1 mg of alloferin in premature babies. The healthy 3 kg infant usually requires 1–1.5 mg of tubocurarine or 0.5–0.75 mg of alloferin initially and after 30–40 min incremental doses of $^1/_4$ or $^1/_8$th of the initial dose depending on the degree of recovery of the neuromuscular block, the efficiency of pulmonary hyperventilation and the expected duration of the operation. In vigorous older infants in the neonatal period of life in whom conscious intubation is not so rigidly indicated and which may be unnecessarily traumatic, full doses of tubocurarine or alloferin may be safely given.

In considering the primary mode of removal of these antidepolarising agents from the myoneural junction by redistribution to the extracellular fluid rather than destruction by enzymatic processes, the clinical duration of these two relaxants should be similar providing an equipotent dose has been administered. Using the recommended initial dose schedule the clinical duration of these relaxants of 35–45 min has been found to be identical for both drugs. Similarly the cumulative effect over a period of 120 min did not suggest any significant difference (Bush 1965). Similar results were obtained in adults over a period of 180 min (Lund and Stovner 1962).

At the termination of the operation, because of the severity of the neuromuscular block produced by these large doses of relaxants, the long duration of action of these agents in relation to complete return of normal function of the myoneural junction and the vital necessity to prevent postoperative muscular insufficiency of the respiratory, pharyngeal and laryngeal muscles, the neuromuscular blocking action of these antidepolarising drugs must be reversed by anticholinesterase drugs. Owing to the difficulty in evaluating the state of the myoneural junction in clinical practice, anticholinesterases are routinely administered in full doses. This practice has proved to be both clinically and electrocardiographically satisfactory and safe. Atropine 0.02 mg/kg body weight is administered intravenously followed a few minutes later by neostigmine 0.07 mg/kg body weight. Pulmonary hyperventilation is continued throughout the period of reversal until the return of spontaneous respiration allows the withdrawal of the nitrous oxide and subsequent removal of the endotracheal tube. Failure of adequate reversal of the neuromuscular block five minutes after the administration of the neostigmine is due either to overdosage of the relaxant or the presence of potentiating factors such as the excessive administration of intrapleural or intraperitoneal antibiotics. Providing sufficient time has been allowed to elapse between the administration of the relaxant and the anticholinesterase, neostigmine has appeared to be equally effective against the myoneural block produced by tubocurarine and alloferin (Bush 1965).

The effects of these relaxants upon histamine release and arterial blood pressure have recently been investigated clinically in a series of children when the relaxant used was unknown to the administrator. Histamine release was judged according to the degree of erythema and whealing along the course of the vein used for this injection, and it was apparent that alloferin administration was associated with statistically significant less reaction than that following tubocurarine (Bush 1965). Whilst it is difficult to correlate local histamine release with more generalised histamine liberation and although both relaxants have been used successfully in children with an asthmatic diathesis, it would seem that alloferin rather than tubocurarine should be preferred in these cases.

Contrary to the results found in adults under different conditions (Hunter 1964), a fall in arterial blood pressure following the administration of either tubocurarine or alloferin occurs in only a minority of cases, and in the major-

ity of instances a steady blood pressure was recorded following tubocurarine whilst after alloferin the majority showed a slight rise (Bush 1965). The effect on the systemic blood pressure could not be correlated with the degree of local histamine release. These results are in keeping with the clinical observation of the greater stability of the systemic blood pressure in children compared with adults, and the resistance encountered in this age group in the production of deliberate hypotension.

In children who require long term pulmonary ventilation such as in cases of tetanus, bronchopneumonia, or status asthmaticus, tubocurarine or alloferin may be used to facilitate control of ventilation. These drugs may be administered intramuscularly in a dose appropriate to the weight of the child and the need for muscular relaxation. It has recently been found that there is a wide variation in relaxant requirements in children requiring controlled pulmonary ventilation for severe bronchopneumonia, and is particularly high in those cases with a compensated respiratory acidosis (Owen Thomas 1966).

Whilst there is considerable scope for further clinical evaluation of these drugs in children, particularly in respect of factors modifying their action, and for more detailed analysis of the effects of these relaxants at the myoneural junction such as the study by Churchill-Davidson and Wise (1964), muscle relaxants will undoubtedly continue to occupy a most influential place in the armamentarium of the paediatric anaesthetist.

Summary

Techniques of anaesthesia involving the use of muscle relaxants are becoming increasingly employed in paediatric anaesthesia and age per se is no contraindication to their use. Because of the many variable factors concerned, a routine dose schedule for the use of relaxants to increase muscle relaxation during anaesthesia with other agents cannot be defined. Using only nitrous oxide/oxygen anaesthesia, muscle relaxants have been successfully used over the last ten years in over 100,000 children. Tubocurarine and alloferin are used in operations lasting longer than 20 min in an initial dose of 0.7 mg/kg and 0.32 mg/kg body weight respectively in order to produce satisfactory conditions for intubation and complete control of pulmonary ventilation. Subsequent doses are of the order of $^1/_4$–$^1/_8$ the original dose. In neonates following conscious intubation the requirements for the relaxant are assessed by incremental doses to produce complete control of pulmonary ventilation. The clinical duration of tubocurarine and alloferin under these circumstances is 35–45 min. Because of the large doses of relaxants, reversal with neostigmine 0.07 mg/kg body weight, preceded by atropine 0.02 mg/kg body weight, is considered essential and has proved to be clinically effective and safe. Histamine release and the effects on the systemic blood pressure have been shown to be of less magnitude with alloferin compared with tubocurarine. Further work is required to provide more detailed analysis of the effects of the muscle relaxants on the myoneural function in children.

Zusammenfassung

Anästhesiemethoden, die den Gebrauch von Muskelrelaxantien einschließen, werden in der pädiatrischen Anästhesie immer häufiger angewendet. Das Alter an sich ist keine Kontraindikation. In Anbetracht der vielen verschiedenen Faktoren kann für die Verabreichung von Relaxantien zwecks Steigerung der Muskelentspannung während der Anästhesie mit anderen Agentien kein Dosierungsschema aufgestellt werden. Bei der Anästhesie mit einem Gemisch von Sauerstoff und Lachgas wurden Muskelrelaxantien in den letzten 10 Jahren bei über 100 000 Kindern mit Erfolg angewendet. Tubocurarin und Alloferin werden bei länger als 20 min dauernden Operationen mit einer Anfangsdosis von 0,7 mg/kg bzw. 0,32 mg/kg Körpergewicht verabreicht, um die für die Intubation sowie auch für die einwandfreie Kontrolle der Lungenventilation günstigen Bedingungen zu schaffen. Die nachfolgenden Dosen bewegen sich zwischen $^1/_4$ und $^1/_8$ der Initialdosis. Bei Neugeborenen, die ohne Anästhesie intubiert werden, müssen die Dosen der Muskelrelaxantien bis zur Erreichung einer vollständigen Lungenventilation gesteigert werden. Die klinische Wirkung von Tubocurarin und Alloferin hält unter diesen Umständen 35–45 min an. Die Verwendung höherer Dosen von Relaxantien verlangt als Gegenwirkung die Verabreichung von 0,07 mg/kg Körpergewicht Neostigmin nach vorangegangener Administration von 0,02 mg/kg Atropin. Diese Maßnahmen erwiesen sich als klinisch wirksam und sicher. Nach Alloferin zeigte sich die Freisetzung von Histamin und dessen Wirkung auf den systematischen arteriellen Druck geringer als nach Tubocurarin. Um Genaueres über die Wirkung von Muskelrelaxantien auf die myoneurale Funktion bei Kindern zu erhalten, bedarf es weiterer Forschungsarbeiten.

Résumé

L'usage des myorelaxants s'est largement répandu dans l'anesthésie en pratique pédiatrique, l'âge, en lui-même, n'étant pas considéré comme une contre-indication à l'emploi de telles substances. Un schéma usuel de posologie pour ces médicaments, lorsqu'ils sont utilisés au cours de l'anesthésie avec d'autres agents, ne peut être établi, en raison de la variabilité de nombreux facteurs. Dans l'anesthésie, par le seul mélange oxygène-protoxyde d'azote, les myorelaxants ont été employés avec succès chez plus de 100000 enfants au cours de ces dix dernières années. La tubocurarine et l'Alloférine employées dans les opérations durant plus de 20 min sont administrées à une dose initiale de 0,7 mg/kg et 0,32 mg/kg respectivement, afin de produire les conditions favorables pour l'intubation et le contrôle complet de la ventilation pulmonaire. L'administration subséquente est faite à raison de $^1/_4$ à $^1/_8$ de la dose initiale. Chez les nouveau-nés devant être intubés sans anesthésie, les doses sont augmentées jusqu'à l'atteinte d'un contrôle complet de la ventilation pulmonaire. La durée de l'effet clinique de la tubocurarine et de l'Alloférine dans ces circonstances est de 35–45 min. Les grandes doses de curarisants utilisés nécessitent l'administration de néostigmine 0,07 mg/kg

précédée d'atropine 0,02 mg/kg. Ces mesures se sont révélées très efficaces et d'une grande sécurité. Il a pu être démontré que la libération d'histamine et les effets sur la pression artérielle systématique furent moindres avec l'Alloférine qu'à la suite de l'administration de tubocurarine. Des recherches plus approfondies sont nécessaires afin d'apporter une analyse détaillée des effets des myorelaxants sur la fonction myoneuronale chez l'enfant.

Riassunto

L'uso dei miorilassanti per l'anestesia in pratica pediatrica ha subito un notevole sviluppo, l'età per se stessa non essendo considerata una contraindicazione per quel che riguarda l'impiego di tali sostanze. Data la notevole variabilità di numerosi fattori, non è possibile stabilire uno schema di dosaggio, qualora questi medicamenti vengano adoperati in anestesia in combinazione con altre sostanze. Durante gli ultimi dieci anni i miorilassanti furono adoperati con successo su più di 100 000 bambini nell'anestesia praticata con la combinazione ossigeno-protossido d'azoto. La tubocurarina e l'Alloferina usate nelle operazioni che durano più di 20 min, vengono somministrate con un dosaggio iniziale di 0,7 mg/kg, rispettivamente 0,32 mg/kg; questo affinchè si ottenga una condizione favorevole per l'intubazione ed un controllo completo sulla ventilazione polmonare. In seguito si somministrano delle quantità del valore di $^1/_4$ fino a $^1/_8$ della dose iniziale. Per quanto riguarda i neonati, che devono essere intubati senza anestesia, le dosi vengono aumentate fino ad ottenere un controllo completo della ventilazione polmonare. La durata d'azione della tubocurarina e dell'Alloferina in tali circostanze è di 35–45 min. Le dosi elevate di sostanze curarizzanti utilizzate, necessitano la somministrazione di neostigmina 0,07 mg/kg e prima ancora di atropina 0,02 mg/kg. Tali misure si sono rilevate molto efficaci e sicure. Si potè dimostrare che la liberazione di istamina e gli effetti sulla pressione sanguigna arteriosa furono meno importanti con l'Alloferina che dopo somministrazione di tubocurarina. Sono ancora necessarie delle ricerche più approfondite per ottenere un'analisi dettagliata degli effetti dei miorilassanti sulla funzione mioneurale del bambino.

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