Suxamethonium was introduced into clinical practice in 1951 after the description of its neuromuscular blocking action [1, 2]. It soon became apparent, with reports of myalgia following its use [3, 4], that this drug had adverse effects of skeletal muscle in addition to its desired neuromuscular blocking action. Several techniques aimed at limiting this myalgia have been reported [5–8], but it was not until 1971 that it was realized that the muscle damage caused by suxamethonium could be life-threatening, as opposed to merely inconvenient [9]. This case involved a child who suffered a cardiac arrest after the use of suxamethonium at induction. The child had been presented to the anaesthetist as a healthy boy, but on detailed questioning after the event, it became apparent from the parents that the boy had been slow to walk and was unsteady on his feet. The boy, who survived what was thought to be a hyperkalaemic-induced cardiac arrest, later developed classical features of Duchenne muscular dystrophy. Subsequent research has provided biochemical evidence that the myalgia caused by suxamethonium in normal individuals is associated with rhabdomyolysis [10, 11]. It is to be presumed that the effects of suxamethonium are accentuated when diseased muscle is involved. Similar cases to that reported by Genever [9] have appeared sporadically in the literature since 1971 [12–14].

Given that this problem has been recognized for more than 20 yr it is curious why, especially in the United States, there have now been moves to limit the use of suxamethonium in children. The recent controversy followed the publication of a letter to Anesthesiology [15] which listed four cases of cardiac arrest after administration of suxamethonium reported to MHAUS, the North American malignant hyperthermia hotline. On the basis of these and other cases reported to the German malignant hyperthermia hotline [16], Rosenberg and Gronert predicted an annual US incidence of six cases with 60% mortality [15]. In November 1992, Burroughs Wellcome, the principal supplier of suxamethonium in North America, applied to the Federal Drug Administration (FDA) to change the package insert. The FDA subsequently commissioned its Anesthetic and Life Support Drug Advisory Committee to review the proposed changes. This committee approved a "strong warning" about the dangers of hyperkalaemic cardiac arrest after suxamethonium in children with unrecognized muscular dystrophy. However, when the notification of the change in package insert was distributed, the "strong warning" had reverted to a contraindication to the use of suxamethonium, except for situations where immediate securing of the airway is required. The reintroduction of the contraindication was, apparently, from a second approach by Burroughs Wellcome to the FDA which, on this occasion, was not referred to all members of the advisory committee. The wording of the new package insert came, therefore, as a shock to most anaesthetists with its ramifications for techniques that had been standard for many practitioners.

The response from the profession in North America, especially paediatric anaesthetists, was overwhelming [17–19], with the result that, in 1994, the FDA reconvened its advisory committee which received evidence from the major opponents of the contraindication. The compromise that seems to have been agreed includes a recommendation that the use of suxamethonium in children be reserved for emergency intubation or instances where immediate securing of the airway is necessary.

After the initial change in data sheet in the USA, suppliers of suxamethonium in Canada applied to introduce a similar warning and contraindication. Opposition to this course from Canadian anaesthetists was firm and reasoned. Experience from one large paediatric centre was cited [20], where no case of cardiac arrest in unrecognized muscular dystrophy has occurred: this was attributed to the practice of detailed preoperative assessment, including family history, and routine practice of using i.v. as opposed to inhalation induction before administration of suxamethonium [19]. It is indeed a potentially most important observation that in all published cases, cardiac arrest occurred following suxamethonium given after inhalation induction with a volatile anaesthetic drug.

The reports of sudden death in children with unrecognized muscular dystrophies to the North American and German MH hotlines were not mirrored in the United Kingdom, where no such deaths were reported to the National MH referral centre in Leeds. In order to ascertain the scale of the problem in the UK, therefore, the author attempted to survey all practising UK anaesthetists via a letter to the Royal College of Anaesthetists' tutors in each hospital. The letter requested reports of all cardiac arrests in children after the use of suxamethonium, irrespective of the perceived cause and outcome. The majority of replies (many of which were collective responses from whole departments) indicated that the only cases known to them were vagal episodes which responded promptly to treatment with atropine. Several letters were strongly supportive of the continued availability of suxamethonium for routine paediatric use.

There were 15 cases of cardiac arrest (three fatal) that could not be confidently attributed to vagal stimulation in the non-atropinized child: they occurred between 1965 and 1993. Of these 15 cases, seven were, or most likely to be, children with myopathies. One case, from 1965, involved a boy with known muscular dystrophy. This case preceded the first published report [9] and had a successful outcome: at this time there was no specific advice to avoid suxamethonium in myopathic patients, although it was advised to use all drugs with caution [21]. However, a similar case occurred in 1991 and,
fortunately, the child was again successfully resuscitated. Another patient, a boy aged 5 yr who survived, was noted, while recovering from the episode in the intensive care unit, to have pseudo-hypertrophy of the calf muscles and was later confirmed as having Becker’s muscular dystrophy.

Two cases involved children who were mentally handicapped. The first of these died from the reaction which appeared of similar nature to the hyperkalaemic cases reported elsewhere: histological examination of post-mortem muscle specimens revealed dystrophic changes. The second mentally handicapped child survived hyperkalaemic arrest, but the paediatric referral centre noted clinical features suggestive of a myopathic syndrome. These two cases illustrate that a myopathy may be associated with congenital mental handicap and its presence should be considered when anaesthetizing such individuals.

The second fatal case was that of a 2-yr-old boy in whom no clinical features had been apparent before the incident: muscular dystrophy was diagnosed on examination of post-mortem specimens. However, in this case the reaction was not typical of a purely hyperkalaemic event; in fact, there is considerable doubt as to whether there was any significant increase in serum potassium concentration. A more consistent explanation is that the child died from myocardial failure secondary to a dystrophic cardiomyopathy which is why the most vigorous and appropriate attempts at resuscitation were not successful.

The third fatal case is mentioned for completeness as insufficient data are available to draw any conclusions. The only information I have is that the case involved a 6-yr-old child who died during an emergency appendicectomy in which suxamethonium was presumably used to aid intubation.

Four cases, all of whom survived, presented with transient cardiac arrest after suxamethonium and biochemical evidence of rhabdomyolysis. Three of these have been investigated for malignant hyperthermia susceptibility. Two were clearly not susceptible, while the third gave an equivocal result; muscle histology and histochemistry were normal in all three cases. It is not possible to state if the child with the equivocal test result for malignant hyperthermia truly had the condition, but the contracture test result suggested that her muscle was abnormal. What is becoming clearer to those involved in this area is that there appears to be a spectrum of muscle abnormalities that may be manifest under certain conditions (e.g. heat stroke [22], exercise-induced rhabdomyolysis) that current diagnostic tools cannot always detect. These four cases may represent such a muscle problem.

All four remaining cases of cardiac arrest associated with the use of suxamethonium had alternative explanations for the arrest; three involved children with heart disease and the other was consistent with an anaphylactoid response.

To my knowledge, one other case occurred in the United Kingdom, this being reported in the literature and alluded to earlier [12]. However, it is not clear as to the immediate cause of the arrest of this body, first because there was a period of 7 min preceding the arrest when oxygenation was compromised and, second, because the maximum recorded serum potassium concentration was 5.4 mmol litre$^{-1}$. The child was successfully resuscitated.

In discussing the place in clinical practice of any drug, it is clearly necessary to mention all of the disadvantages. In this respect it should be remembered that suxamethonium can provoke hyperkalaemia in other situations, such as after burns, trauma or spinal cord injuries. Other problems associated with its use include triggering of malignant hyperthermia, delayed recovery with atypical plasma cholinesterase, an increase in intraocular pressure and anaphylaxis. In fact, anaphylactoid reactions are reported to occur in 1:5000–1:20 000 anaesthetics, the majority of which are thought to be caused by neuromuscular blocking drugs, especially suxamethonium [23]. Anaphylaxis would therefore appear to be a much more significant hazard of suxamethonium than cardiac arrest in unsuspected cases of muscular dystrophy. It is thus difficult to rationalize why there is this very recent clamour, especially by the manufacturers in the USA, to limit its use in elective cases.

There would, of course, be good reason not to use suxamethonium if another drug had the same advantages with fewer side effects. While the rapid onset of suxamethonium can be mimicked with large doses of non-depolarizing drugs (and even approached with rocuronium), it is the rapid recovery from suxamethonium that is unique and is vital if potential disaster is to be avoided in the emergency situation. The position is not so clear for elective cases when suxamethonium might be selected for one of two main reasons. The first indication for the elective use of suxamethonium is as part of an approach to the potentially difficult intubation. In such a case, a “sleep dose” of i.v. induction agent is given while maintaining spontaneous ventilation. After ensuring that artificial ventilation using bag, mask and, if necessary, airway is possible, a neuromuscular blocking drug may be given. Suxamethonium is advantageous in this situation because it provides profound relaxation (note that intubating conditions using different techniques are invariably formally compared only in the normal population, which may be irrelevant when considering the patient with a difficult airway) and, if intubation is not successful using conventional manoeuvres, the return of spontaneous ventilation will facilitate blind naso-intubation or the use of the fibreoptic intubating laryngoscope. Alternatively, the adult patient can be allowed to wake up, and awake intubation performed. The second main use for suxamethonium in the elective patient is when a spontaneously ventilating technique is to be used in a patient requiring intubation (e.g. for dental extractions, nose and throat operations). As with many controversies regarding anaesthetic techniques, there are no adequate data to compare spontaneous with artificial ventilation for such procedures because the most important outcome measures, mortality and major morbidity, are rare, and the determinants are multifactorial. Thus the use of one technique rather
than another might, for example, inherently double the risk of major morbidity, which would be a most important clinical consideration, and yet a study to compare the techniques would need to include several thousand patients if it were to be powerful enough to demonstrate such an increased risk. There is thus no scientific basis upon which it can be stated that one technique is safer than another. As there are plausible reasons why a spontaneously ventilating technique might be safer, it would perhaps be unwise to contraindicate, or even advise against, the use of suxamethonium as part of such a technique.

In conclusion, therefore, suxamethonium is a drug with unique advantages. There is no scientific evidence to support the contention that, despite their lower incidences of side effects, alternatives are as safe or efficacious when used for airway management. The rare occurrence of cardiac arrest in children with undiagnosed myopathies might be reduced even further by taking a careful family history, by considering the possibility of coexisting myopathy in cases of congenital mental handicap, and by using, where possible, an i.v. as opposed to inhalation induction when suxamethonium is to be used. Although most cases of cardiac arrest after the use of suxamethonium are caused by vagal overactivity, hyperkalaemia and appropriate treatment thereof should be considered if response to atropine is not rapid.

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References