

# Malignant hyperthermia: pharmacology of triggering

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## Editor's key points

- In this review, the author explores the evidence for triggering mechanisms for malignant hyperthermia (MH), and reinforces the ability of all modern volatile anaesthetic agents to trigger a reaction.
- Other triggering drugs are explored and the evidence-base (or lack of it) for their role in triggering MH is examined.

**Summary.** Over the past 50 yr, many drugs have been implicated as triggers of malignant hyperthermia (MH), a potentially fatal pharmacogenetic disorder of skeletal muscle calcium regulation. This review discusses the potent inhalation agents as the principal triggers and evidence that the modern agents, desflurane, sevoflurane, and isoflurane, can cause florid MH reactions in the same way as halothane but also are associated with reactions whose onset is delayed for several hours into anaesthesia. There is evidence that the triggering of MH by drugs is dose-dependent but the minimum dose that will trigger the condition is unknown. This has implications for the preparation of anaesthetic machines when used for known or suspected MH patients. While succinylcholine enhances the response of potent inhalation anaesthetics, its role as an inherent trigger of the condition is controversial. Non-depolarizing neuromuscular blocking drugs appear to protect against the development of MH and this may be by blocking excitation-coupled calcium entry—a recently described route of skeletal muscle calcium entry that may also explain the mechanism of the effect of succinylcholine in MH. Another mechanism for extracellular calcium influx, store-operated calcium entry, is activated in MH muscle and may explain how a triggered reaction is sustained. Finally, reports of drugs that have been implicated as additional triggers of MH over the past 10 yr are discussed.

**Keywords:** calcium, excitation-coupled calcium entry, store-operated calcium entry; dihydropyridine receptor; inhalation anaesthetics, desflurane, halothane, isoflurane, sevoflurane; malignant hyperthermia; methylene blue; neuromuscular blocking drugs, succinylcholine; ondansetron; ryanodine receptor; RYR1; serotonin

Experience informs us that certainty derived from incomplete or inadequate knowledge is a dangerous state. Two cases from the United Kingdom Malignant Hyperthermia (MH) Registry illustrate this. The first occurred more than 20 yr ago and involved a child brought into an Accident and Emergency Department with a fractured wrist. The child's mother told the admitting doctor that the child's cousin had nearly died under anaesthesia from a problem that ran in the family. 'Scoline apnoea' was recorded in the medical records and the child died later that day from MH triggered by a halothane anaesthetic. The second case is more recent and involves a patient who survived two MH reactions: the second reaction was triggered by sevoflurane, which the attending anaesthetist believed not to be a trigger of MH.

Contrast this to the case of Roy Evans, the first patient known to have survived an MH reaction.<sup>1</sup> He had been advised to avoid general anaesthesia because of the death of 10 relatives under anaesthesia and indeed he had undergone an appendectomy under local infiltration anaesthesia. In 1960, he presented with a compound fracture of the leg. Having excluded porphyria, the anaesthetist Villiers considered the most likely explanation to be a

reaction to ether—a condition known as 'ether convulsions' associated with pyrexia was known, but a familial tendency had not been reported. Villiers (personal communication, 1998), recognizing his uncertainty, proceeded cautiously using thiopental for induction of anaesthesia and a new inhalation anaesthetic, halothane, for maintenance. Within minutes, Villiers recognized that there was a problem, the patient becoming tachycardic and hypotensive, with rapid exhaustion of the soda lime. The halothane was discontinued, a blood transfusion administered, and because the patient felt hot and was sweating, he was cooled with ice-soaked cloths. The case and family history were published in 1962.<sup>2</sup>

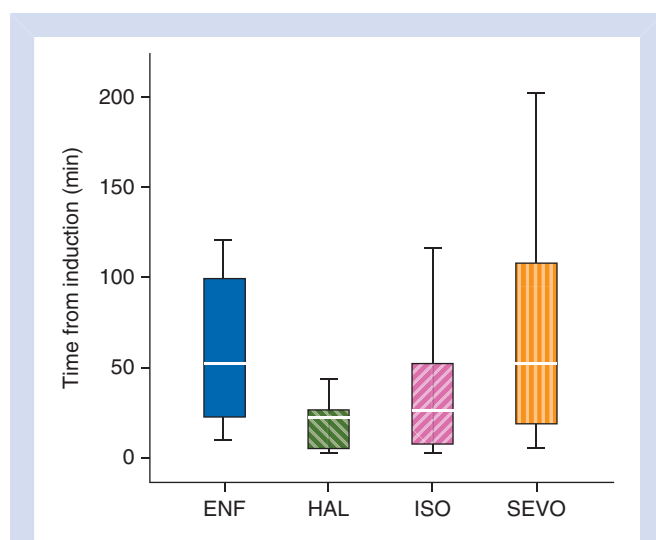
In this review, I will highlight how much we know about the pharmacology of the triggering of MH but, just as importantly, emphasize where knowledge is incomplete or evidence contradictory. My aim is for the reader to be more certain of their knowledge of MH but to be cautious when dealing with the condition through an appreciation of how much we do not know. I will first discuss the clinical pharmacology of MH triggering before briefly covering exciting developments in its experimental pharmacology.

## Potent inhalation anaesthetics

Denborough and colleagues<sup>2</sup> study of the Evans family concluded that the 10 deaths attributed to MH were associated with the use of ether or ethyl chloride, while the patient who survived received halothane. Subsequently, every potent inhalation agent has been implicated as a clinical trigger. Although there is no evidence to the contrary, the isolated clinical reports of reactions triggered by methoxyflurane<sup>3</sup> and cyclopropane<sup>4</sup> do not provide convincing support for these drugs being triggers of MH. The porcine model of MH has often provided useful data when human evidence is lacking, but, at least in the case of cyclopropane,<sup>5</sup> this seems as equivocal as the case reported by Lips and colleagues.<sup>4</sup> Porcine studies of the capacity of methoxyflurane to trigger MH, on the other hand, do indicate its capability.<sup>6</sup> The introduction of each of the newer potent inhalation agents was soon followed by reports of their use in anaesthetics complicated by MH (e.g. for enflurane,<sup>7, 8</sup> isoflurane,<sup>9, 10</sup> sevoflurane,<sup>11, 12</sup> and desflurane).<sup>13, 14</sup>

### Are all potent inhalation anaesthetics equal as triggers of MH?

The number of MH cases reported annually to the UK MH Unit triggered by each of the potent inhalation anaesthetics has reflected the relative usage of that agent in the UK over the past 40 yr (unpublished observations). While in the 1970s, cases triggered by halothane predominated, over the past 3 yr, sevoflurane has been the most common trigger with isoflurane accounting for the greatest number of cases overall.



**Fig 1** Box and whisker plot of the time from induction of anaesthesia to the onset of MH in 73 patients (eight received enflurane, 11 halothane, 42 isoflurane and 12 sevoflurane). The boxes delineate the inter-quartile range, the white horizontal line within the box is the median value, and the whiskers indicate the range. Using a general linear regression model, there was a statistically significant faster onset of the MH reaction with halothane vs enflurane and sevoflurane but not isoflurane.

Given that all of the currently available potent inhalation anaesthetics are qualitatively similar triggers of MH, and that this has been recognized for more than 15 yr, I find it curious to be confronted on an infrequent but persistent basis by colleagues who query the need to be concerned about MH because, to paraphrase, 'it is a historic condition now that halothane is not used clinically'. I am convinced that this incorrect and dangerous information (refer back to the introduction of this article) must appear in a reference text, but I am yet to find the source. But what evidence might this source have misinterpreted?

Perhaps two early laboratory studies provide a clue.<sup>15, 16</sup> Both of these reports studied the effect of various inhalation agents on the magnitude of caffeine-induced contracture in skeletal muscle specimens in a tissue bath. Reed and Strobel<sup>15</sup> used frog sartorius muscle and demonstrated that caffeine contractures were enhanced by halothane approximately three times more than enflurane and four times more than isoflurane at 1 MAC concentrations. They postulated that these findings might indicate the relative potency for the anaesthetics in triggering MH. Examination of their data, however, reveals that ether had a relatively weak effect and also that the model predicted nitrous oxide to be a potential trigger of MH. Using excised muscle fascicles from MH-susceptible patients, Britt and colleagues<sup>16</sup> found halothane to have a greater effect on caffeine contracture than isoflurane, which in turn produced a greater effect than enflurane and methoxyflurane. As there are profound physiological differences between amphibian and human skeletal muscle and significant overlap in effects of halothane on caffeine-induced contractures between muscle from MH-susceptible and normal humans,<sup>17</sup> the validity of extrapolating the results of these two studies<sup>15, 16</sup> to the clinical potency of MH triggering agents is questionable.

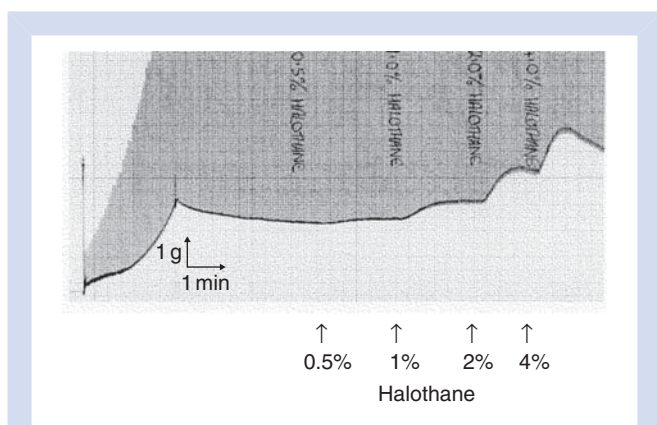
Recently, we proposed that the time interval between induction of anaesthesia and development of clinical features of MH might be used as a marker of severity of an MH reaction.<sup>18</sup> Similarly, this interval could be used as a surrogate for the relative potency of the inhalation anaesthetics as triggers of MH. With this in mind, we conducted a preliminary analysis of 75 cases of confirmed MH referred to the UK MH Unit between 1990 and 2005 (K. Wragg and colleagues, unpublished observations). There were too few patients (two) to include desflurane in the analysis, and of the remainder, eight received enflurane, 11 halothane, 42 isoflurane, and 12 sevoflurane. There was a statistically significant faster onset of the MH reaction with halothane (median 20 min, range 5–45 min) vs enflurane (55, 20–480 min) and sevoflurane (60, 10–210 min) but not isoflurane (30, 5–210 min) (Fig. 1). We found no evidence for a confounding effect of succinylcholine, which may be a reflection of the small sample, but these data do provide a clinical evidential basis for differences in ability to trigger MH at clinical concentrations among the potent inhalation agents. However, the most important clinical message is that any of these drugs can produce a rapidly progressing MH reaction within a few minutes of induction of

anaesthesia, as indeed can desflurane.<sup>13</sup> The data also confirm reports that an MH reaction can take several hours to become apparent.<sup>19</sup>

### Triggering of MH as a dose-dependent process

Assuming that agent-dependent differences in the delay in onset of an MH reaction are related to differences in relative potency of the MH-triggering effect compared with the anaesthetic effect of the inhalation anaesthetics implies that the ability of any of the agents to trigger an MH reaction is dose-dependent. This would not be surprising considering the graded incremental contracture response of MH muscle to increasing concentrations of halothane observed with the diagnostic *in vitro* contracture test (Fig. 2).<sup>20</sup> Although it cannot explain all instances of lack of clinical penetrance of MH, a time-weighted dose-dependency of the clinical response is one possible contributing factor to the common finding that many MH-susceptible individuals have had apparently uneventful exposure to potent inhalation anaesthetics.<sup>21 22</sup>

Acceptance of the triggering of an MH response as a dose-dependent phenomenon has important implications for administering anaesthesia to patients at risk of developing MH in terms of preparing the anaesthesia machine. This has led to abandonment of an early recommendation that every major hospital should keep an anaesthetic machine that had never been used to administer potent inhalation anaesthetics for use in MH-susceptible patients.<sup>23</sup> The minimum concentrations capable of triggering MH have, however, not been established. Various studies have used target concentrations ranging from 1<sup>24</sup> to 10 ppm<sup>25</sup> in testing protocols for preparation of a number of anaesthetic machines. One assumes that even 10 ppm leaves a very wide margin for error based on *in vitro* muscle contracture concentration–response relationships, experience with porcine MH,



**Fig 2** A trace showing muscle tension in a skeletal muscle (*Vastus medialis*) specimen biopsied from a MH-susceptible patient. The test is a static halothane contracture test conducted according to the protocol of the European Malignant Hyperthermia Group ([www.emhg.org](http://www.emhg.org)) with an additional concentration of halothane (4% v/v) applied. The trace demonstrates the dose-dependent response of MH muscle in this system.

and the lack of reports of occupational triggering of MH in anaesthetic, surgical, and operating theatre personnel. Most countries stipulate through occupational health and safety legislation that time-averaged exposure to potent inhalation anaesthetics should be <50–100 ppm, while exposure to higher concentrations for shorter periods occurs with facemask anaesthesia and in the post-anaesthesia care unit.<sup>26</sup>

Interestingly, a recent review of studies of elimination kinetics of potent inhalation anaesthetics from modern anaesthesia machines<sup>27</sup> concludes that generic protocols will be inadequate for preparing some machines before using them in anaesthesia for MH-susceptible patients. A similar note of caution should be applied to protocols for the management of a suspected MH crisis. Some such protocols suggest that elimination of triggering anaesthetic is not significantly enhanced by changing the anaesthetic machine or adding a charcoal filter to the inspiratory limb of the breathing circuit.<sup>28</sup> However, this recommendation is based on a study published in 1993,<sup>29</sup> which used much simpler anaesthetic machines than some in use today. My advice remains to hyperventilate the patient's lungs through a non-rebreathing circuit, such as a Bain's circuit, using high flows of 100% oxygen: the use of a charcoal filter on the inspiratory limb of a rebreathing circuit would be an alternative for complex modern anaesthesia machines.

### Succinylcholine

After Denborough and colleagues' description of an MH reaction triggered by halothane,<sup>2</sup> further reports appeared and these, along with a series of unpublished cases, were meticulously reviewed by Britt and Kalow.<sup>30</sup> An emerging feature was profound and prolonged rigidity of the jaw muscles in response to succinylcholine. This occurred in 59 of 73 patients who received succinylcholine.<sup>30</sup> Britt and Kalow also noted a trend towards poorer survival rates in those who had received succinylcholine.

Confirmation of a role for succinylcholine in the triggering of MH appeared to be consolidated by Ellis and colleagues<sup>31</sup> who found that *in vitro* contractures in some subjects from MH families occurred when their muscle specimens were exposed to succinylcholine and halothane but not halothane alone. Interestingly, they noted that succinylcholine applied alone did not cause muscle contracture in muscle from any of the subjects. Harrison,<sup>32</sup> using muscle rigidity as a marker of the development of an MH reaction in susceptible pigs, proposed that succinylcholine did induce MH but, because the response could be prevented by prior administration of curare, this was secondary to muscle fasciculation. Both Hall and colleagues<sup>5</sup> and Nelson and colleagues,<sup>33</sup> however, could not elicit porcine MH with succinylcholine alone. Iaizzo and Wedel<sup>34</sup> revisited this paradigm in 1994 and concluded that succinylcholine did trigger porcine MH and the response could be ameliorated by prior treatment with pancuronium. These data are, however, by no means convincing: the initial response to succinylcholine in the



susceptible pigs was marked hypotension accompanied by tachycardia and, when the hypotension was treated with i.v. infusion of saline, acidosis, and hypercarbia. The latter, which were resolving before administration of dantrolene, could be explained by reperfusion of hypoperfused tissue: there was no change in the body temperature of the pigs. The cause of the hypotension observed in these animals eludes me, as it did Iaizzo and Wedel.<sup>34</sup> Sigg and Iaizzo<sup>35</sup> later conducted a comprehensive study of this phenomenon but were still unable to identify a mechanism.

In humans, many cases of MH have been diagnosed on the basis of abnormal *in vitro* muscle contracture responses after succinylcholine-induced jaw rigidity, or masseter muscle spasm.<sup>36 37</sup> Convincing reports of fulminant MH triggered by succinylcholine in the absence of potent inhalation anaesthetics are lacking however. Laurence and colleagues<sup>38</sup> reported a case of masseter muscle spasm that was accompanied by tachycardia and an increase in temperature, albeit to only 37.9°C before dantrolene was administered. It is possible, however, that these effects may have resulted from a catecholaminergic response to muscle fasciculation and rigidity, as demonstrated in pigs.<sup>34</sup> Strazis and Fox<sup>39</sup> summarized 503 reports of apparent MH; of which, 428 received potent inhalation anaesthetics, succinylcholine, or both, with no indication of the precise number receiving succinylcholine alone, indeed if any did. In fact, the lack of critical appraisal of the source articles or criteria for inclusion as cases of MH makes this a very limited publication. Larach and colleagues,<sup>22</sup> on the other hand, systematically applied a clinical grading score<sup>40</sup> to cases of possible MH reported to the North American MH Registry. They identified two of 284 (0.7%) cases rated as 'very likely' or 'almost certain' of being MH where the patient had received succinylcholine but not a potent inhalation anaesthetic: unfortunately, no further details are presented.

The likelihood of succinylcholine-induced fulminant MH is important when considering the treatment options after masseter muscle spasm. As the probability appears to be extremely low and assuming the airway can be secured, continuing anaesthesia with i.v. agents is perhaps preferred to the more conservative approach of abandoning the surgical procedure.<sup>38 41</sup> In these circumstances, however, consideration should be given to the presence of a myopathy other than MH, in which case acute and massive rhabdomyolysis might ensue.<sup>42</sup> I would therefore recommend that serial serum potassium measurements are made. Although hyperkalaemic cardiac arrest is rare after succinylcholine given to MH-susceptible individuals,<sup>43</sup> rhabdomyolysis can be sufficient to threaten renal damage in the postoperative period<sup>38</sup> and this too should be actively sought and managed. Of course, any patient suspected of being at increased risk of MH should receive appropriate counselling and referral for definitive diagnosis.<sup>44</sup>

Finally with respect to succinylcholine, there remains little doubt that its combination with a potent inhalation agent produces a more marked clinical MH response. For example, the increase in serum creatine kinase after an MH reaction

is approximately six to 10 times greater when succinylcholine is used in combination with an inhalation agent as when an inhalation agent is the only 'trigger'.<sup>45</sup> Similarly, Pollock and colleagues<sup>46</sup> found that the onset of MH reactions was significantly enhanced when succinylcholine was used.

## Other drugs implicated as triggers of MH

In a previous review for this journal, I presented the evidence against drugs other than the potent inhalation anaesthetics and succinylcholine as triggers of MH.<sup>47</sup> Since then, further studies have been conducted on serotonergic drugs and phosphodiesterase type III inhibitors, while there have been published reports of MH associated with the use of statins, tetracaine, methylene blue, and ondansetron.

### Serotonergic drugs

Gerbershagen and colleagues<sup>48</sup> compared the effects of a 5-HT<sub>2A</sub> agonist on anaesthetized MH-susceptible pigs with normal pigs and found that muscle fasciculation, body temperature increase, increase in end-tidal CO<sub>2</sub>, and acidosis occurred in both groups with quantitative differences in these variables between the MH and normal pigs demonstrated at only the highest dose of 5-HT<sub>2A</sub> agonist. These data suggest that serotonergic agents do not trigger MH and also that MH-susceptible individuals are unlikely to be at increased risk of developing the serotonin syndrome. It is possible, however, that MH-susceptible patients who develop serotonin syndrome may experience a more severe reaction.

### Phosphodiesterase type III inhibitors

In my previous review,<sup>47</sup> I discussed *in vitro* studies that demonstrated a contracture response to application of enoximone, a phosphodiesterase type III inhibitor, in human MH and normal muscle but that this developed at lower concentrations of enoximone in the MH muscle. However, the concentrations of enoximone required to initiate contractures in the MH muscle were much higher than achieved clinically. Similar findings have since been reported for enoximone<sup>49</sup> and amrinone<sup>50</sup> in porcine MH muscle. In their study of enoximone, Fiege and colleagues<sup>49</sup> also administered increasing doses of i.v. enoximone to susceptible and normal pigs. None of the pigs developed signs of MH before they died of cardiovascular failure. Despite these results, the authors conclude that enoximone should not be administered to MH-susceptible patients because of a case they reported previously.<sup>51</sup>

The case in question involved a man who developed rhabdomyolysis after aortic valve replacement and coronary artery bypass grafting.<sup>51</sup> The patient subsequently tested positive for MH and was found to have a diagnostic *RYR1* mutation. It is therefore irrefutable that the patient was susceptible to MH but I am not as convinced as the authors that the rhabdomyolysis can be attributed to enoximone. Riess and colleagues<sup>51</sup> themselves acknowledge that several features of their case, including prolonged cardiopulmonary

bypass, post-bypass hypoperfusion, and epinephrine infusion, are known risk factors for the development of rhabdomyolysis after cardiopulmonary bypass. It appears that they favoured enoximone as the cause because of its *in vitro* effects on MH muscle, thus completing the circle of their argument.

While it is impossible to categorically state that enoximone at clinical concentrations will not stimulate or damage MH muscle, I think it unlikely. I consider there to be insufficient evidence therefore to restrict the use of this potentially valuable drug in MH patients. It would be prudent, however, to be alert to the possibility of rhabdomyolysis. Similarly, should an unexpected hypermetabolic or rhabdomyolytic response to enoximone occur in a patient with no family history of MH, consideration should be given to investigation for MH susceptibility.

### Statins

Treatment with statins has also been implicated in causing rhabdomyolysis in MH patients.<sup>52 53</sup> In these three cases, use of the statin was associated with myalgia, which is a common side-effect of statin therapy. The first case,<sup>52</sup> however, reported dark urine, indicating myoglobinuria, and her statin treatment was stopped while in the other two cases,<sup>53</sup> creatine kinase remained elevated after discontinuation of the statin treatment. All three were investigated for MH by muscle biopsy and *in vitro* contracture tests and were found to be susceptible. Subsequently, Guis and colleagues<sup>54</sup> reported the results of MH contracture testing in a group of nine patients with symptomatic statin myopathy associated with raised creatine kinase concentrations. Apart from the case previously reported,<sup>52</sup> the size of contracture was small, although outside the limits of normality. These results are likely to reflect the lack of specificity of the *in vitro* contracture tests in the presence of myopathy or muscle damage.<sup>55</sup>

There does appear to be a consensus however that statin treatment should not be withheld from MH-susceptible individuals. Indeed, over the past 10 yr, many patients attending our unit for MH testing have been taking a statin with no evidence of adverse clinical or biochemical responses associated with MH status. It would seem sensible, though, when initiating statin treatment in a known MH patient to take a pre-treatment creatine kinase level and instruct the patient to report muscle symptoms or dark urine.

### Tetracaine

Sheu and colleagues<sup>56</sup> suggested that spinally administered tetracaine triggered an MH response that developed 1 h into a transurethral resection of the prostate procedure. Tetracaine is known to inhibit skeletal muscle sarcoplasmic reticulum calcium release<sup>57</sup> and to have similar effects to dantrolene in inhibiting halothane-induced calcium release from sarcoplasmic reticulum of MH pigs.<sup>58</sup> The sequence of events described by Sheu and colleagues<sup>56</sup> could be explained by hyponatraemia.

### Methylene blue

Mathew and colleagues,<sup>59</sup> who reported a case of hyperpyrexia and prolonged confusion after parathyroidectomy, which involved an infusion of methylene blue, raised the possibility of MH in their differential diagnosis. They appear not to consider MH the most likely explanation but do not discount it. The features they report, however, are entirely consistent with serotonin syndrome, which is now a recognized consequence of interaction between methylene blue, an inhibitor of monoamine oxidase, and other serotonergic drugs.<sup>60</sup> The patient of Mathew and colleagues<sup>59</sup> was taking citalopram before his surgery.

### Ondansetron

The latest drug to be implicated as a triggering agent for MH is ondansetron.<sup>61</sup> This case involved a boy who had suffered a suspected MH reaction during sevoflurane anaesthesia when aged 3 yr. Clinical evaluation was of a child with myopathic facies, scoliosis, genu varum, and a history of delayed motor milestones. Subsequent muscle biopsy was interpreted as multi-minicore disease (a congenital myopathy) and DNA analysis revealed a novel p.Arg3983His *RYR1* variant. He subsequently presented to the emergency room at age 5 yr with vomiting and abdominal pain, but he was afebrile with unremarkable vital signs and normal clinical examination. He was given ondansetron 2 mg sublingually and discharged home. Three hours later, he developed muscle rigidity and a temperature of 41°C. By the time he was brought back to hospital, he had sustained an asystolic cardiac arrest and he subsequently died: serum potassium concentration 15 min after readmission was 15.3 mmol litre<sup>-1</sup>. The postmortem examination identified acute bronchopneumonia, bacterial colonized hepatic thrombus, and enteroviral infection.

What Gener and colleagues<sup>61</sup> may not have known when they submitted this case is that the *RYR1* variant found in their patient involves the same amino acid residue as a variant found in two other cases of non-anaesthetic MH-like fatal reactions.<sup>62</sup> In these cases, the arginine at position 3983 was replaced by a cysteine, but it would appear that substitution of this highly conserved arginine residue predisposes patients to massive myoplasmic calcium release even without pharmacological triggers. There is therefore no need to implicate ondansetron.

### Drugs that protect against triggering of MH

From the earliest<sup>30</sup> to the latest<sup>22</sup> collections of MH cases, it has been apparent that many patients do not have an evident MH reaction in one or more general anaesthetics before their presenting episode. The explanation for this phenomenon is likely to be multifactorial and some very likely factors are anaesthesia using non-triggering anaesthetics or insufficient time-weighted dose of triggering agent. Another possible factor is co-administration of drugs that oppose the triggering effects of the potent inhalation

anaesthetics: candidates include i.v. induction agents and non-depolarizing neuromuscular blocking drugs.

### I.V. induction agents

In pigs susceptible to MH, thiopental reproducibly delays the onset of MH induced by halothane alone, sevoflurane alone, or halothane with succinylcholine.<sup>5 63 64</sup> The effect is dose-dependent,<sup>34</sup> but the mechanism is unknown. Neither etomidate<sup>64</sup> nor propofol<sup>65</sup> appears to offer any protection in the pig model, which argues against the depth of anaesthesia *per se* as an explanation for the effect of thiopental. While a degree of protection from thiopental, if it translates to human MH, may explain some untoward anaesthetics in MH-susceptible individuals, this should not be relied upon as illustrated by the first case of MH reported by Denborough and colleagues.<sup>2</sup>

### Non-depolarizing neuromuscular blocking agents

Although Harrison<sup>32</sup> had suggested that tubocurarine protected MH pigs from excessive rigidity in response to succinylcholine, Britt and colleagues<sup>66</sup> advised that curare should be contraindicated in patients potentially susceptible to MH. This recommendation was based on two cases from known MH families where potent inhalation anaesthetics and succinylcholine were avoided but curare was administered. Both patients developed a marked tachycardia and a rapidly increasing temperature soon after the curare was given. It is worth highlighting that ECG and core temperature monitoring were not routine in the early 1970s and so these authors would not have been as familiar with post-induction increases in heart rate and temperature that the modern anaesthetist will commonly observe in patients with acute inflammatory/infective conditions. Also of note is that the depth of anaesthesia at the time these patients received curare and were subjected to tracheal intubation must have been 'light'.<sup>66</sup>

In contrast to tubocurarine, complete neuromuscular block using pancuronium administered to susceptible pigs prevented the MH response to halothane in 50% of animals,<sup>67</sup> while another study demonstrated a consistent delay in the development of MH.<sup>64</sup> Vecuronium on the other hand does not appear to protect against the development of porcine MH.<sup>68</sup>

While it is often difficult or impossible to obtain human data to compare with data from the porcine MH model, we have recently presented a preliminary analysis of the association of the use of non-depolarizing neuromuscular blocking drugs as part of the triggering anaesthetic on the onset time of the MH reaction and the maximum postoperative serum creatine kinase concentration.<sup>69</sup> On the basis of 214 MH episodes, we found that non-depolarizing neuromuscular blocking drugs were associated with significantly increased onset time and lower maximum postoperative serum creatine kinase concentration. We are in the process of statistically modelling various confounding factors, but our findings are potentially interesting observations.

### Cellular mechanisms of the triggering process

Although the focus of this review is the clinical pharmacology of MH triggering, there have been recent advances in our knowledge of the pathophysiology of MH that potentially enhance our understanding of the clinical disorder. These are the mechanism of action of potent inhalation anaesthetics on the skeletal muscle sarcoplasmic reticulum calcium release channel (the ryanodine receptor protein) and recently identified mechanisms of calcium entry into skeletal muscle cells.

### Action of potent inhalation anaesthetics on the skeletal muscle ryanodine receptor protein

It is intriguing how so many different mutations that are spread across the entire coding region of a gene as large as *RYR1*<sup>70</sup> produce qualitatively the same phenotype, but there is now a substantial body of evidence that a fundamental defect in MH is that potent inhalation anaesthetics overcome the inhibitory regulatory effect of magnesium ions on the ryanodine receptor protein. This is interesting as an important role for magnesium was suggested more than 30 yr ago.<sup>71</sup> At rest, magnesium ions inhibit the opening of the ryanodine receptor calcium ion pore and muscle activation under physiological conditions is achieved through interaction between the t-tubule voltage sensor (dihydropyridine receptor or DHPR) and the ryanodine receptor protein to overcome magnesium inhibition of the latter.<sup>72</sup> A reduced inhibitory effect of magnesium was first demonstrated in porcine MH,<sup>73</sup> but this has subsequently been confirmed in human tissue for the response to halothane<sup>74</sup> and subsequently sevoflurane.<sup>75</sup> Unfortunately, it seems unlikely that the theoretical possibility of raising intracellular magnesium concentration to inhibit the effect of potent inhalation anaesthetics could be a viable therapeutic intervention.

### Skeletal muscle calcium entry

Traditional teaching of skeletal muscle physiology has emphasized the lack of reliance of muscle contraction on extracellular calcium influx. However, two newly described mechanisms for extracellular calcium entry have been described, whose role is postulated as sustaining intracellular calcium levels at times of high physiological demand. This is exciting from an MH perspective because without such processes, it is difficult to explain how an MH reaction is sustained. The first mechanism is store-operated calcium entry which is stimulated by sarcoplasmic reticulum calcium depletion. We have recently demonstrated that store-operated calcium entry is activated in experimental MH and that the process can be inhibited by an antibody to a protein involved in the process.<sup>76</sup>

The second mechanism for calcium entry is perhaps even more intriguing with regard to MH. It is termed excitation-coupled calcium entry and, as the name implies, involves a calcium conductance through the sarcolemma when the t-tubule is depolarized. Yang and colleagues<sup>77</sup> have demonstrated that excitation-coupled calcium entry is enhanced



in myotubes expressing *RYR1* mutations found in MH. Further work has identified the DHPR as the channel involved and demonstrated that retrograde signalling from the ryanodine receptor protein to the DHPR is aberrant with an *RYR1* MH mutant.<sup>78</sup> These findings are particularly exciting as they provide a possible explanation for how sarcolemmal depolarization (succinylcholine) could enhance MH triggering and also how block of sarcolemmal action potentials through neuromuscular junction inhibition can delay or prevent an MH reaction.

## Conclusion

This review has highlighted the capacity for all potent inhalation anaesthetics to trigger MH and the role of succinylcholine in inducing early muscle rigidity and enhancing the response to inhalation drugs. The ability of succinylcholine to initiate a life-threatening metabolic MH reaction as the sole trigger is doubtful. There is no convincing evidence to support the restriction of other drugs in MH-susceptible patients.

## Conflict of interest

None declared.

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