REVIEW ARTICLE

Statins and succinylcholine interaction: A cause of concern for serious muscular damage in anesthesiology practice!

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ABSTRACT

Statins are being extensively used in cardiac patient throughout the globe. Succinylcholine has been the mainstay of profound relaxation during induction and intubation of anesthesia for almost six decades now. The interactive properties of these drugs have been of major concern during routine anesthesiology practice in the last few years. However, no major research trial, prospective studies or meta-analysis are available, which can truly allay the fears of possible potential negative synergistic interactions between these two commonly used drugs. Whatever the evidence is available is hardly enough to support a positive outcome and the results have been drawn from observations of only few small studies. As a result, a continuous need among anesthesiologist fraternity is felt to arrive at a suitable inference, which can predict definite consequences of this synergistic interaction. The present article reviews some of the important observations of few handful studies which were carried out to observe any potential adverse interactions between succinylcholine and statins.

Key words: *Myopathy, myotoxicity, renal failure, statins, succinylcholine*

INTRODUCTION

Cardiac diseases have been rising exponentially in the last two to three decades. This can be attributed to various factors that may include but are not limited to lifestyle changes, dietary modifications, professional stress, reduced physical exercise, early diagnosis and so on. All these and many more factors are responsible for an ever increasing number of such patients presenting for surgery either for one indication or the other.[1] Invariably majority of such patients are either taking or are prescribed various drugs for cardiac ailments. The increasing concerns of harmful interactions between succinylcholine and statins have emerged in clinical practice.[2] The present article has been compiled with search strategies aimed at analyzing the full text articles and literature on PubMed, Scopus, Science direct, Embase, Medscape and Google scholar with key words such as statin, succinylcholine, myopathy, myotoxicity and depolarizing agents. Only those studies were included which highlighted the side-effects of statins and succinylcholine and their possible additive interaction.

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STATINS IN CLINICAL USE

Beneficial effects

Statins are commonly prescribed drugs throughout the globe for prophylactic and therapeutic management of ischemic heart disease and in patients with deranged lipid profile. The anti-lipidemic action is responsible for decreasing the plasma levels of low density lipoproteins thereby reducing the risk of myocardial infarction and stroke.[3] At molecular and cellular levels, long-term administration of statins inhibit the synthesis of 3-hydroxy-3-methyl-glutaryl co-enzyme A reductase thereby inhibiting the rate of conversion of acetate molecules into cholesterol and exerting cardio-protective effects such as reduced frequency of atherosclerotic plaque formation and stabilization of previously formed plaques.[4,5]

Side effect profile of statins

The therapeutic advantages of statins can be seen on long term usage but such chronic use is also associated with possible potential adverse skeletal muscle effects. These

manifestations can occur in the form of muscle weakness, fatigue, myositis and rhabdo-myolysis in approximately 10-90% of patients.[6-9] The exact mechanism of muscular damage remains unknown but possible causes include: Depletion of essential protective lipid components of muscle membrane, decrease synthesis of ubiquinone leading to muscle cell mitochondrial dysfunction, induced apoptosis and possible interference in ionic conductance across cellular membranes.[10-13]

Genetic predisposition

It is estimated that 3-5% of patients taking statins suffer from myalgia[7] while higher doses of statins can cause myalgia in 10% of patients as reported by various observational studies.[14] Patients with genetic variant of solute carrier organic anion transporter family, member 1B1(SLCO1B1 gene) (encoding for organic anion transport) are highly vulnerable to statins induced rhabdo-myolysis. A higher incidence of myopathy is associated with genetic variants in hepatic uptake mechanisms and statins catabolism.[15] It has also been established in literature that serotonergic gene variants have a significant role in severity of myalgia induced by statins.[15] In one study, rhabdo-myolysis was reported in 3500 patients who were administered statins with a mortality rate of 7.8%.[16]

Type of statin and variable adverse effects

Some lipid lowering agents like cerivastatin and rosuvastatin are associated with a higher incidence of rhabdo-myolysis.[17] Food and Drug Administration (FDA) has prohibited the use of Simvastatin in higher doses (>80 mg) as it associated with increased incidence of diabetes. Evidence of renal failure possibly caused by statins is difficult to estimate as plasma creatinine increases only after more than 50% reduction in glomerular filtration rate occurs in elderly.[18] Fluvastatin and pravastatin induced rhabdo-myolysis has also been incriminated in causation of renal failure in patients undergoing laparoscopic surgery.[19] Cerivastatin was finally withdrawn from market in 2001 after a higher incidence of rhabdo-myolysis was reported with its use.

STATIN-SCH INTERACTION AND ANAESTHETIC CHALLENGES

The degree of clinical and anesthetic difficulties is accentuated if such patients are regularly taking statins for their deranged lipid profile. As such, anesthetic management of high-risk cardiac patients during any elective or emergency surgery is a daunting task for the attending anesthesiologist. The challenges start right from the stage of pre-operative evaluation and do not end until the patient is safely discharged home from the hospital. The most challenging situation is encountered during induction of anesthesia as there is enough independent evidence which demonstrates a possible damaging additive action of statins and succinylcholine.[2,20] Few randomized clinically controlled trials and observational studies have shown a negative synergistic action with simultaneous use of statins and succinylcholine.

Sch-statin synergism: Literary evidence

During the period of one important clinical study, it was observed that administration of I.V. succinylcholine in doses of 1.5 mg/kg is associated with greater myoglobinemia and fasciculations in patients who were receiving statin medications before surgery.[2] However, the level of myoglobin reached with this interaction was far below to cause any renal toxicity. The most prominent cellular damage in myocytes can be seen in the form of disruption of T-tubular system and rupture of sub-sarcoplasma.[8,7,21] The interruption of sarcoplasmic reticulum calcium cycling pathway at mitochondrial level can have varied consequences ranging from apoptosis oxidation injury which interrupt the growth and development of muscular tissue causing muscular toxicity and damage.[21]

Current indications of Sch

Succinylcholine has been used for so many decades as a depolarizing agent. With advent of various newer short and rapid acting non-depolarizing muscle relaxants, succinylcholine is not favored in the modern day anesthesiology practice. However, still few definite indications do exist which mandates administration of Sch. These indications are guided by rapid onset, faster recovery and lower cost of succinylcholine such as.[22]

- Refractory laryngospasm in pediatric patients when intramuscular Sch can be extremely useful in the absence of intravenous line. These patients are never on statins
- Rapid sequence intubation but the interplay of such drug interaction has not been studied in American Society of Anaesthesiologist (ASA)-III and above patients
- Procedures of short duration where profound relaxation is required
- 'Can Not Intubate and Can Not Ventilate' situation. Here comes the role of suggamadex provided it becomes easy available. Moreover, stress is being given to explore newer methods of airway securing in such situations whether Sch or rocuronium will be used in future.

Side-effect profile Sch

Among the known biochemical harmful effects of succinylcholine, hyperkalemia, rise in creatine phosphokinase levels and rise in serum myoglobin levels can be extremely deleterious in patients taking statins. A higher incidence of post-operative myalgia due to bio-chemical trauma to muscles and subsequent release of lytic enzymes can

be extremely agonizing to the patients clinically.[23,24] Ronald. D. Miller, while highlighting the adverse properties of Sch in his editorial in anesthesia and analgesia has labeled this drug as "Dirty" and "Dangerous." According to him, it is an "Obligatory" pharmaceutical agent whose safety should be improved.[25] Attempts were made to replace succinylcholine with rapacuronium and rocuronium in the past but the failure should not deter the anesthesiology fraternity from finding a suitable alternative.

Risk and safety concerns in Sch-statin interaction

These interactive side-effects of Sch and statins can be accentuated in patients with known muscular pathologies which can be detrimental to a varying degree.[26] Till date not many trials and studies are available which can directly establish the safety of Sch administration in patients on statins. Whatever the literary evidence is available, it is certain that the side-effect profile of these drugs is similar which has given birth to the possible concerns of muscular tissue damage. A major point of concern is "shall we label a combination of drugs safe on the basis of only a few trials involving a handful of patients when the synergistic side effects of these drugs are not established?" Definitely not, as inter-individual variability may involve numerous factors such as age, gender, geographical distribution, ethnic variations, genetic differences, dietary variances, lifestyle differences and associated co-morbidities. It is not clear from the methodology of the available trials that all these confounding variables were taken into account when observing and analyzing the results of these studies.[2,20]

Scientific reasoning

The logic and truth go hand in hand during scientific exploration and it cannot be denied that when two drugs of similar adverse effects are administered together, they definitely will have additive effect. In anesthesia, studies are commonly undertaken to decrease the dose of the said anesthetics or analgesics so as to decrease the incidence of side effects associated with that higher dose. The most common method is to choose another drug exerting similar actions so as to decrease the dose of each drug or to add an adjuvant drug. Statins and Sch do not have any positive additive but concerns of negative additive effects cannot be dismissed as such. Till date, there is no landmark study available or for that matter no large study or meta-analysis has been carried out which can allay the fear of using Sch and statins together. Whatever the literary evidence is available, it is just the confluence of very few small studies which were also not done without completely eliminating the various confounding biases.[2,20]

Ethical concerns

Human beings should not be subjected to such therapeutic interventions on the basis of results of few studies. The favorable data available from literature that advocates the use of Sch in patients on statins are just suggesting borderline results and in no way can be adopted as definite recommendations. Not a single study has come out with definite conclusions that use of Sch is safe in patients taking statins. The irony being that in developing countries where maximum consumption of Sch occurs, not a single study has been carried out highlighting the merits and demerits of simultaneous use of Sch and statins with an emphasis on measurement of myoglobin and creatine phosphokinase.

Literary limitations and expert recommendations

In his editorial, "Sch should be avoided in patients on statin therapy" Chingmuh Lee has beautifully summarized the concerns associated with use of Sch in patients on statins by elaborating on famous Chinese proverb " Spare no virtue even if minor, do no harm even if trivial."[20] The editorial also highlighted the weakness and strengths of a major landmark study "Consequences of succinylcholine administration to patients using statins" published in the same issue of the journal.[2,20] The type of surgeries performed has not been mentioned in this major landmark study as orthopedic and vascular surgeries are associated with higher incidence of muscle tissue damage as evident by rise in creatine kinase levels. No clarification of dose of statins in these patients has been done as it is successfully established that adverse effects due to statins are dose related. No specific prospective matching of co-variates was done, although some adjustments for unbalanced co-variates were performed. The study seems to be grossly under-powered to evaluate any serious adverse effects. To detect a clinically significant outcome a much larger sample size is needed. Therefore it should be considered a joint obligation on our part towards all surgical patients that we should use only those drugs and techniques on them which have clearly established the risk/benefit and cost-benefit ratio.

Various high risk factors such as female gender, age >80 years, high doses of statins, type of statins, use of more than one statin, renal insufficiency, hepatic derangement, diabetes, hypothyroidism and co-administration of CytochromeP3A4 (CYP3A4) co-enzyme inhibitor or the drugs metabolized by this co-enzyme were not taken into account in entirety while drawing the inferences about the safety and myotoxicity caused by statins. Some of the drugs belonging to this category such as nicotinic acid, fibrates, azole antifungal agents, cyclosporine and macrolide antibiotics inhibit the metabolism of statins by inhibiting the co-enzyme CYP3A4.

Considering the definite established side-effect of statins, that is, muscle injuries, it becomes mandatory that no additional harm in these patients with use of Sch should be

done. The easy availability, low cost, a long-term habitual comfort in Sch use and reluctance to adopt other methods should not guide us to indiscriminately use Sch in patients receiving statins. The main limitation in present clinical scenario is scarce availability of suggamedex; otherwise, rocuronium can be an easy answer to all these problems.

It is high time that Sch-statins interaction be adequately quantified in view of the facts that a large number of aging population who have become increasingly health aware are nowadays taking statins for various cardiac ailments. Whatever the data is available from literature; all the studies denying any adverse additive interaction of Sch-statins have been studied in healthy patients. However, majority of patients on statins will invariably have some co-morbid diseases which may include but are not limited to cardiac, hepatic, renal, neuromuscular disorder, and chronic pain.[2,17,20]

Even if Sch use is advocated in emergency surgeries, there is no study highlighting the effect of Sch is ASA-III and above patients on statin treatment. Data is also scarce related to these additive interactions as patients undergoing orthopedic and spine surgeries have not been the part of any such major trial.

Room for improvement

It is mandatory that indications for all drugs including Sch should be evaluated on regular basis when more and more information becomes available. Ever since its introduction into clinical anesthesiology practice 60 years ago as an almost ideal muscle relaxant, the indications of Sch have been shrinking over the last five decades.[25] Numerous efforts have been made to replace the Sch from anesthesia cart with non-depolarizing muscle relaxants since 1975 but all have tasted only partial success. The bottom-line is that "why the replacement is needed at first place if Sch is such a good drug?" The answer may not be a straight forward logical reasoning but with an increasing use of Sch, numerous side-effects and disadvantages have come to the fore from time to time which has been dealt with partially successful to futile attempts to replace the drug. In the studies where the concomitant safety of succinylcholine stains has been stressed, have not taken into account the type of statin being used pre-operatively. As such it is not wise to label the safety of all statins on the basis of results obtained from a single agent study. It is a well-known fact that the lipophilic statins causes greater damage to the muscles as they can penetrate easily into the cells.

Present clinical scenario

Presently, statin-Sch interaction has occupied the center stage of controversies but the results have not been clearly known. Since the issue has given birth to serious thinking and the concerns have been ignited, it has become mandatory to re-evaluate administration of Sch in patients taking statins in the light of these facts. The major drawback in exploring and producing literary evidence is that in developing countries where maximum consumption of Sch occurs, not a single study is available to document these concerns so as to clear the myths and controversies associated with such interaction. Limitations such as scarce resources, non-availability of facilities to measure creatine phosphokinase and myoglobin in all the health centers will exist for many years to come. Still, we are mentally adamant to use Sch in the entire vulnerable group as there are no clear cut guidelines from any existent supreme authorities.

Time for self-introspection

How many times we can courageously and honestly tell our patients that he or she can suffer from additional effects of such possible interaction. The cost factor is hardly explained to the patient and the relatives so as to minimize the incidence of these unwanted side effects by resorting to other costly alternatives. In our country there is no practice to tell the patient that he can have minimal chances of sinus arrest, catecholamine release effects, malignant hyperthermia, fasciculations and masseter spasm if he can pay more for costly non-depolarizers.[27,28]

CONCLUSION

At present, the safety issues of potential negative synergistic actions between succinylcholine and statins have not been adequately addressed. A large number of trials and observational studies are required to arrive at some definite conclusions. The results of few prospective studies involving a handful of patients analyzing the potential interactive behavior of succinylcholine and statins have not been convincing. Precautions should be taken in lieu of such possible damaging interactions until some definite guidelines become available for a carefree use of succinylcholine in patients taking statins.

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