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Original article

CHANGES IN PROPOFOL ANAESTHESIA AND DICHLORVOS TOXICITY IN MICE FOLLOWING REPEATED DOSING WITH THREE HYPOLIPIDEMIC STATINS

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Summary

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Undesirable effects of hypolipidemic statins in rodents are characterised by neurobehavioural alterations with changes in the cholinergic/cholinesterase and neurotropic systems. The purpose of the study was to administer repeatedly three different statins: atorvastatin, simvastatin and rosuvastatin, in male Swiss mice and explore their behavioural outcomes after challenging them with the anaesthetic propofol and the cholinesterase inhibitor dichlorvos. A total of 92 mice were randomly allocated to each statin (200 mg/kg/day) or distilled water-control (10 mL/kg/day) treatment groups (n= 8 or 10 mice/group)for 28 consecutive days. Twenty-four hours after last statin or control dosing, mice were subjected to a pharmacological challenge with propofol at 100 mg/kg, intraperitoneally or to a toxicological challenge with dichlorvos at 150 mg active ingredient/10 mL distilled water/kg, orally. Propofol anaesthesia and dichlorvos-induced cholinergic toxidrome were separately monitored. Brain cholinesterase activity was also determined in statin-treated mice. Statins significantly decreased the latency to onset of propofol sleep and reduced the sleep duration. Following the toxicological challenge, statins significantly increased the latency to onset of signs of poisoning and delayed the latency to onset of death within 4 h after the dichlorvos dosing. Statin treatments variably decreased signs of poisoning and death (37.5%–87.5%) vs. control group (62.5%–100%). Atorvastatin, simvastatin and rosuvastatin also significantly decreased dichlorvos toxicity score by 42%, 33% and 21%, and significantly reduced whole brain ChE activity by 54%, 42% and 42%, respectively. The results support values of pharmacological and toxicological challenges in mice to uncover changes in responses to propofol anaesthesia and dichlorvos intoxication following repeated statin treatments. Further studies are needed to explore neurochemical bases of statin effects.

Key words: atorvastatin, cholinergic toxidrome, cholinesterase, dichlorvos, rosuvastatin, simvastatin, pharmacological challenge, propofol, toxicological challenge

INTRODUCTION

Statin-based hypolipidemic drugs are widely used to reduce high blood cholesterol level by inhibiting the rate-limiting enzyme hydroxyl-methyl-glutaryl-CoA reductase in the liver (Sirtori 2014; Hirota *et al.*, 2020; Climent *et al.*, 2021). However, many undesirable effects have been found to be associated with repeated use of these statins, such as myotoxicity, liver injury, kidney dysfunction as well as alterations in blood and tissue biochemical indices (Darvesh *et al.*, 2004; Tatley & Savage, 2007; Sakaeda *et al.*, 2011; Sirtori, 2014; Pal *et al.*, 2015; Attardo *et al.*, 2022). Additionally, studies have reported statin intolerance, which is a condition not related to drug dosage or its duration of therapy (Alonso *et al.*, 2019; Bytyçi *et al.*, 2022). Within this context, and in the light of pleiotropic effects of statins (Sitori, 2014; Profumo *et al.*, 2014; Sørensen *et al.*, 2019), several animal models that differ pharmacokinetically and pharmacodynamically have been used to address undesirable effects of various statins.

In spite of the wide margin of safety of statins, experimental animal studies have demonstrated various undesirable effects in several animal species. Statins cause alterations in the cholinergic system and reduce blood or brain cholinesterase (ChE) activity in rats (Cibicková *et al.*, 2007; Vukšić *et al.*, 2019), mice (Al-Shalchi & Mohammad, 2024a) and chicks (Rashid & Mohammad, 2023a). These compounds also cause neuromuscular dysfunction in rats (Bouitbir et al., 2011), and induce oxidative stress which is characterised by reduced glutathione level and increased malondialdehyde level in the plasma and brain of mice (Al-Shalchi & Mohammad, 2024b). Others have reported increased plasma ChE activity and decreased malondialdehyde level in statin-treated rats (Macan *et al.*, 2015). Furthermore, examining the neurobehavioural functional aspects of experimental animals treated with statins has shown various behavioral performance alterations such as cognitive impairment in rats (Husain *et al.*, 2018), memory dysfunction in mice (Ghodke *et al.*, 2012), depressive behaviours in mice (Hai-Na *et al.*, 2020; Al-Shalchi & Mohammad, 2024a), reductions in general locomotion, changes in swimming performance (Oliveira *et al.*, 2018; Al-Shalchi & Mohammad, 2024a) and epilepsy (Oliveira *et al.*, 2018) in mice, as well as modulation of social behaviour in rats (Durankuş *et al.*, 2023). It was also recently reported, , that statins reduce the duration of anaesthetic action of xylazine-ketamine in chicks, with reductions of the toxicity outcome of the reversible ChE inhibitor carbaryl (Rashid & Mohammad, 2023b). This latter approach of pharmacological and toxicological challenges has been used when there are no overt actions of drugs in experimental animals, but rather changes appear when they are subjected to challenges with drugs or toxicants (Frankel *et al.*, 2007; Rashid & Mohammad, 2023b). Overall, these studies cited above have shown that various neuronal and functional-behavioural aspects of statins in experimental animals should be explored to understand possible undesirable effects of these drugs. In the light of recent findings regarding neurobehavioral changes, reduced brain ChE activity and the induction of oxidative stress in mice without overt toxicity (Al-Shalchi & Mohammad, 2024a,b), it became imperative to pursue this line of relatively unexplored undesirable effects of statins in mice. This is important in the light of suggestions to further characterise and explore undesirable effects or even

pleiotropic effects of statins in animal models (Al-Shalchi & Mohammad, 2024a,b), considering the fact that statin-induced intolerance is being implicated in various adverse outcomes of these medications (Alonso *et al.*, 2019; Bytyçi *et al.*, 2022).

The purpose of the present study was to administer repeatedly three statins (atorvastatin, simvastatin and rosuvastatin) that differ in their pharmacokinetic and pharmacodynamics aspects (Sirtori, 2014; Hirota *et al.*, 2020; Climent *et al.*, 2021) to mice, and explore their behavioural outcomes after challenging with the short-acting anaesthetic propofol (Sahinovic *et al.*, 2018) and the irreversible ChE inhibitor dichlorvos (Saravanakumar *et al.,* 2024).

MATERIALS AND METHODS

Animals and ethics

Ninety two male Swiss-origin adult mice (age 100–120 days; body weight 30–35 g) were used. The mice were housed at a temperature between 20 to 24 ºC and a 12-h light/dark cycle, with water and laboratory rodent food *ad libitum*. The protocol of the study was approved by the Departmental Scientific Committee on Research and Animal Care and Use and the Committee of Postgraduate Studies at the College of Veterinary Medicine (No. 2144, November 2, 2022), University of Mosul (No. 4S/29927, October 30, 2022), Iraq. The study was in accordance to the institutional regulations and ethics on the use and handling of laboratory animals which are in compliance with guidelines of Animal Research: Reporting of In Vivo Experiments (ARRIVE) (Percie du Sert *et al.*, 2020) and the Guide for the Care and Use of Laboratory Animals (National Research Council, 2011).

Drugs used and experimental protocol

The statins used, atorvastatin, simvastatin and rosuvastatin, were obtained from the State Company for Drugs Industry and Medical Appliances, Samarra, Iraq. Each statin dosage (200 mg/kg of body weight/day for 28 consecutive days) was prepared in distilled water as a vehicle for

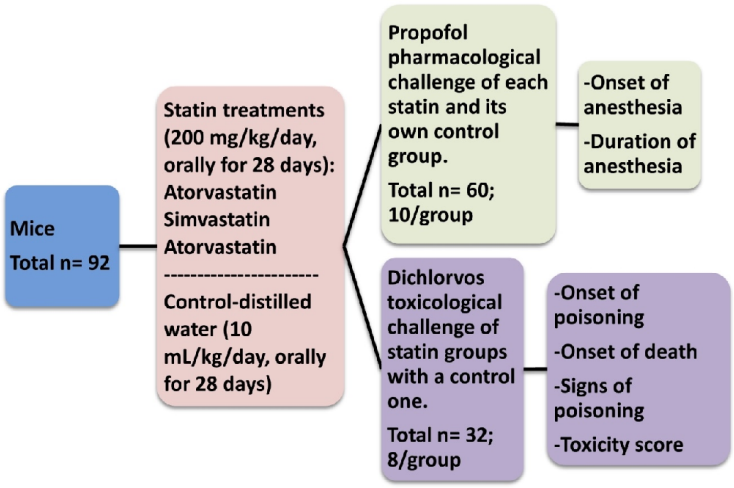

Fig. 1. The integrated experimental design of the study and allocation of male mice treated with statins to propofol pharmacological and dichlorvos toxicological challenges.

oral administration using a stomach tube at a volume of 10 mL/kg of body weight. These dose rates of the three statins were found to produce oxidative stress in mice, but no overt signs of toxicosis (Al-Shalchi & Mohammad, 2024b). As shown on Fig. 1, the 92 mice were randomly allocated to statin or distilled water (control) treatment groups (n=8 or 10/group). The time of daily drug administration was between 9 to 10 AM.

Pharmacological challenge with propofol

Twenty four hours after each statin or distilled water (control) repetitive dosing for 28 days, each mouse was injected intraperitoneally (i.p.) with propofol (Diprivan 1%, Corden Pharma SpA, Caponago, Italy) at 100 mg/kg of body weight (Luo *et al.*, 2022) as a pharmacological challenge (n=10 mice/group). The lag time of 24 hours for the pharmacological challenge was based on literature data in order to avoid possible acute statin effect that might result from the last day dosing on the challenge outcome (Rashid & Mohammad, 2023b). The latency to onset of loss of the righting reflex (sleep as an index of anaesthesia) and the duration of anaesthesia were recorded for each mouse.

Toxicological challenge

As with the pharmacological challenge, a toxicological challenge was introduced 24 hours after each statin- or distilled water (control) repetitive dosing for 28 days. Mice were dosed orally with dichlorvos (Nicoz, 50% EC Royal Brand, India) at 150 mg-active ingredient/10 mL distilled water/kg of body weight (n=8 mice/group) (Mohammad *et al.*, 1989). After the dichlorvos dosing, each mouse was observed for appearance of signs of acute organophosphate toxidrome which was characterised by excessive salivation, frequent defecation and tremors, as well as any 4- and 24 h lethality (Mohammad *et al.*, 2023). The latencies to onset of signs of acute poisoning and death were recorded. The severity of dichlorvos poisoning was rated by the toxicity score from the grades of one to four allocated to the percentage of occurrence of signs of organophosphate poisoning as well as 4- and 24 h lethality (Mohammad *et al.*, 2023). Briefly, the percentages of occurrence of each sign of poisoning, and the 4- and 24 h lethality were scored as follows: 1 (1–25%), 2 (26–50%), 3 (51–75%) and 4 (>75%). The highest toxicity score would be 6×4=24 in intoxicated mice within a group, when all the signs of poisoning and death would occur.

Determination of whole brain ChE activity

Twenty four hours after repetitive statin or distilled water (control) dosing for 28 days, mice were sacrificed by cervical dislocation. The whole brain was dissected out and homogenised in sodium chloride-phosphate buffer (1:9) using a homogenizer (OMNI Bead Ruptor, OMNI International, USA) at a speed of 400 rounds/second (Mohammad *et al.*, 2014; Al-Shalchi & Mohammad 2024a). The ChE activity in the whole brain was determined spectrophotometrically by a commercial kit (Elabscience Biotechnology Inc., Houston, TX, USA).

Statistical analysis

The statistical package SPSS-version 20 (IBM) was used to analyse data statistically. Parametric data were subjected to the one-way analysis of variance followed by the least significant difference test, whereas non-parametric data were analysed by the Fisher's exact probability test. The scores of organophosphate poisoning were subjected to the Kruskal-

Wallis test followed by the Dunn's test. The level of statistical significance was at $P<0.05$.

RESULTS

Propofol pharmacological challenge

Oral dosing of mice with the three statins, atorvastatin, simvastatin and rosuvastatin at 200 mg/kg/day for 28 days caused a significant ($P<0.05$) decrease in the latency period to onset of propofol sleep compared with the respective control value (Table 1). Subsequently, the duration of propofol sleep was significantly reduced from respective control values in mice treated with atorvastatin and simvastatin by 46.6% and 31.6%, respectively, but not with rosuvastatin (7.3%) (Table 1).

Dichlorvos toxicological challenge

Statin treatments significantly increased the latency period to onset of signs of poi-

Table 1. Propofol anaesthesia (100 mg/kg, intraperitoneally) 24 h after the last repeated oral dosing of mice with statins (200 mg/kg/day for 28 consecutive days). Values are mean ± SE of 10 mice/statin group

Statin treatment	Latency to onset of sleep (s)	% decrease from control	Duration of sleep (min)	% decrease from control
Control	39.2 ± 0.66	–	11.80 ± 0.42	–
Atorvastatin	31.5 ± 0.70*	19.6	6.30 ± 0.30*	46.6
Control	40.2 ± 0.84	–	13.30 ± 0.62	–
Simvastatin	33.3 ± 1.90*	17.2	9.10 ± 0.38*	31.6
Control	37.2 ± 0.47	–	13.10 ± 0.43	–
Rosuvastatin	28.5 ± 0.54*	23.4	12.15 ± 0.33	7.3

*Significantly different from the respective control value, $P<0.05$.

Table 2. Dichlorvos (150 mg/kg, orally) poisoning 24 h after the last repeated oral dosing of mice with statins (200 mg/kg/day for 28 consecutive days). Values are mean ± SE of 8 mice/statin group

Variable	Control	Atorvastatin	Simvastatin	Rosuvastatin
Latency to onset of signs of poisoning (min)	2.41 ± 0.11	7.36 ± 0.27*	5.64 ± 0.17*[a]	5.65 ± 0.22*[ab]
Latency to onset of death in 4 h (min)	90.6 ± 1.1	200.0 ± 3.5*	195.0 ± 4.3*	156.6 ± 3.1*[ab]
Occurrence of signs of poisoning, %				
Salivation	100	62.5	75	75
Lacrimation	87.5	37.5*	50	62.5
Frequent defecation	100	62.5	62.5	87.5
Tremors	87.5	37.5*	50	75
Death				
4 h death (%)	87.5	37.5*	50	62.5
24 h death (%)	87.5	37.5*	62.5	75

*Significantly different from the respective control value ($P<0.05$); [a] Significantly different from the respective atorvastatin value ($P<0.05$); [b] Significantly different from the respective simvastatin value ($P<0.05$).

Table 3. Dichlorvos (150 mg/kg, orally)-induced toxicity score in mice treated with each of the statins at 200 mg/kg/day for 28 consecutive days n= 8 mice/statin group.

Signs/death	Grades allocated to % occurrence of signs of poisoning and death †			
	Control	Atorvastatin	Simvastatin	Rosuvastatin
Salivation	4	3	3	3
Lacrimation	4	2	2	3
Frequent defecation	4	3	3	4
Tremors	4	2	3	3
4 h death	4	2	2	3
24 h death	4	2	3	3
Toxicity score statistics				
Median toxicity score	4	2	3	3
25 percentile	4	2	2	3
75 percentile	4	3	3	3.25
Mode	4	2	3	3
Total toxicity score (maximum 24)	24	14*	16*	19*

† Data of Table 2 were used; * Significantly different from the control value: Kruskal-Wallis test for equal medians, H (Chi^2) 14.69, P=0.0007124; Dunn's test, P=0.0001119, 0.001827, and 0.04821, respectively.

soning and delayed the latency period to onset of death within 4 h after the dichlorvos oral dosing at 150 mg/kg (Table 2). As expected, dichlorvos dosing produced cholinergic signs of organophosphate poisoning in both control and statin treated mice. The toxidrome of dichlorvos poisoning in mice was characterised by excessive salivation, lacrimation, frequent defecation and tremors, followed by death at varying percentages that ranged from 37.5% to 100% (Table 2). Statin treatments variably decreased the occurrence of signs of poisoning and death (37.5%–87.5%) in comparison with the control group (62.5%–100%). As shown in Table 2, atorvastatin treatment significantly reduced the occurrence of dichlorvos-induced lacrimation, tremors and the 4- and 24 h lethality.

Considering the total toxicity score as calculated from the occurrence of signs of cholinergic poisoning and the 4- and 24 h lethality (grades of 1–4) in mice, the three statin treatments significantly decreased dichlorvos toxicity score by 42%, 33% and 21%, respectively in comparison with that of the control group (Table 3).

Brain ChE activity

Repeated treatments with atorvastatin, simvastatin and rosuvastatin at 200 mg/kg/day for 28 consecutive days significantly reduced whole brain ChE activity by 54%, 42% and 42%, respectively, compared to respective control values (Fig. 2).

DISCUSSION

The pharmacological challenge with the short-acting anaesthetic propofol revealed that statin treatments for 28 days altered the response of mice to anaesthesia. This

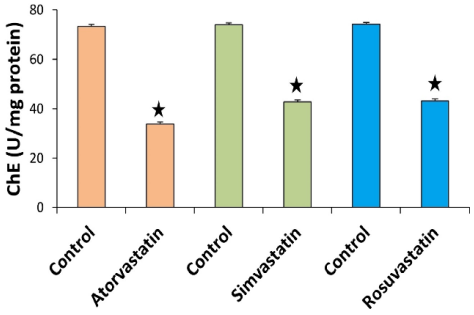

Fig. 2. Brain cholinesterase (ChE) activity (U/mg protein) in mice dosed orally with statins at 200 mg/kg/day for 28 consecutive days. Values are mean ± SE of 10 mice/statin group. *Significantly different from the respective control value ($P<0.05$).

became evident by the decrease of the time to onset of anaesthesia with the three statins and reduction of the duration of propofol anaesthesia by atorvastatin and simvastatin, but not by rosuvastatin. This partial effect of rosuvastatin on propofol anaesthesia in mice could be related to its low bioavailability into the central nervous system due to its hydrophilicity nature compared to more lipophilic statins atorvastatin and simvastatin (Fong, 2014; Climent *et al.*, 2021; Ward *et al.*, 2019). Propofol anaesthesia results from potentiation of $GABA_A$-receptor-mediated inhibitory effect in the central nervous system as well as inhibition of the N-methyl-D-aspartate receptors (Kotani *et al.*, 2008; Sahinovic *et al.*, 2018). The nature of drug-drug interaction of propofol with the statins at the level of the central nervous system is not clear at present. However, it could be associated with the reported neurotropic effects of high doses of statins in decreasing hippocampal neurotropins and irisin levels in conjunction with impaired cognitive function (Husain *et al.*, 2018; Okudan & Belviranli, 2020) and neurobehavioural alterations at the levels of locomotion, memory, anxiety, and depressive responses (Ghodke *et al.*, 2012; Husain *et al.*, 2018; Oliveira *et al.*, 2018; Hai-Na *et al.*, 2020; Al-Shalchi & Mohammad, 2024a). Further, in accordance with the present results on propofol anaesthesia, a single dose of simvastatin (100 mg/kg, orally) reduced xylazine-ketamine anaesthesia when the latter was used as a pharmacological challenge in young chicks (Rashid & Mohammad 2023b). Pharmacological challenges with centrally active drugs (Frankel *et al.*, 2007; Rashid & Mohammad 2023b) would be a suitable tool to further examine potential actions of statins on the brain and the associated behavioural outcomes, especially when considering exploration of additional pleiotropic effects of statins.

Dichlorvos is an organophosphate compound used as an insecticide that inhibits central and peripheral ChEs in the animal body (Okoroiwu & Iwara, 2018). This toxicant was used as a toxicological challenge in mice treated with statins. As expected (Mohammad *et al.*, 1989; Okoroiwu & Iwara, 2018; Mohammad *et al.*, 2023), dichlorvos induced a toxidrome of cholinergic poisoning in control and statin-treated mice, which was characterised by excessive salivation, lacrimation, frequent defecation and tremors, followed by death at varying percentages (Table 2). However, the three statin treatments reduced the dichlorvos-induced toxicosis in mice by prolonging the onset times of poisoning and death as well as by reducing the total toxicity score (21–42%) which is based on the occurrence of cholinergic toxidrome and death. These results are in agreement with those of a previous study in which atorvastatin and fluvastatin reduced the toxicity of carbaryl, another anti-ChE, but reversible, insecticide, in young chicks (Rashid &

Mohammad, 2023b). Furthermore, the results also highlight the diversity of statin effects, and suggest involvements of the cholinergic pathways in their protective action against ChE inhibitors.

To further elucidate the possible mechanism of action of statins on the cholinergic system, statins have been reported to reduce brain and blood ChE activities in mice (Al-Shalchi & Mohammad, 2024a), rats (Vukšić *et al.*, 2019) and chicks (Rashid & Mohammad, 2023a). In accordance with these studies, the results of the present study also indicated reduced brain ChE activity in statin treated mice (Fig. 2). It is likely, therefore to deduce that the mechanism of statin-mediated protection against dichlorvos poisoning in mice is associated with prior inhibition of neuronal ChE activity in a manner that prevents additional ChE inhibition, thus reducing the cholinergic toxidrome and lethality. Such a protective mechanism of organophosphate poisoning has been reported earlier with the use of weak ChE inhibitors like physostigmine, pyridostigmine and metoclopramide to shield the animal against the ChE inhibitor poisoning (Al-Zubaidy & Mohammad, 2007; Hrvat & Kovarik, 2020). This is because the single most important mechanism of dichlorvos-induced toxicity, as is the case with other organophosphates, is irreversible inhibition of ChE activity at neuronal endings that leads to build up of acetylcholine, which in turn produces cholinergic toxidrome (Okoroiwu & Iwara, 2018).

Another possible reason for the interaction of statins with pharmacological and toxicological challenges is the induction of oxidative stress reported as undesirable effects of high doses of statins (Al-Shalchi & Mohammad 2024b), probably as a result of reactive oxygen species buildup burst (Thomas *et al.*, 2022). In line with this consideration, oxidative stress was reported to modulate the action of centrally acting drugs (Mousa & Mohammad, 2012) or toxicants (Al-Baggou *et al.*, 2011), and what complicates the matter more, organophosphates were reported to cause oxidative stress (Vanova *et al.*, 2018). However, more in depth exploration of statin actions on the oxidative stress inducing systems and cholinergic modulation are needed.

CONCLUSIONS

The present results, being one of its kinds, support the values of pharmacological and toxicological challenges of mice repeatedly treated with statins to uncover undesirable behavioural modifications of the anaesthetic response to propofol and the desirable reduction of dichlorvos-induced cholinergic toxidrome. Because of two types of challenges, the results also suggest and additionally ascertain differential alterations in neuronal functions in mice following statins treatments. The involvement of the cholinergic system in statin action has been suggested by the present results, however, a multidisciplinary approach is recommended to deeply explore the neurochemical bases of statin effects.

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