Experimental evaluation of the antinociceptive and anti-inflammatory effects of rosuvastatin and its interaction with celecoxib and paracetamol

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ABSTRACT

Background: **Studies revealed that statins can result in a larger mortality benefit than can be readily explained by their cholesterol-lowering effect alone. These benefits might be related to the anti-inflammatory and other effects statins may have.**

Aim: **To find out the extent to which rosuvastatin can be considered as an antinociceptive and anti-inflammatory drug in comparison to two standard drugs; paracetamol and celecoxib.**

Methods: **Mice (a total of 132) of either sex, 3-4 weeks of age, 20-25 gm body weight, were used. Tests for nociception: tail flick, hot plate and formalin tests; and for inflammation (formalin for chronic inflammation, carrageenan-induced paw edema, and TNF alpha level in blood) were used. Rosuvastatin (7mg/kg), paracetamol (40mg/kg), celecoxib (6mg/kg) or their combination were administered orally once daily in a volume of 0.2 ml. TNF alpha level in blood was measured using ELISA kit.**

Results: **The antinociceptive effect of rosuvastatin was mild and was much less than that of paracetamol and celecoxib when tested in the tail-flick, hot-plate and formalin tests. It increased the latency for tail flick by only 13.3% when compared to pre-treatment measurements, and in formalin test, it reduced the licking time by 20.9% in comparison to control. The administration of rosuvastatin with either paracetamol or celecoxib did not add to the antinociceptive effects of the latter two drugs except in formalin test for pain. None of the above mentioned drugs reduced hind-paw edema when measured 24 hours after formalin injection, while they produced a significant edema-reducing effect after 14 days. Again there was no additive effect between rosuvastatin and either paracetamol or celecoxib; in contrast, rosuvastatin reduced nearly all the effects of celecoxib when given in combination. Similar trend was found when edema-induced by carrageenan injection.**

Conclusion: **Rosuvastatin showed a significant antinociceptive effect in tail flick and in formalin test, but not in hot plate test in mice. It had anti-inflammatory and edema-reducing effects in models of inflammation but the effect was less than that of celecoxib and even paracetamol. These rosuvastatin effects did not add to those of paracetamol and had caused a reduction in celecoxib effects, when given in combination, except in formalin test for pain where there were additive effect.**

Keywords: **Rosuvastatin, paracetamol, celecoxib, antinociceptive, antiinflammatory**

التقييم التجريبي لتأثير الروزفستاتين المضاد للألم والمضاد للالتهاب وتداخله مع السليكوكسب والباراسيتامول

خلفية الدراسة: أظهرت الدراسات بأن الستاتينات تؤدي الى تقليل الوفيات بدرجة أكبر من أن تعزى الى تأثيرها الخافض للكوليستيرول بمفرده لأن الفائدة حدثت بشكل أسرع مما يمكن تفسيره على وفق الالية سالفة الذكر. هذه الفوائد يمكن أن يكون لها علاقة بتأثيرات الستاتينات المضادة للالتهاب وغيرها.

الهدف: لايجاد المدى الذي يمكن من خلاله اعتبار الروزفستاتين دواءً مضاداً للألم وللالتهاب وذلك مقارنة لدوائين قياسيين هما الباراسيتامول والسليكوكسب.

طرائق العمل: تم استعمال ما مجموعه ١٣٢ فأراً مختبرياً من الجنسين وبأعمار ٣–٤ أسابيع، وبأوزان ٢٠–٢٥ غرام. وتم استعمال اختبارات الألم (اختبارات رجفة الذيل والصفيحة الحارة والفورمالين) واختبارات الالتهاب (اختبارات الفورمالين للالتهاب المزمن ووذمة القدم المحدثة بالكارجنان ومستوى عامل نخر الورم نوع ألفا في الدم). وأعطيت أدوية الرزفستاتين (٧ملغم/كغم)، والباراسيتامول (٤٠ملغم/كغم) والسليكوكسب (٦ملغم/كغم) أوتوليفهما عن طريق الفم مرة واحدة يومياً بحجم ٠.٢ مل. وتم قياس مستوى عامل نخر الورم نوع ألفا في الدم باستعمال عدة ألاليزا.

النتائج: عند اختبار التأثير المضاد للألم للروزفستاتين في الفئران باستعمال اختبارات رجفة الذيل والصفيحة الحارة والفورمالين، ظهر أن للروزفستاتين تأثيراً بسيطاً ضد الألم وهو أقل من تأثير الباراسيتامول والسليكوكسب في الاختبارات نفسها. وسبب الروزفستاتين زيادة الوقت اللازم لرجفة الذيل

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بمقدار ١٣.٣% مقارنة بالقياسات قبل المعالجة بالدواء. وفي اختبار الفورمالين، قلل الروزفستاتين الوقت اللازم للعق القدم بعد زرق الفورمالين بمقدار ٢٠.٩% مقارنة بالمجموعة الضابطة. أن اعطاء الروزفستاتين مع الباراسيتامول أو السليكوكسب لم يعزز التأثير المضاد للألم للدوائين الأخيرين عدا في اختبار الألم بالفورمالين. ولم ينقص أي من الأدوية سالفة الذكر من وذمة مخلب القدم عند قياسها بعد ٢٤ ساعة من زرق الفورمالين ولكنها سببت انقاصاً معتداً بعد ١٤ يوماً من المعالجة، ولم يكن هناك تأثيرتعزيزي بين الروزفستاتين والباراسيتامول أو السليكوكسب. بالمقابل أنقص الروزفستاتين كل تأثيرات السليكوكسب تقريباً عند اعطائهما معاً. وكان هناك الاتجاه نفسه عند احداث الوذمة بزرق الكارجنان.

الاستنتاج: لم يظهر الروزفستاتين تأثيراً معتداً مضاداً للألم عدا في اختبار الفورمالين. وكان له تأثير مضاد للالتهاب ومنقص للوذمة في اختبارات الالتهاب في الفئران لكن تأثيراته أقل بكثير من تلك التي يسببها السليكوكسب وحتى الباراسيتامول وهذه التأثيرات لم تعزز تأثيرات الباراسيتامول وأنها أنقصت تأثيرات السليكوكسب.

INTRODUCTION

Patients who received statins had been shown to have low levels of several inflammatory mediators.[1,2] The interaction between leukocyte and endothelial cells can be inhibited by statins. This interaction is necessary for leukocytes rolling and emerging through blood vessels.[3] In collagen-induced arthritis in animals, simvastatin, atorvastatin and rosuvastatin had been found to decrease disease activity and histologic scores.[4] The antinociceptive and antiinflammatory effects of 3 statins; two lipophilic (lovastatin, atorvastatin) and one hydrophilic (rosuvastatin) in single oral doses in rat acute (carrageenan-induced) and subacute (cotton pellets implanted subcutaneously) inflammatory models had been studied and compared with aspirin 200mg/kg. The results showed that these statins had a significant antiinflammatory effect in both models.[5] Rosuvastatin and atorvastatin had also been shown to have dose- dependent antinocecptive, anti-inflammatory and antioxidant effects in mice.[6] The antiinflammatory effect of 20mg/kg rosuvastatin was investigated in acute phase (carrageenan-induced) and in chronic phase (cotton pellet-induced) inflammatory rat models significantly reduced carrageenan-induced rat paw edema. The results also showed that rosuvastatin was effective in the chronic model of inflammation probably by inhibiting proliferation of macrophages and neutrophils.[7] The effect of orally administered 5mg/kg rosuvastatin was assessed for its antinociceptive activity and compared with aspirin 100mg/kg in mice. The antinociceptive activity was evaluated in hot plate and acetic acid writhing tests. Rosuvastatin showed a minimal analgesic effect in hot plate test. However, in writhing test there was a reduction in the number of wriths by around 61% compared with control, while aspirin reduced them by 89.6%.[8] With the accumulating evidence that statins have potential anti-inflammatory effects, the present study aims to investigate the extent rosuvastatin can be considered as an effective antinociceptive and anti-inflammatory drug in comparison to two standard drugs: paracetamol and celecoxib and whether its potential effects differ in different models of pain and inflammation. In addition, the interaction of rosuvastatin with celecoxib and paracetamol when given in combination will also be investigated.

MATERIALS AND METHODS

Mice (a total of 132) of either sex, 3-4 weeks of age, 20-25 gm body weight, were kept in plastic cages under laboratory conditions of 25±Ċ temperature, and fed with standard laboratory pellets with free access to tap water. Mice were left under these conditions for one week for acclimatization before commencement of experiments. Each animal was tested once only. The doses for rosuvastatin, paracetamol and celecoxib used in this study were selected based on a literature review; the final choice was made

depending on a pilot study conducted for evaluating these doses. For celecoxib; a dose of 0.124 mg/20 gm of mouse (6mg/kg) was selected,[9-11] for rosuvastatin, the dose was 0.144 mg/20 gm mouse (7 mg/kg),[5,7,12] and for paracetamol the dose used in the present work was 0.8 mg/20 gm mouse (40mg/Kg).[13-15] A dose of 0.1ml of vehicles consisting of 0.03 ml of dimethyl sulfoxide (DMSO) which is the highest concentration used in rosuvastatin group and the rest (0.07 ml) was distilled water was given for control. Three pain models; hot plate, tail flick (thermally-induced nociception) and formalin (chemically- induced nociception) pain models, were used.[16-17] Carrageenan-induced paw edema (acute inflammation),[18] formalin test for chronic inflammation[17] were used to induce and assess the degree of inflammation. Measurement of TNF alpha level in the blood (ELISA kits, CUSABIO WUHAN HUAMEI BIOTECH Co. LTD, China) was used as a biomarker of inflammation (The concentration of TNF alpha of a normal mouse is typically less than 3.9 picogram/ml). Comparison between measurements within and between groups were made by analysis of variance (ANOVA) using SPSS program (Statistical Package for Social Sciences) version 15. Paired and unpaired T-Tests were used to test the significance of changes between groups or between pre- and post-treatment measurements

RESULTS

(A) The potential antinociceptive effect of rosuvastatin (7 mg/kg), paracetamol (40 mg/kg), celecoxib (6mg/ml) or their combinations given as a single daily dose for 7 days and measured in mice by tail-flick, hot-plate and formalin tests

Rosuvastatin showed only a mild but statistically significant antinociceptive effect through increasing the latency of tail flick by 13.8% and 13.3% one hour after the first and last doses of a single daily drug administration for 7 days respectively (Table-1A). Paracetamol significantly increased the tail flick latency by 44% and 27.8% in the two periods of measurement respectively and celecoxib by 70.4% and 50.3%. Rosuvastatin slightly reduced the antinociceptive effect of paracetamol and attenuated the effect of celecoxib particularly after 7 days in this type of pain model. Rosuvastatin in hot-plate test did not show a significant change in hot plate latency in comparison to pre-treatment measurements. Paracetamol increased the latency one hour after the first dose by 55% and by only 8.1% after 7 days. Celecoxib showed a similar trend; an increase by 42.4% and 24.5% after the first and last doses respectively. Rosuvastatin did not increase the antinociceptive effect of paracetamol except after the last dose. However, it reduced the effect of celecoxib when given in combination.. When the time of licking of formalin-injected hind paw is taken as a measure of antinociceptive effect, all three drugs and their combinations showed significant antinociceptive effects when compared with control group; the least with rosuvastatin, followed by celecoxib and then by paracetamol (reductions by 20.9%, 22.4% and 29.84% respectively). Rosuvastatin added to the antinociceptive effect of paracetamol, and that of celecoxib (reductions by 40.8% and 39.5% for the combination with paracetamol and celecoxib respectively, compared to 29.8% and 22.4% for paracetamol and celecoxib given alone).

(B) The antiinflammatory effect of rosuvastatin (7mg/kg), paracetamol (40mg/kg), celecoxib (6mg/kg) or their combinations given as a single daily dose for 14 days and measured in mice by formalin test and hind-paw edema.

The anti-inflammatory effect (reduction in paw thickness) of rosuvastatin, paracetamol and celecoxib or their combinations 24 hours after formalin injection is not significantly different. However, 14 day-administration of these drugs resulted in a significant anti-inflammatory effect for the tested drugs when compared with control group. The highest anti-inflammatory effect was achieved with celecoxib (73%), followed by

paracetamol and rosuvastatin (anti-inflammatory effect by 58.4% and 54% respectively). However, combination of rosuvastatin with paracetamol or celecoxib showed no significant change in anti-inflammatory effect with respect to each drug given alone (Table-1B). No significant change in carrageenan-induced paw edema had occurred 3 hours after carrageenan injection. Six hours after carrageenan injection, paracetamol and celecoxib produced a significant anti-inflammatory effect (reduction in edema by 46% and 56% after paracetamol and celecoxib administration respectively). The 23% anti-inflammatory effect by rosuvastatin is not statistically significant. Combination of rosuvastatin with paracetamol or celecoxib did not add to the effect of each drug given alone (Table-1B). Although the blood level of the proinflammatory mediator TNF alpha at day 14 after formalin injection had been reduced by rosuvastatin (48%), paracetamol (66%), celecoxib (69%), rosuvastatin and paracetamol (76%) and by rosuvastatin and celecoxib (26%), these reductions did not reach statistical significance except, for rosuvastatin with paracetamol group (Table-1B).

Table 1. Summary of results of rosuvastatin and its interactions with paracetamol and celecoxib in models of nociception and inflammation.

(A) Nociception tests

Tests / Groups	Hot plate after 1st dose	Tail flick after 1st dose	Formalin Anti-nociception	Hotplate after 7th dose	Tail flick after 7th dose
Control	- 11.3%	- 4.4%	-----	- 10.5%	- 10.1%
Rosuvastatin	- 2.3%	+13.8%	-20.9%	- 12.9%	+13.3%
Paracetamol	+55%	+44.4%	-29.84%	+8.1%	+27.8%
Celecoxib	+42.4%	+70.4%	-22.4%	+24.5%	+50.3%
Rosuvastatin+ paracetamol	+40.2%	+42%	-40.8%	+34.8%	+14%
Rosuvastatin+ celecoxib	+22.4%	+25.5%	-39.5%	+7%	+1.8%

(B) Inflammation tests (Percent change with respect to control group)

Tests / Groups	Carrageenan-induced paw edema		Formalin-induced inflammation		TNF alpha level after 14days (Pg/ml)
	Antiinflam. after 3hrs	Antiinflam. after 6hrs	Antiinflam. after 24hrs	Antiinflam. after 14 d	
Control	----	----	-----	-----	207.3 ± 173.3
Rosuvastatin	----	- 23%	+ 5.5%	- 54.12%	- 48.3%
Paracetamol	- 12.5%	- 46%	- 7.3%	- 58.37%	- 66.6%
Celecoxib	- 20.8%	- 56%	- 16.5%	- 73%	- 69.5%
Rosuvastati+paracetamol	- 12.5%	- 39%	- 1.9%	- 60.5%	- 76.8%
Rosuvastatin+celecoxib	- 4%	- 39%	- 10.3%	- 68%	- 26.3%

Data are presented as percent change with respect to pre-treatment measurements (A) and to control group (B). + and – marks indicate an increase and decrease in the respective measurement).

DISCUSSION

Statins were found to improve atherosclerotic plaques before lowering lipid levels.[19] Improvement had also been observed in different models of murine-induced arthritis.[6,9,20,21] These benefits were attributed to the anti-inflammatory and other effects of statins. The anti-nociceptive and antiinflammatory effects of rosuvastatin had been previously investigated and found to have significant effects.[5,7] However, there are areas still to be investigated such as its effects in different models and after repeated administration, in addition to its interaction with other analgesic and anti-inflammatory drugs. In the dose used in the present study, rosuvastatin showed a significant antinociceptive effect in tail flick and not in hot plate tests. The results of Anand, et al[8] who investigated the antinociceptive effect of rosuvastatin in hot plate test are in agreement with our results where they found minimal antinociceptive effect in this pain model. On the other hand, Ghaisas *et al*[6] found that the antinociceptive, anti-inflammatory and antioxidant effects of rosuvastatin and atorvastatin are dose-dependent. The dose of rosuvastatin used in the present study was based on a review of previous works and preliminary tests. Thus, there is a possibility that the antinociceptive effect might appear at doses higher than the one used in the present study. Hashilkar, *et al* [5] and Kumar, *et al*[7] found a significant anti-inflammatory effects in both acute (carrageenan-induced) and chronic (cotton pellet-induced) inflammatory models. Our findings point to a significant anti-inflammatory effect in formalin test at day 14 after drug administration and also in carrageenan test 6 hours after subcutaneous injection.

Results in formalin-induced nociception are in agreement with the study of Ghaisas *et al*.[6] The latter study had evaluated rosuvastatin and atorvastatin (1-3-10mg/kg) and showed that both drugs had insignificant effect in hot plate test. However, in formalin-induced nociception, rosuvastatin produced statistically significant antinociceptive effect. This might be related to its hydrophilic properties or due to inhibition of bradykinin and substance P release.[22-24] The antinociception effects of rosuvastatin in hot plate and tail flick tests, measured at 7 days, were lower than that measured after first dose. This is in contrast to the study of Noriega et al 2014 who found that rosuvastatin after 3-day-treatment had a better antinocicptive effect than after the first dose. This result could be attributed to the stressful consequences of the 7-day drug daily administration increasing the sensitivity to noxious stimuli and resulting in a state of hypernociception which reduces the antinociceptive effects of drugs.[25] The overall trend is that rosuvastatin when combined with paracetamol produced either no additive effect or slightly reduced the effects caused by paracetamol alone, except in formalin test. These results might indicate that addition of rosuvastatin to paracetamol does not result in a beneficial effect at least in certain types of tests. In addition, such combination might increase the toxicity of paracetamol, since simvastatin was found to induce CYP3A4 and resulted in increased hepatoxicity.[26.27] Administration of rosuvastatin with celecoxib reduced the effect of celecoxib in most tests performed in this study including the TNF alpha levels, again with the exception of formalin test. This result is in contrast to the study of Refaat et al,[9] who showed a strong synergistic anti-inflammatory effect between atorvastatin (10mg/kg/day) and celecoxib (3mg/kg/day) administered daily for 14 days in rats with arithritis. This could be due to differences in the lipophilicity of different statins where atorvastatin is a lipophilic drug, whilst rosuvastatin is a hydrophilic compound. Moreover, rosuvastatin was found to upregulate COX-2,[28] while simvastatin and atorvastatin inhibit COX-2[29] and thus, can potentiate the anti-inflammatory effect of celecoxib. In the present study, only formalin- induced nociception model showed that the combination of rosuvastatin with celecoxib reduced the licking time more than celecoxib given alone

(39.5% and 22.4% respectively) which could point to involvement of mediators other than those produced by COX-2 enzyme. In conclusion, in the dose used in the present study, rosuvastatin showed a significant antinociceptive effect in formalin test, mild in tail flick and none in hot plate tests. Its anti-inflammatory effect was significant when measured after 14 days of drug administration and can reduce edema 6 hours after carrageenan injection with a statistically insignificant reduction in TNF alpha levels in the blood. In most tests used in this study, the use of rosuvastatin with paracetamol, did not add significantly to the effect of paracetamol used alone. Administration of rosuvastatin with celecoxib reduced the effect of celecoxib in nearly all tests performed including the TNF alpha levels except in formalin test. Thus, drug effect might differ in different models of pain and inflammation.

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