NCX-6560, a nitric oxide-donating atorvastatin, lowers portal pressure with a better toxicity profile than atorvastatin in cirrhotic rats

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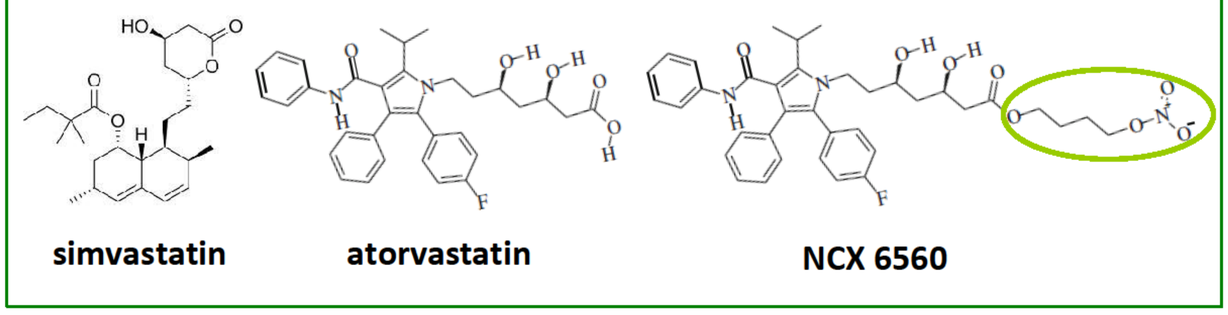
1. Background

Statins ameliorate portal hypertension and liver function in cirrhotic patients and animal models.

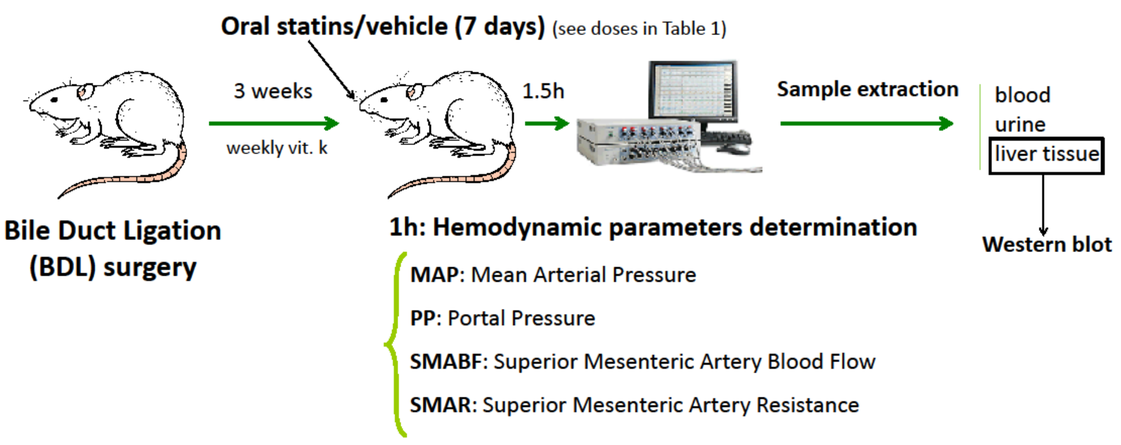


simvastatin atorvastatin NCX 6560

2. Aim

To evaluate whether NCX 6560, a nitric oxide (NO)-releasing derivative of atorvastatin, is superior to conventional statins (simvastatin, atorvastatin) in improving portal hemodynamics and intrahepatic vascular alterations, while decreasing the potential side effects of statins.

3. Methods



4. Results

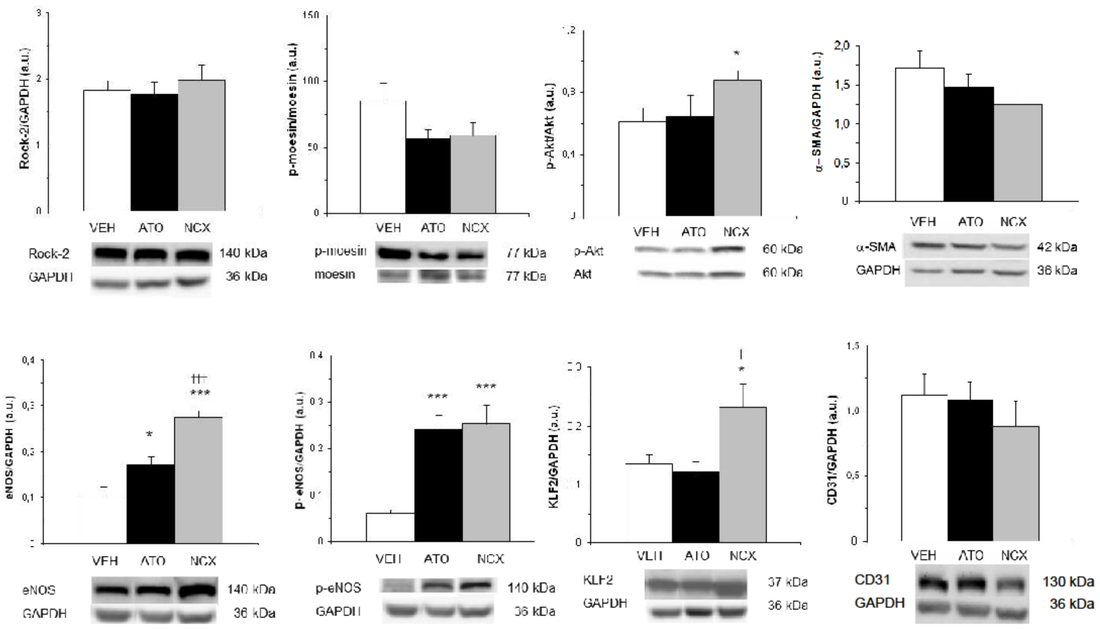
Table 1. Adverse events in the different treatment groups.

	Dose (mg/kg/day)	n	Mortality rate (%)	Hepatic toxicity rate (%)	Muscular toxicity rate (%)
Vehicle (PEG 70%)		12	16.7	0	0
Simvastatin	25	10	80	100	100
	10	11	18.2	66.7	77.8
Atorvastatin	15	14	0	14.3	35.7
	10	15	6.7	6.7	33.3
NCX 6560	35.1	15	6.7	20	33.3
	17.5	11	0	0	9.1
	11.7	15	0	0	13.3

Mortality rate: % of animals that die during the experimental protocol (through treatment or anesthesia); Hepatic toxicity rate: % of animals with serum ALT levels > 200 IU/L; Muscular toxicity rate: % of animals with serum CK levels > 1000 IU/L.

- Simvastatin treated BDL rats showed a higher mortality rate (80% at the higher dose) compared with the other treatment groups and the remaining animals presented both muscular and hepatic toxicity.
- At equivalent doses (NCX 6560 17.5mg/kg/day vs. atorvastatin 15mg/kg/day and NCX 6560 11.7mg/kg/day vs. atorvastatin 10mg/kg/day), treatment with NCX 6560 reduced and eliminated muscular and hepatic toxicity caused by atorvastatin, respectively.

Fig. 1: Liver protein quantification by Western blot.



VEH: vehicle, n=8; ATO: atorvastatin 15mg/kg/day, n=9; NCX: NCX 6560 17.5mg/kg/day, n=9. a.u.: arbitrary units. * p ≤ 0.05, *** p ≤ 0.001 compared with vehicle. † p ≤ 0.05, ††† p ≤ 0.001 compared with the equivalent dose of atorvastatin.

- NCX 6560 treatment lowered p-moesin/moesin ratio, α-SMA and CD31 protein expression, and significantly increased p-Akt/Akt ratio and eNOS, p-eNOS and KLF2 protein expression compared with vehicles.
- The increments in eNOS and KLF2 expression were significantly higher in NCX 6560 than in the atorvastatin group.

Table 2. Hemodynamic measurements in 4-week BDL rats after one-week treatment (values taken 2h30min after the last dose of treatment).

	Dose (mg/kg/day)	n	MAP (mmHg)	PP (mmHg)	SMABF (mL/[min·100g])	SMAR (mmHg/mL·min·100g)	Heart rate (bpm)
Vehicle		8	96.39 ± 6.84	18.53 ± 0.56	4.42 ± 0.31	17.99 ± 1.73	318.10 ± 12.88
Atorvastatin	15	9	82.46 ± 4.44	16.27 ± 0.67 *	4.98 ± 0.41	13.95 ± 1.34	314.82 ± 9.96
	10	11	84.11 ± 4.22	15.77 ± 0.59 **	3.63 ± 0.26	19.60 ± 1.59	314.65 ± 12.75
NCX 6560	35.1	9	105.83 ± 5.11	17.75 ± 0.64	4.30 ± 0.41	22.10 ± 2.43	327.77 ± 15.92
	17.5	9	85.35 ± 5.95	16.25 ± 0.86 *	3.88 ± 0.37	19.24 ± 2.22	310.84 ± 13.40
	11.7	9	95.67 ± 6.42	16.43 ± 0.63 *	3.91 ± 0.41	22.17 ± 3.18	330.51 ± 9.05

* p ≤ 0.05, ** p ≤ 0.01 compared with vehicle.

- Atorvastatin and NCX 6560 treatment significantly reduced portal pressure (PP) levels without changing systemic hemodynamics.
- There were no significant differences in the PP lowering effect among the different statin groups.

Table 3. Characteristics and biochemical parameters of 4-week BDL rats after one-week treatment.

	Vehicle	Atorvastatin (15mg/kg/day)	Atorvastatin (10mg/kg/day)	NCX 6560 (35.1mg/kg/day)	NCX 6560 (17.5mg/kg/day)	NCX 6560 (11.7mg/kg/day)
n	8	9	11	9	9	9
Body weight (g)	331.10 ± 9.86	313.78 ± 20.55	278.21 ± 11.07 **	297.47 ± 12.10	300.99 ± 10.54	305.26 ± 9.25
Weight loss during treatment (g)	2.13 ± 3.54	41.59 ± 6.03 ***	34.93 ± 6.39 ***	42.30 ± 5.36 ***	25.70 ± 5.31 **	29.01 ± 4.45 ***
Ascites volume (mL)	0.19 ± 0.09	1.22 ± 0.81	4.01 ± 2.29	0.33 ± 0.33	1.06 ± 0.66	1.08 ± 0.66
Urinary volume (mL/h)	0.71 ± 0.17	0.34 ± 0.08	0.21 ± 0.07 **	0.99 ± 0.15	0.76 ± 0.15 †	0.69 ± 0.15 ††
Serum Na^+ (mmol/L)	142.10 ± 1.44	140.81 ± 0.43	140.56 ± 0.70	141.34 ± 0.82	141.20 ± 0.74	141.30 ± 0.98
Serum K^+ (mmol/L)	4.72 ± 0.28	4.65 ± 0.20	4.57 ± 0.19	4.75 ± 0.21	4.84 ± 0.25	4.66 ± 0.13
Serum creatinine (mg/[dL.100g])	0.12 ± 0.01	0.17 ± 0.02 *	0.19 ± 0.02 **	0.17 ± 0.02	0.14 ± 0.01	0.15 ± 0.01
Serum osmolality (mOsm/kg)	310.88 ± 2.36	304.44 ± 2.63	302.18 ± 2.34 *	316.11 ± 8.08	300.78 ± 1.61 **	304.50 ± 3.09
Total bilirubin (mg/dL)	8.15 ± 0.21	9.45 ± 0.44 *	7.62 ± 0.91	8.61 ± 0.50	8.27 ± 0.59	8.06 ± 0.57
AST (IU/L)	509.14 ± 76.10	615.75 ± 79.07	530.00 ± 88.61	1022.89 ± 253.93	462.11 ± 38.53	465.11 ± 26.15
ALT (IU/L)	68.38 ± 6.12	76.63 ± 9.57	80.00 ± 7.60	91.11 ± 10.26	72.78 ± 6.69	82.67 ± 7.98
Alkaline phosphatase (IU/L)	566.50 ± 62.92	438.38 ± 31.36	405.73 ± 26.83 *	376.67 ± 20.85 **	423.11 ± 36.53	410.89 ± 54.13
Creatine kinase (IU/L)	586.63 ± 72.03	640.22 ± 142.49	810.36 ± 209.00	830.50 ± 182.17	473.56 ± 85.25	428.00 ± 47.40
Serum cholesterol (mg/dL)	138.88 ± 13.87	153.67 ± 22.40	141.55 ± 11.35	138.56 ± 10.03	147.33 ± 15.56	130.11 ± 9.58
Serum albumin (g/dL)	2.37 ± 0.11	2.25 ± 0.11	2.23 ± 0.11	2.32 ± 0.06	2.26 ± 0.10	2.22 ± 0.15

* p ≤ 0.05, ** p ≤ 0.01, *** p ≤ 0.001 compared with vehicle. † p ≤ 0.05, †† p ≤ 0.01 compared with the equivalent dose of atorvastatin.

- Animals treated with statins experienced a significant weight loss compared with vehicles.
- Treatment with NCX 6560 significantly increased diuresis and decreased serum creatinine compared with equivalent doses of atorvastatin.

5. Conclusions

NCX 6560 decreases portal pressure in cirrhotic rats and has a safer toxicity profile compared with conventional statins. Additionally, due to its liver NO release, it might have a more long-term beneficial effect in the intrahepatic vascular alterations contributing to portal hypertension.

NCX 6560 could be a safer option for long-term statin treatment of portal hypertension in cirrhotic patients.

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Complicaciones de la cirrosis

Sarai Rodríguez Navarro

La impresión de pósters está patrocinada por: GILEAD