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cardiovascular morbidity/mortality, including atherosclerosis or hypertension, two contexts of vascular wall inflammation and oxidative stress [1]. However, less is known about GGT activity inside the vascular wall. Our aim was to evaluate GGT activity in cells and tissue from the vascular wall in several models of inflammation and oxidative stress.

Material and methods: GGT activity (quantified using L-γ-glutaryl-p-nitroanilide and intracellular GSH concentrations (measured by 2,3-dihydroxybenzaldehyde) were measured in (i) a rat smooth muscle cells line (SMC A-10) stimulated with either lipopolysaccharide (10 μg/ml) or LPS (30 μg/ml) for 24 h at 37 °C or L2,2'-anabostil-2-saminopropionate) dihydrochloride (AAPP; 50 μM, 2 h at 37 °C) to mimic inflammation oxidative stress respectively, and (ii) in aorta homogenates from male Spontaneously Hypertensive Rats (SHR) compared to their normotensive Wistar Kyoto rats (WKY). In homogenates of human atherosclerotic carotid plaques, GGT expression was assayed by SDS-PAGE analysis, using macrophages infiltration as marker of inflammation.

Results: In human atherosclerotic plaques homogenates, the presence of a high-molecular weight GGT similar to that expressed by macrophage was observed, with the highest GGT expression in presence of high vs. low macrophage infiltration (score: 2: 5–10%; 3: >10% vs. 1: <5%). GGT activity increased in the cell model of inflammation (Table 1), while it decreased in the cell and tissue models of oxidative stress in parallel with the decrease in GGT content.

Table 1. GSH content and GGT activity in several models of inflammation or oxidative stress (n = 3–5; *P < 0.05 vs. control).

<table>
<thead>
<tr>
<th></th>
<th>Control LPS</th>
<th>LPS</th>
<th>Control AAPH</th>
<th>AAPH</th>
<th>SHR</th>
<th>Control W/K</th>
<th>SHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSH</td>
<td>0.07±0.006</td>
<td>0.07±0.006</td>
<td>0.05±0.005</td>
<td>0.05±0.002</td>
<td>5±4</td>
<td>5±4</td>
<td></td>
</tr>
<tr>
<td>activity</td>
<td></td>
<td></td>
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</table>

Discussion/Conclusion: We planned to further evaluate the possible modulation between activated macrophages and promotion of pro-atherosclerotic process in SMC. Future experiments may also help to fully elucidate the mechanisms of GGT release and/or activity during inflammatory and/or oxidative stress.


PS2-057 Effect of total flavonoids of Cydonia oblonga Mill. on the pressure, the main target organs and related biomarkers in spontaneously hypertensive rats
W Zhou, University of Medical College (China)
Introduction: Cydonia oblonga Mill. (COM) is used for the treatment of hypertension in traditional Yuyang medicine. In this study, the main active anti-hypertension components, flavonoids of COM (COMF) were separated and purified, the anti-hypertensive effect was observed in spontaneous hypertensive rats (SHR).

Material and methods: SHR were divided into groups as control, captorlip (25 mg/kg/day), low (40 mg/kg/day) and high dose (120 mg/kg/day) COM. Eight Wistar-Kyoto rats were used as normal control. Tail-cuff systolic (SBP) and diastolic blood pressure (DBP) were measured every 2 weeks. After 16 weeks of intragastric administration, the histological and pathological changes of heart, kidney and thoracic aorta were examined. IL-1β, IL-6, ET-1, TNF-α, CRP, IL-10, and ALD concentrations in serum were measured to evaluate the effect on inflammatory factors. AngII, ALD, ET-1, NO, NOS, SOD, MDA and COX concentrations in serum were measured to evaluate the effect on Renin-angiotensin-aldosterone system (RAAS) and vascular endothelial function.

Results: Compared with control SHR, in COMF groups: SBP, DBP, heart weight (HW), HW/BW (body weight), left ventricular mass (LVM) and LVM/BW were decreased; Cardiomyocyte-diameter (CD) and cross-sectional area of cardiac myocyte (CAS) were decreased. Incresence of tunica media thickness of thoracic aorta and injury of endothelial cells was inhibited. Thromic aorta thickness/length (AW/length) were decreased, intimamedia thickness (IMT) was reduced and IMT/ID (inner diameter) was decreased. The levels of IL-1β, IL-6, TNF-α and CRP were lower, while the levels of IL-10 was significantly increased; the concentration of AngII and ALD in blood was decreased and the levels of DBP and MDA were lowered, while the levels of IL-1β, IL-6, TNF-α and CRP were elevated significantly.

Discussion/Conclusion: Flavonoids appear to be active components and the anti-hypertensive mechanism was related with: inhibition of activity of RAAS, resulting in reduced vasoconstriction, retention of sodium and water, proliferation of vascular smooth muscle; Inhibition of synthesis and release of inflammatory factors to prevent their development and prolongation of hypertension; alleviating peroxidation damage to the vessel endothelium.

PS2-058 S.S.-Dinitrosothiourea, a new nitric oxide donor, induces hypotension at lower doses than each of its intrinsic components S mono-nitrothiourea: S-nitroso-N-acetylpenicillamine (SNAP), S-nitroso-N-acetylcysteine (NACNO) or than the mixture SNAP + NACNO (pG2 log higher, rat isolated aortic rings) [1]. Here we evaluated its hypotensive effect in vivo.

Material and methods: The nitrothiols were synthesized as previously described [1]. Male Wistar rats (n = 5) equipped with telemetry device were injected subcutaneously with SNAP and/or NACNO at 5 mg/kg alone or in combination, with SNAP + NACNO (pG2 log higher, rat isolated aortic rings) [1]. Here we evaluated its hypotensive effect in vivo.

PS2-059 Effect of total flavonoids of Cydonia oblonga Mill. on cardiac function and left ventricular hypertrophy in spontaneously hypertensive rats and impact on the cardiac Renin-angiotensin-aldosterone system
Y. Tubabi, University of Medical College (China)
Introduction: Cydonia oblonga Mill. (COM) is used for the treatment of hypertension in traditional Yuyang medicine. Left ventricular hypertropy (LHV) is the main complication of hypertension. In this study, the main effective anti-hypertensive components, flavonoids of COM (COMF) were separated and purified to observe the effect on the structure and function of heart in SHR. Impact on the cardiac Renin-angiotensin-aldosterone system (RAAS) was further investigated.

Material and methods: Spontaneously hypertensive rats (SHR) were divided into six groups: SHR control, captorlip (25 mg/kg/day), low (40 mg/kg/day), medium (60 mg/kg/day) and high dose (160 mg/kg/day) COMF. 8 Wistar-Kyoto rats were used as normal control. SHR were anesthetized with a mixture of sodium pentobarbital (60 mg/kg) for baseline and thus continuously in awake animals for 4 h after administration. Variations of MAP (AMP) vs. baseline were averaged on 1 min during MAP, and expressed as mean ± SEM. For each substance, significant differences in blood pressures with PBS were determined by a two-way ANOVA (variables: "time" and "dose") followed by a post-hoc Bonferonni test. The duration of effect was evaluated as the last time point which still showed significant difference from the corresponding PBS effect.

Results: The administration of PBS was followed by an immediate and transient rise in MAP related to an increased activity during wake-up. This increase in MAP was masked by SNAP and NACNO which produced similar dose dependent depressions in MAP with same durations (Table 1). However, SNAP, NACNO also produced falls in MAP of similar intensity and duration but with doses five times lower than those used for SNAP or NACNO.

Table 1. Impact of drug administration on MAP (n = 5)

<table>
<thead>
<tr>
<th>Drug</th>
<th>MAP (mmHg)</th>
<th>Difference vs. Control</th>
<th>SEM</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNAP</td>
<td>14</td>
<td>-23 ± 15</td>
<td>8</td>
<td>0.004</td>
</tr>
<tr>
<td>NACNO</td>
<td>15</td>
<td>-32 ± 15</td>
<td>8</td>
<td>0.004</td>
</tr>
<tr>
<td>COMF</td>
<td>15</td>
<td>-28 ± 15</td>
<td>8</td>
<td>0.004</td>
</tr>
<tr>
<td>PBS</td>
<td>15</td>
<td>-1 ± 1</td>
<td>8</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Discussion/Conclusion: Our in vivo results show that COMF is a potent hypotensive drug, active at doses five times lower than its intrinsic components SNAP and NACNO. This interesting effect appears however lower than in our previous in vivo findings (10 times higher difference) and could be related to differences in bioavailability between the different drugs.


PS2-060 Effects of Cydonia oblonga Miller total flavonoids on blood lipids and anti-oxidant potential in hyperlipidemia rats
A Wummer University Medical College (China)
Introduction: To study the effects of Cydonia oblonga Miller (COM) total flavonoids (TF) on the blood lipids and antioxidative initial using hyperlipidemia models.

PS2-061
Sex differences in the development of renovascular hypertension
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Introduction: The experiments were performed with 10-week-old Sprague-Dawley rats which were prepared by the narrow side of the renal artery to develop renovascular hypertension (2KIC). After 32 weeks of regular feeding, hypertension was induced by injecting 4mg/kg of angiotensin-converting enzyme (ACE1, ACE2), and Ang II receptor (AT1R, AT2R).

Results: In the thoracic aorta, the protein levels of ACE1 and ACE2 were increased in 2KIC-males (0.95±0.204 vs 0.841±0.176, P<0.05). However, the protein level of ACE1 in thoracic aorta was increased in 2KIC-females (1.26±0.452 vs 1.33±0.214, P<0.05). In heart tissue, the protein levels of ACE1 were increased in 2KIC-males (2.03±0.144 vs 1.76±0.103, P<0.05). ACE2 were no difference (0.682±0.108 vs 0.654±0.103). ACE2 were no difference (0.682±0.108 vs 0.654±0.103). ACE2 were increased in 2KIC-females (1.478±0.235 vs 1.223±0.193, P<0.05). AT1R were increased in 2KIC-males (1.075±0.417 vs 0.924±0.146, P<0.05).

Discussion/Conclusion: The severity of hypertension was greater in 2KIC-females than in 2KIC-males. It is likely that the effect of females on renovascular hypertension was determined by the role of Ang II by increasing the release of ET-1, increasing the protein expression levels of ACE1 in thoracic aorta, kidney, and heart tissue, and increasing the protein expression levels of AT1 receptors in heart tissue.

PS2-062
Epigenetic changes in the renal tissues of patients with diabetic nephropathy
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Introduction: Epigenetic changes are implicated in the progression of diabetic nephropathy, which is the leading cause of ESRD. DNA methylation, histone modifications, and miRNA expression are altered in diabetic nephropathy. However, the role of epigenetic changes in the progression of diabetic nephropathy in humans is still unclear.

Methods: We analyzed DNA methylation, histone modifications, and miRNA expression in the renal tissue of patients with diabetic nephropathy and healthy controls. DNA methylation was measured using bisulfite sequencing. Histone modifications were measured using ChIP-seq. miRNA expression was measured using qPCR.

Results: We found that DNA methylation, histone modifications, and miRNA expression were altered in the renal tissue of patients with diabetic nephropathy compared to healthy controls. The specific epigenetic changes associated with diabetic nephropathy included increased DNA methylation of gene promoters, decreased histone acetylation, and increased miRNA expression.

Discussion/Conclusion: Epigenetic changes play a role in the progression of diabetic nephropathy. Understanding these changes may lead to the development of new therapeutic strategies for this disease.

PS2-063
Voriconazole pharmacokinetics in experimental models of disseminated aspergillosis: effect of infection and cyclosporine dosing regimen on voriconazole disposition
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Introduction: Voriconazole is a triazole antifungal drug with a broad-spectrum inhibiting activity on aspergillosis species. The filamentous fungi may cause severe infections with cerebral involvement, in immunocompromised patients and occasionally in immunocompetent patients (neuro-invasive syndrome). Although voriconazole is the first-line treatment for these infections, only few pharmacokinetic data are available. The pharmacokinetics of voriconazole was investigated in rats experimental models previously developed, with a particular attention on the effects of the infection and of the cyclosporine dosing regimen (1).

Cyclosporine was used because of its pharmacokinetic and pharmacodynamic properties.

Material and methods: Voriconazole (30 mg/kg, i.v.) was administered to six groups of rats for 30 minutes and infusion of cyclosporine dosing regimen was used to quantify a validated iPLC/MS/MS method and documented up to 48 h after administration. Pharmacokinetic parameters were compared using computational modelling.

Results: Two mono-compartmental models with first-order elimination and Michaelis-Menten elimination were evaluated. As data exhibited on input phase, this model was Towards other zero-order input kinetics. The first-compartmental approximation version of expectation maximization analysis revealed that a zero-compartmental model with zero-order input and Michaelis-Menten elimination fits the data better. The population modelling showed that the cyclosporine dosing regimen affected the volume of distribution of voriconazole (1.4 L/kg for groups receiving cyclosporine vs. 1.70 L/kg for control group). As previous approaches to the interaction between infection status and the cyclosporine dosing regimen, which may be due to inhibition of CYP3A4-mediated metabolism of voriconazole and action of cyclosporine on the inflammatory process.

Discussion/Conclusion: Together these results suggest that both cyclosporine dosing regimen and infection should be taken into account in voriconazole dosing adjustment.


THERAPEUTIC

PS2-064
The use of Tramadol oral solution in outpatient care
A Gommeren, C Glaude de la Carre - Carr (France)

Introduction: Pain in elderly patients is a public health concern. Pain management in this population is complex because of the assessment difficulties and because of pharmacological and pharmacological changes. The naloxone challenge test is a problem in terms of risk/benefit ratio. Tramadol is an analgesic at step 2 of the WHO ladder. Its use is debated because of dose-dependent tolerance problems and drug interactions especially in geriatrics. However, the dose can be decreased with the pediatric galenic oral solution which allows fixed and adjusted titration. In this study, the aim of this study is to evaluate the potential use of Tramadol oral solution in outpatient care. The Tramadol oral solution receives special interest in the units with elderly patients, because its use can increase its prescription. But we know nothing about the follow-up of this management with outpatients.

Material and methods: TRAMADOM is a prospective observational study about the feasibility of a taking of low dosage Tramadol oral solution in outpatients aged more than 75 years. The first taking of medication occurred during hospitalization or during outpatient care. The Tramadol titration was done with a Pain Management Board's validated protocol in 2013. Prescription is adjusted to the patient's weight and renal function.

Results: 82% (n = 18/20) of the patients took Tramadol in outpatient care and 95% (n = 18/20) found it easy to use. However, the prescription of Tramadol oral solution should be rational and safely be used, taking into account the whole older patient with cognitive disorder, disabilities, functional or sensory impairments. Tramadol was an effective medicine in 80% (16/20) of the patients. The link between an improvement of independence and the Tramadol efficacies shows a significant trend (P = 0.01). 51.6% (n = 6/12) of the patients reported a mild adverse side effect. Loss of vitamin K antagonist balance was not observed. The adverse effects of Tramadol pharmacokinetics model is unknown. Finally, qPCR seems too restrictive for the detection of genetic changes. Next Generation Sequencing would certainly allow a more comprehensive investigations.