A disease map for the blood pressure and glomerular filtration regulatory network on which antihypertensive and analgesic drugs act

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Pre-renal acute kidney injury occurs as a result of glomerular hemodynamic alterations resulting in reduced glomerular filtration rate (GFR) with no parenchymal compromise. Renin-angiotensin system inhibitors, such as angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor antagonists (ARAs), non-steroidal anti-inflammatory drugs (NSAIDs) and diuretics are highly prescribed drugs that are frequently administered together. Double and triple associations have been associated with increased pre-renal AKI incidence; which have been termed in the literature as “double whammy” and “triple whammy”, respectively. We have mapped the systemic and renal hemodynamic regulation network to analyze, in an integrative way, the complex interplay among the pathophysiological effects produced by NSAIDs, ACEIs/ARAs and diuretics, when acting alone and also in double and triple therapies altogether. And also, how and to what extent does each of these scenarios alter the physiological equilibrium regulating blood pressure (renal perfusion pressure) and GFR, in order to understand how the additive effect of these drugs increases the odds of inducing AKI by concomitantly reducing blood pressure and distorting renal autoregulation. From this knowledge, a more general model of pre-renal AKI arises, which is based on a multi whammy model whereby several factors are necessary to effectively reduce net filtration. The triple whammy would be only one model leading to pre-renal AKI with the concourse of other risk factors, among numerous potential combinations of clinical circumstances causing hypoperfusion, in which renal autoregulation is not operative or is deregulated. This would lead to uncoupling of the normal BP-GFR relationship, where new (lower) GFR values are obtained at every BP value, or at least in a determined range of BP.