

## Drug Repurposing in PDE3-inhibitors; good drug wrong indication

Jan Beute MD

St. Antonius Hospital, Nieuwegein

Around 1980 several new drugs were developed for the treatment of chronic heart failure, attempting to produce an oral drug with positive inotropic properties. In this spirit PDE3 inhibitors were developed. After an initially favourable effect in short-term treatment, showing increased myocardial contractility and vasodilatation, the drugs failed miserably in long-term treatment. Some progress was made by lowering the doses, but eventually they were merely registered and admitted for short-term treatment of heart failure and poor tissue perfusion in intensive or cardiac care settings. After revealing the mechanisms of PDE3 inhibition in the failing myocardium (Ding et al, 2005) it became clear that higher doses are contra-indicated in chronic heart failure. In non-failing hearts the positive inotropic activity of PDE3 inhibitors turned out to be propitious (Beca et al, 2013). Reviewing the original IP of e.g. PDE3 inhibitor enoximone three claims were filed. Besides myocardial contractility and vasodilation,

bronchodilation was claimed. Before 2014 only one article described bronchodilation in COPD patients (Leeman et al, 1987). This property stayed with me and ever since I have always used the bronchodilatory capacities of enoximone when treating pulmonary ICU-patients. This resulted in an article describing the life-saving use of enoximone in status asthmaticus (Beute, 2014). A recent prospective study using the PDE3 inhibitor milrinone confirmed the principle (Sobhy et al, 2019). After recognizing an excessively favorable response, far beyond the half life of the drug, research was initiated to discover possible additional properties of PDE3 inhibitors. Anti-allergic qualities were demonstrated, resulting in more research into the specific mechanism of counteracting allergies with PDE3 inhibitors as well as research in PDE3 knock-out mice. I will elaborate on the results of this research, and will reveal a fourth property of PDE3 inhibitors.