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Commentary

Clevidipine-induced Dyspnea Relief in Acute Heart Failure Patients

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Recently, *EBioMedicine* published a study proposing that clevidipine's complex mechanism of action might be responsible for relieving dyspnea in acute heart failure (AHF) patients Dahl et al. (2016). Clevidipine was approved by Food and Drug Administration (FDA) (2008) as a third generation dihydropyridine (DHP) calcium channel blocker for the management of perioperative acute hypertension (Merry et al., 2014; Powroznyk et al., 2000; Aronson et al., 2008; Levy et al., 2007; *Cleviprex (clevidipine butyrate) injectable emulsion for intravenous use [package insert]*, 2008). In 2014, Peacock et al. published the results of a randomized, open-label active control study (PRONTO) evaluating the efficacy of clevidipine versus standard of care (SOC) anti-hypertensive therapy and concluded that clevidipine was responsible for a rapid reduction in blood pressure and dyspnea improvement in hypertensive AHF patients (Peacock et al., 2010).

Calcium influx during depolarization in vascular smooth muscle (VSM) is prevented by clevidipine administration, blocking intracellular phosphodiesterase with an increase in guanosine monophosphate. This mechanism is responsible for an inhibition in VSM contractility associated with cardiopulmonary and systemic vasodilation (Murphy and Brower, 2011). A reverse translational medicine approach was used by Dahl et al. (2016) in order to test the idea that, in human lungs, a unique combination of $Ca_v1.2$ splice variants is expressed with a higher affinity for clevidipine than the same splice variant in other tissue. The authors refine the general understanding of how pannexin-1 (Panx1), known to act as a major adenosine triphosphate (ATP) release channel, affects $Ca_v1.2$ pharmacology and increases its affinity for clevidipine. Further research was encouraged in order to clarify the role of splice variants to the pathophysiology of AHF in the light of a new paradigm generated by Panx1/$Ca_v1.2$ interaction (Dahl et al., 2016).

Dahl et al. (2016) acknowledged the extended body of research conducted over the last 18 years since clevidipine was approved as an investigational new drug, and its importance in gaining a better understanding of its mechanism of action (Dahl et al., 2016). Their work focused on testing the hypothesis that specific CACNA1C splice variants are encoding for $Ca_v1.2$ in lung tissue with a different pharmacological profile for clevidipine when compared to the same variants expressed in other tissues. They also considered the hypothesis that clevidipine-induced dyspnea relief is due to clevidipine acting on Panx1 channels in lung tissue. The authors considered the possibility that Panx1 associates with $Ca_v1.2$ in lung tissue, resulting in an increased affinity of $Ca_v1.2$ for clevidipine (Dahl et al., 2016).

Human lung tissue from eight donors "without overt disease, but unsuitable for transplant" was provide by the Life Alliance Organ Recovery Agency. cDNA was obtained from human lung parenchyma and used to amplify regions of CACNA1C known to present splicing variation. Eight splice variant combinations of CACNA1C exons found in human lung tissue were tested. The effect of DHP nicardipine on different $Ca_v1.2$ splice variants was tested as well. The authors concluded that $Ca_v1.2$ splice variants with different affinities for clevidipine are identified in lung tissue and the higher affinity variants also present a selectively higher affinity for different DHPs (Dahl et al., 2016). The experiment found no direct effect of clevidipine on Panx1 channels, known to mediate muscle relaxation and contraction in VSM. However, the coexpression of Panx1 with the high affinity $Ca_v1.2$ splice variants showed a significant reactivity to lower clevidipine - but not nicardipine – concentrations.

The authors acknowledged the importance of previous research in identifying the $Ca_v1.2$ splice variants altering DHP sensitivity (Dahl et al., 2016). They established that "different splice variants of $Ca_v1.2$ confer differences in the specificity of different DHPs". Further research should clarify the coexpression of Panx1/$Ca_v1.2$. Although some technical aspects are questioned, such as the presence of mixed tissue in harvested donor lungs (lung parenchyma, arterioles, venules) influencing the expression pattern of the splice variants, new insights were provided in response to previously unexplained clinical observations. An extensive body of scientific evidence supports the fact that clevidipine is a superior drug for treatment of acute hypertension, providing a rapid blood pressure adjustment in the surgical and critical care setting, as demonstrated by the ECLIPSE Trials (2008) (Aronson et al., 2008).

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The article published by Dahl et al. (2016) represents further progress into elucidating clevidipine's effects on dyspnea in hypertensive AHF patients, prompted by the well-known PRONTO pilot study.

Disclosure

The authors declared no conflicts of interest.

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