Levosimendan

Levosimendan is a calcium sensitizer that is an established treatment for congestive heart failure. In coronary vessels, levosimendan has a vasorelaxant, endothelium-independent effect and an antagonistic effect on endothelin-1 (ET-1). There is also some data for a neuroprotective effect in a traumatic brain injury model, and levosimendan can prevent the reduction of the luminal area of the basilar artery.

We considered that patients who suffer heart attack after subarachnoid hemorrhage (SAH) might respond well to levosimendan, which might also be useful to induce hypertension in patients with cerebral vasospasm.However, the functional effects of levosimendan in the cerebrovasculature are unknown. Here, we investigated the functional role of levosimendan on rat basilar artery by assessing vasocontractile reactivity in response to ET-1, sarafotoxin S6c, acetylcholine, sodium nitroprusside, cGMP, and prostaglandin F2α (PGF).Contrary to observations in coronary vessels, levosimendan did not affect the ET-1 system in cerebral arteries; neither ET(A)-receptor-induced contraction nor ET(B)-receptor-dependent relaxation were changed. For the nitric oxide (NO) pathway, only a slight increase was detected. Rather, levosimendan caused significant and dose-dependent relaxation after PGF precontraction.To our knowledge, this is the first report that describes levosimendan-induced functional changes of cerebrovascular contractility and relaxation. Under physiological conditions, levosimendan did not influence ET(A)/ET(B)-receptor signaling or the NO pathway. Interestingly, levosimendan seemed to affect the prostaglandin system and dosedependently reversed PGF-induced contraction. We did not detect a vasospastic potential for levosimedan in cerebral arteries, suggesting that it would be safe for use in SAH patients [1)].

Under physiological cerebral conditions, levosimendan, has a dose-dependent antagonistic effect on prostaglandin F2alpha (PGF)-induced vasoconstriction. This circumstance could be used in antagonizing delayed cerebral vasospasm (dCVS), one of the main complications after subarachnoid hemorrhage (SAH), leading to delayed cerebral ischemia and ischemic neurological deficits. Data already exist that identified neuroprotective effects of levosimendan in a traumatic brain injury model and additionally, it has been proven that this compound prevents narrowing of the basilar artery (BA) luminal area after SAH in an in vitro rabbit model. Takotsubo cardiomyopathy, a severe ventricular dysfunction, is also a well-known complication after SAH, associated with pulmonary edema and prolonged intubation. METHODS:

The polypeptide endothelin-1 (ET-1) plays a key role in the development of dCVS after SAH. Therefore, the aim of the present investigation was to detect functional interactions between the calcium-sensitizing and the ET-1-dependent vasoconstriction after experimental-induced SAH; interactions between levosimendan and a substrate-specific vasorelaxation in the BA were also examined. It was reviewed whether levosimendan has a beneficial influence on endothelin(A) and/or endothelin(B1) receptors (ET-(A) and ET-(B1) receptors) in cerebral vessels after SAH. We also examined whether this drug could have antagonistic effects on a PGF-induced vasoconstriction. RESULTS:

Under treatment with levosimendan after SAH, the endothelin system seems to be affected. The ET-1-induced contraction is decreased, not significantly. In addition, we detected changes in the nitric oxide-cyclic guanosine monophosphate (NO-cGMP) pathway. Preincubation with levosimendan causes a modulatory effect on the ET-(B1) receptor-dependent vasorelaxation. It induces an upregulation of the NO-cGMP pathway with a significantly increased relaxation. Even after PGF-induced

precontraction a dose-dependent relaxation was registered, which was significantly higher (Emax) and earlier (pD2) compared to the concentration-effect curve without levosimendan. CONCLUSIONS:

After experimental-induced dCVS, levosimendan seems to restore the well-known impaired function of the vasorelaxant ET-(B1) receptor. Levosimendan also reversed the PGF-induced contraction dose-dependently. Both of these mechanisms could be used for antagonizing dCVS in patients suffering SAH. Levosimendan could even be used additionally in treating patients developing takotsubo cardiomyopathy [2].

1)
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2)
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