Can drugs ever improve outcome after cardiac arrest?

This issue of Resuscitation includes a review of beta-blocker treatment for cardiac arrest. At first, the very idea of administering a beta-blocker simultaneously with the recommended vasopressor might seem like driving your car with one foot on the brakes and the other on the gas pedal. How did we get here?

There has been a great search for the optimal vasopressor to improve coronary and cerebral blood flow and thereby facilitate resuscitation after cardiac arrest. Adrenaline (epinephrine) was introduced as the vasopressor of choice in the American Heart Association guidelines in 1974 based largely on animal experiments. Being a crude drug with a promiscuous pharmacological profile, positive effects of adrenaline were initially believed to be related to both alpha- and beta-adrenergic stimulation. Subsequent laboratory experiments by Yakaitis and colleagues challenged this perception after comparing effects of selectively blocking alpha- and beta-adrenergic receptors during resuscitation with adrenaline only to find that resuscitation without alpha stimulation was far inferior. Alpha-adrenergic stimulation causes peripheral vasoconstriction that increases aortic diastolic pressure and coronary perfusion pressure, subsequently aiding resuscitation. Beta-adrenergic effects are no longer considered irrelevant, and there is increasing concern about use of adrenaline due to beta-adrenergic mediated increased oxygen demand and post-arrest myocardial dysfunction. By this logic it would make more sense to administer a drug with more alpha-adrenergic selective properties or non-adrenergic vasopressors.

The avenue of selective alpha adrenergic agonists has been studied thoroughly in the laboratory setting. The two most studied drugs are phenylephrine and methoxamine. Although laboratory results of these drugs have been promising, clinical randomized trials have failed to prove any benefit compared to adrenaline. A similar story may be found with the non-adrenergic vasopressor vasopressin. Results from experimental models have been compelling, yet large clinical randomized trials fail to prove benefit. So almost forty years later, current guidelines for resuscitation are back were they started recommending adrenaline as the vasopressor of choice based largely on animal experiments with no evidence of long-term survival benefit in humans.

The billion euro question seems to be: why has no drug ever made a successful transition from the laboratory to the clinical setting? Is it because none of them work in humans during cardiac arrest, or is it because the clinical trials were not good enough?

Experimental data have elegantly made the point that good chest compressions are needed to circulate the drugs given in order for them to have any effect, and that the quality of CPR initially reported from clinical observations would not suffice. Very few clinical drug trials performed in the cardiac arrest setting provide data on chest compression quality, and there is a real possibility that poor resuscitation quality has confounded negative drug trials leaving the drugs in the peripheral vein they were administered, due to lack of generated blood flow. We know it is possible to administer drugs without compromising chest compression quality — but our current drug regimens do not seem optimal.

Perhaps we need to consider not only which effects we want to enhance, but also which we want to inhibit? In addition to the confounding effects of variations in CPR quality, a possible partial explanation for the failures of both alpha-adrenergic and non-adrenergic vaspressors could be the negative contribution of endogenous beta-adrenergic stimulation. As pointed out in this issue’s review paper very high levels of endogenous catecholamines are released during cardiac arrest and CPR. Administering a beta-blocker might therefore have beneficial effects also combined with a non-beta-adrenergic vasopressor. One of the experimental series sited in the review thus reports benefits from blocking both exogenous and endogenous adrenaline. Animals treated with a beta-blocker in addition to either a selective alpha-adrenergic (phenylephrine) or a non-selective adrenergic (adrenaline) vasopressor had better outcome compared to animals treated with one of the vaspressors alone.

The review by de Oliveira et al. of beta-blockers in cardiac arrest in this issue of Resuscitation makes a convincing argument for beta-blockers in a range of animal models. The human data presented are limited, yet still encouraging. Has the time come to put beta-blockers to the ultimate test: will they improve survival after cardiac arrest in a randomized controlled trial? The idea has merit, and could turn out to make a significant contribution in our quest to save more lives after sudden cardiac arrest. If we are ever going to uncover beta-blockers’ true potential in treatment of cardiac arrest, we need to know how treatment with these drugs will impact outcome. To truly evaluate the drug effects would require testing during optimal resuscitation care with vigorous chest compressions, adequate ventilation, timely defibrillation and goal-directed post-resuscitation care including hypothermia. If not, the risk of not discovering an effect due to confounders is large.

Conflict of interest statement

There is no conflict of interest.

References

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