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When less is more (brain)—Comment on “Rivaroxaban plasma levels in acute ischemic stroke and intracerebral hemorrhage”

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We have known that ‘time is brain’ for a few decades. Marler et al first published the now canonical graph showing the declining odds of good outcome with every minute delay after stroke onset¹. Emberson, Lees, and others confirmed and extended the now-famous graphic using pooled analysis of patient-level data from nearly every modern randomized, placebo controlled trial of alteplase for acute ischemic stroke². Saver quantified the mantra using inferences from primary biology: with every minute of untreated ischemia our patients lose almost 2 million brain cells³. Every innovation that comes along seeking to improve stroke treatment—a new imaging technique, a new biomarker, a new adjunct to thrombolysis or thrombectomy—must overcome the ‘time is brain’ barrier if it will enter clinical use. For example, advanced vascular imaging of acute stroke patients—first proposed by Lou Caplan over 20 years ago⁴—failed to enter the mainstream standard practice until modern thrombectomy treatment proved the invested time paid off⁵.

The increasing use of novel oral anticoagulants, or NOACs, presents a new conundrum for the Stroke Code Team. Data clearly shows that NOACs prevent embolic stroke in selected atrial fibrillation patients, with either no increase or actual reductions in cerebral hemorrhage rates⁶. Since we avoid thrombolysis in patients taking vitamin-K antagonist anticoagulants, by analogy we hesitate to offer thrombolytic therapy to patients reported to be taking NOACs. Several investigators have suggested that a rapid, reliable way to measure NOAC blood levels in acute ischemic stroke could guide clinical decision making.

In this issue of the *Annals*, Seiffge et al report elegant results from the NOACISP study⁷. The authors measured rivaroxaban levels in stroke patients presenting acutely with either ischemic or hemorrhagic stroke and sought to determine whether such levels could guide decision making. The authors used pre-specified cut-off values above which clinicians should avoid tpa in ischemic stroke (100ng/ml), and another level above which clinicians should consider reversal agents in acute hemorrhages (75ng/ml). Patients (n=241) were identified in a large network of European stroke centers, and the basic enrollment/data collection procedures were handled in standard fashion. The acute ischemic stroke patients

(n=113) and the intracerebral hemorrhage patients (n=51) all stated they had taken a dose of rivaroxaban within 48 hours of their last known well time; the patient demographics matched the typical stroke study population; rivaroxaban levels were associated with dose taken, renal function, and time since last dose, all suggesting the sample reflects a realistic study population. The authors found that blood rivaroxaban levels did not differ between patients presenting with ischemic vs hemorrhagic stroke. Using the pre-defined cut-off values, about half the patients with ischemic stroke had “elevated” levels of rivaroxaban and about 2/3 of the hemorrhages showed rivaroxaban levels high enough to consider reversal agents.

To interpret the NOACISP results, one first might consider the current context around using thrombolysis in acute stroke. The notion that thrombolysis causes harm in patients taking anti-coagulants, although logical, has little data to support it. Retrospective reviews suggest that thrombolysis in the setting of warfarin use is safe if the INR is less than 1.7⁸⁻¹⁰. In patients whose medication-induced INR was greater than 1.7, no evidence of increased hemorrhage risk could be found in thrombolysed patients^{11, 12}. The NOACISP authors themselves have published retrospective data suggesting flat or possibly reduced cerebral hemorrhage rates in thrombolysed patients who were taking NOACs or vitamin K antagonists^{13, 14}.

Not only does limited data suggest that using thrombolysis in the presence of anticoagulants is safe there is considerable evidence that thrombin inhibitors are vasculo- and neuro-protective. The direct thrombin inhibitor argatroban was shown to be powerfully neuroprotective using a functional assay and to significantly reduce lesion size in rodents¹⁵. Similar experiments suggested rivaroxaban reduced infarct volumes and improved neurological outcomes after middle cerebral artery occlusion¹⁶. Two clinical trials have confirmed safety of thrombolysis in stroke patients with argatroban-induced coagulopathy: PTT driven to 1.75 to 2.25× control values^{17, 18}. Similar studies are underway with Factor Xa inhibitors, such as rivaroxaban. Thus, if the limited data available warrants any conclusion, it would be that thrombolysis in the presence of a direct thrombin inhibitor, and possibly Factor Xa inhibitors too, may promote better outcomes, not harm

In any event, when facing a patient with acute ischemic stroke and a history of perhaps taking a NOAC, would it make sense to delay therapy for a blood test to measure the level of the NOAC? On the one hand, time is brain, minutes matter, and every delay costs the patient part of their likelihood to improve. Further, in the acute phase of the Code Stroke, history is unclear—did he take it today? Yesterday? If so, why is he presenting today with an ischemic event? In the face of definite proof that delay causes harm, and an absence of firm data showing harm due to thrombolysing a patient taking a NOAC, the data presented by Seiffge et al clearly reassure us: more than half of such patients will have a low rivaroxaban blood level and the delay for a measured level is not justified. In the other half levels will be above 100ng/ml, but only 7.4% will have “very high” levels, greater than 343ng/ml. On balance, it appears that there is no rationale for avoiding thrombolysis in a patient who says they took a NOAC recently and delaying for a blood level will add little value to the decision making; thrombolysed stroke patients pretreated with a NOAC may actually do much better than patients not taking NOACs.

Similarly, reversing coagulopathy in patients with cerebral hemorrhage appears logical, but data has been very mixed so far and "...it remains unclear whether reversal improves clinical outcomes..." in patients so treated¹⁹. The Neurocritical Care Society does recommend reversal in hemorrhage patients who were taking vitamin K antagonists and exhibit coagulopathy²⁰. The question before us here—regardless of whether reversal benefits patient outcomes—is whether a rivaroxaban level could or should guide the decision-making. Again, the NOACISP data provides considerable reassurance: almost 2/3 of the hemorrhage patients qualified for reversal agents using the cut-off value of 75ng/ml. Thus, a cost-effective approach might be to reverse all hemorrhage patients with a history of rivaroxaban use, knowing that 1/3 of such patients would be treated unnecessarily. No blood level measurement will be helpful, due to the delay in ordering the reversal agent. On the other hand, should a rapid, reliable, and valid point-of-care version of the assay become available, one could speculate about a role for immediate rivaroxaban level in the Emergency Department.

The NOACISP authors found that rivaroxaban levels were the same in patients with ischemic vs. hemorrhagic strokes, and they considered this counterintuitive. To a first approximation, we at the bedside prefer to assume that an ischemic stroke occurs when our patients fail to take their anticoagulants, and they hemorrhage when they take too much. Reality is more complicated, and the authors rightly point out there are additional mechanisms to consider when evaluating a stroke patient. Therapeutic anticoagulation prevents many, but not all, ischemic events. Intracerebral hemorrhage is associated, but not perfectly, with supratherapeutic anticoagulation. More and more, we should observe 'counter-intuitive' clinical events because our notion of what is 'intuitive' is based less on data and more on group-think. Increasingly, we rely on expert opinions, review articles, and 'bullet point' summaries of data. Clinical decision making is difficult, no more so than in the pressured environment of an Emergency Department evaluation of critically ill patients²¹. Over-reliance on intuition, clinical experience, expert opinion, and the advice/tutelage of mentors will lead us further into hazardous waters. The NOACISP authors are to be congratulated for seeking data and presenting it clearly—we may differ on our interpretation of the clinical implications, but the data are unambiguous and helpful. While reassuring, blood levels of rivaroxaban, or indeed any anti-coagulant, do not provide enough benefit to justify the lost time, and lost opportunity for a good outcome. Time is brain, still, and the less we do to our patient prior to thrombolysis—no matter how intuitively good the potential benefit of more information may seem—the more brain we will save: less is more (brain) in this setting.

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