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The Medical Case for the Development of an Intravenous Statin Formulation – Beyond Ischemic Stroke

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Statins, i.e., HMG-CoA reductase inhibitors, are orally administered drugs to treat patients with hypercholesterolemia and for secondary prevention of coronary artery disease and stroke [1–3]. In addition to reducing stroke risk, there is experimental evidence that statin treatment also improves stroke outcome even when given after the event [4]. In support of this notion, prospective data from the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial showed that the severity of ischemic strokes was reduced in patients treated with atorvastatin [5] and the MISTICS trial demonstrated improved outcome in patients treated with simvastatin within 12 h after stroke onset [6].

Orally administered drugs, however, are ill-suited for acute treatment protocols. Hydrophilic statins are suitable for an intravenous formulation. We have recently tested the effect of an intravenous statin formulation in a model of focal brain ischemia in the mouse (1-h middle cerebral artery occlusion/reperfusion). Intravenous rosuvastatin reduced lesion size when given up to 4 h after ischemia. Compared to intraperitoneal treatment, intravenous administration extended the treatment window by 3 h and reduced the minimally protective concentration from 20 to 0.2 mg·kg⁻¹ [7]. We propose that an intravenous statin formulation, which is presently not available, should be developed and tested in clinical trials. In addition to acute stroke patients, intravenous statins could be employed in a number of clinical situations.

The authors have previously received support from AstraZeneca, Pfizer and Novartis for studies with statin drugs.

There is evidence that the abrupt discontinuation of statin medication in patients with acute vascular syndromes may have adverse effects on vascular function [8]. The molecular mechanism may relate to overshoot activation of small G proteins. Clinical evidence suggests that the discontinuation of previous statin treatment in patients with acute myocardial infarctions, acute ischemic stroke and possibly also subarachnoidal hemorrhage has a negative effect on morbidity and mortality [8].

Atrial fibrillation is the most frequent complication after cardiac surgery (up to 30–60%). Postoperative atrial fibrillation is frequently complicated by increased risk of stroke and mortality. Recent animal data, small clinical studies and one randomized trial provide evidence that statin treatment is able to prevent postoperative atrial fibrillation [9, 10]. In many patients undergoing surgery, including patients with a high risk for atrial fibrillation, oral medication is withdrawn at the time of the highest risk of atrial fibrillation. We believe that an intravenous formulation would be a valuable tool to reduce the risk of atrial fibrillation after surgery.

Taken together, we propose the following potential indications for an intravenous statin formulation:

- (1) Immediate administration in patients with acute vascular syndromes including ischemic stroke, acute coronary syndrome, ST segment and non-ST segment myocardial infarction;
- (2) Critically ill patients pretreated with statins whenever enteral administration is not possible (including via nasogastric tube); these could be patients with vascular disease, those undergoing major surgery, or trauma patients;
- (3) Pretreatment of patients undergoing surgery with a high vascular risk;
- (4) Perioperative treatment of patients with a high risk of atrial fibrillation.

Of course, appropriate pharmacological assessment, appropriate trials and standard regulatory approval are needed before clinical use of an intravenous statin formulation in humans. For example, it is not known whether established side effects of statins (e.g. myopathy) are amplified.

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Isolated Hemiataxia of the Cerebellar Type after a Small Internal Capsular Infarct

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Hemiataxia is classically ascribed to lesions involving the cerebellar system or interrupting the sensory pathways that control movement. Hemiataxia after supratentorial brain infarction is not uncommon. It, however, rarely occurs in isolation and most

Table 1. Case reports of isolated hemiataxia after a capsular infarct

Authors	Lesion	Cases
Luijckx et al. [1], 1993	haemorrhage in the posterior limb of the internal capsule	1 case
Luijckx et al. [2], 1994	infarct in the posterior limb of the internal capsule	2 cases

of the time is accompanied by either pyramidal or sensory defects, or a combination of both. Isolated hemiataxia after supratentorial brain lesion is infrequent. To our knowledge, only 3 cases of internal capsular lesions, of which 2 were ischaemic and 1 haemorrhagic in nature, have been described to date [1, 2] (table 1). The case reported here therefore provides further illustration of hemiataxia of the pure cerebellar type resulting from an ischaemic lesion restricted to the posterior limb of the internal capsule.

Case Report

A 65-year-old man with a history of hypercholesterolaemia, hypertension and smoking suddenly developed clumsiness of the left arm and unsteadiness of gait, without weakness. Neurological examination performed on admission 24 h after onset of symptoms showed left hemiataxia consisting of left-sided dysmetria, dysidiadochokinesia and Holmes rebound phenomenon, hypermetria and intention tremor on finger-to-nose, finger-to-finger and heel-to-shin tests. This incoordination remained unchanged with the eyes open or closed. Ataxia of the arm was severer than that of the leg. Left-sided hypotony and decomposition of movement at tendon reflexes of the left leg were present. When standing, the patient showed a wide-based unsteady gait and a slight tendency to fall to the left. There was no weakness or pyramidal signs, and a normal plantar response. Position and vibration sense as well as touch, temperature and pain sensation were preserved. The patient had no signs of brainstem involvement, no pathological nystagmus or saccadic pursuit. There was no cognitive impairment. Computed tomography of the brain performed at admission disclosed a small hypodense lesion restricted to the posterior limb of the right internal capsule, compatible with a small deep infarct as well as an older lesion in the right centrum semiovale. MRI on day 3 confirmed these lesions with the internal capsular one appearing as new on diffusion-weighted MRI sequences and thus responsible for symptoms (fig. 1a, b).

There was a moderate improvement of the ataxia within the 3 days following the attack.

Discussion

Hemiataxia after supratentorial brain infarction is not uncommon and has been reported by several authors [3–7]. The latter, mainly related to a thalamic or capsular lesion, rarely occurs in isolation, being currently accompanied by either motor or sensory signs, or both [7–10]. Among hemiataxia secondary to supratentorial brain lesion, both ataxic hemiparesis and thalamic atax-