Effect of apomorphine on plasma large neutral amino acids in volunteer subjects

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Brain dopaminergic receptor activation, either by levodopa or by direct dopamine receptor agonists, remains the bulwark of treatment of Parkinson's disease.[1] Levodopa and direct dopamine agonists are often used concurrently. Although it is known that apomorphine does not affect the pharmacokinetics of orally administered levodopa,[2] it is not known whether dopamine agonists alter plasma levels of large neutral amino acids (LNAAs), which compete with levodopa for transport across the blood-brain barrier.[3] Uc et al,[3] found that beta adrenergic agonists increase plasma LNAA levels in rats resulting in a significant decrease in blood-to-brain levodopa transport. If dopamine agonists have a like or opposite effect as that of beta adrenergic agonists, then this will have important therapeutic implications. To address this question, we studied the effect of apomorphine in a single physiologically effective dose, on plasma LNAAs in volunteer subjects.

Five men volunteered for the study, which was approved by our Institutional Review Board. All subjects gave their written informed consent. Their ages ranged from 50-63 (mean 55) years, and their weights ranged from 70-91 (mean 82) Kg. After an overnight fast, subjects presented to the clinical research facility at 0700 hours in the basal state. They were kept fasted, except for sips of water, throughout the study. After a physical examination and electrocardiogram, an intravenous catheter was placed in the non-dominant upper extremity. Thirty minutes later, the baseline blood sample was taken, followed by the subcutaneous injection of 2 mg (approximately 25 μg/Kg) of apomorphine hydrochloride (ApokynTM, Vetter Pharma-Fertigune Gmblt & Co., Ravensburg, Germany). This dose of apomorphine was chosen because it is the highest that can be administered to human volunteers without consistently inducing vomiting.[4] We did not want to prevent nausea and vomiting by pretreatment with Domperidone because blockade of peripheral dopamine receptors may blunt a possible effect of apomorphine on plasma LNAAs. Blood pressure and vital signs were measured every 15 minutes. Venous blood samples were also obtained at 0.5, 1, 2, and 5 hours after apomorphine administration. Heparinized venous blood samples were centrifuged and the plasma collected and stored frozen at -70°C until analyzed for LNAA content using a Beckman 6300 amino acid analyzer with ninhydrin detection and external calibration.[3] The means ± SD of plasma concentrations of leucine, isoleucine, valine, tyrosine, phenylalanine, tryptophan (free) and methionine in the 5 subjects, expressed in umoles/L, were plotted against time after apomorphine administration. Differences between LNAA basal levels and those at various times after apomorphine administration were assessed for their significance by ANOVA. Significance was considered at $p<0.05$.

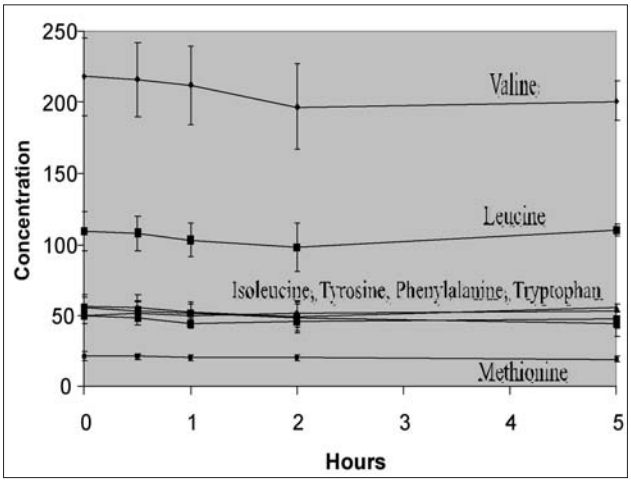

Figure 1 - The plasma concentrations of the 7 LNAAs expressed in μmoles/L, are plotted against time (hours) after the administration of 2 mg of apomorphine subcutaneously. Values represent means ± SD of the results obtained in 5 subjects. ANOVA revealed no significant alteration in plasma LNAA concentrations after apomorphine administration.

Apomorphine elicited many of its known effects in all subjects. All had excessive yawning and became drowsy within 15 minutes after apomorphine administration. Four of the subjects vomited, and 3 had transient hypotension, skin pallor, diaphoresis and bradycardia. The effects of apomorphine subsided and disappeared within one hour. We found no significant effect of apomorphine on any of the 7 LNAA plasma levels up to 5 hours after apomorphine administration (**Figure 1**). Inter-subject variations were relatively small (SD usually <15% of means) and the plasma levels of all 7 amino acids were remarkably stable for the 5 hour duration of the study.

Direct-acting dopamine agonists are effective medications for the treatment of Parkinson's disease.[1] The recent FDA approval of subcutaneous apomorphine injections for Parkinson's disease patients to relieve sudden "off" periods has increased the importance of assessing whether dopamine receptor agonists, generally, and apomorphine particularly, alter plasma LNAA levels. Major alterations in LNAA levels will affect the transport of

levodopa from blood to brain and, hence, the clinical efficacy of levodopa therapy. Dopamine agonists, including apomorphine, are known to induce several physiological perturbations in humans, via their effects on central and peripheral dopamine receptors. These include increased growth hormone and decreased prolactin levels,[5] in addition to other physiological effects. We hypothesized that changes in hormones may alter muscle and liver metabolism with subsequent alteration in plasma LNAAs. This is not without precedent since Uc et al,[3] reported that systemic administration of beta adrenergic receptor agonists profoundly increase LNAAs resulting in decreased levodopa transport at the blood-brain barrier.[3]

Our study documents that acute and effective central and peripheral dopamine receptor stimulation by apomorphine did not result in biologically appreciable or statistically significant changes in all 7 plasma LNAAs that are known to compete with levodopa for transport at the blood-brain barrier. We presume that other dopamine agonists have a similar effect although we have no direct evidence of that.

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