ILLICIT DRUGS & STROKE

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Conflicts of Interest

• Received honoraria for consultation and speakers’ bureau from Boehringer Ingelheim, for consultation from Daiichi-Sankyo and as speaker from Bristol-Myers-Squibb/Pfizer
5% WORLD POPULATION USES ILLICIT DRUGS

- Illicit drugs
  - drugs whose non-medical use has been prohibited under international drug control treaties

- 2010
  - 20 million DALYs
  - 0.8% of global all-cause DALYs

- Drug dependence, violence, infections (HIV, hepatitis), suicide

Degenhardt L et al, Lancet, 2013
ILLICIT DRUGS & STROE

• Specific features of stroke associated with different illicit drugs
  – Psychomotor stimulants
    • Cocaine
    • Amphetamine & ecstasy
  – Opioids
  – Psychomimetic agentes
    • Cannabis

• Screening for illicit drugs in acute stroke
DRUG ABUSERS ARE AT INCREASED RISK OF STROKE

• > 6.5 x risk for both ischemic and hemorrhagic stroke

• Baltimore-Washington Young Stroke Study
  – 12 % young stroke had recent drug use
  – 5% drug use is considered the cause of stroke

• Nationwide Inpatient Sample 2004-11

ILLICIT DRUG USE & STROKE
No drug is safe!

• Psychomotor stimulants
  – Cross-sectional study of hospital discharges
    • Amphetamine: 5 x risk of hemorrhagic stroke
    • Cocaine: 2 x risk of both hemorrhagic and ischemic stroke
  – Nationwide Inpatient Sample 2004-11:
    • Amphetamine: 2.2 x risk of ischemic stroke
    • Cocaine: 1.2 x risk of ischemic stroke

• Opioids

• Psychomimetic drugs
  – Cannabis
    • Case control study: 1.8 x risk of ischemic stroke (IS)
    • Nationwide Inpatient Sample 2004-11: 1.2 x risk of IS
  – LSD

Kaku DA & Lowenstein, 1990; DHWestover AN et al, 2007; Fonseca C & Ferro JM, 2013; Rumalla K et al, 2016
ILLICIT DRUG USE & STROKE
CHLN Stroke Unit 2010-16

CURRENT & PAST USERS (30 pt)

CURRENT USERS (12 pt)

3543 admissions, 2360 new stroke patients (1.2% and 0.5%)
Stroke and cocaine

- Stroke can occur with both cocaine hydrochloride and alkaloid (crack) forms and following IV, smoking, snorting use
- Blocks the reuptake of catecholamines and potentiates sympathetic activity
- Independent risk factor for stroke
  - Ischemic stroke OR – 2.03; 1.32*
  - Hemorrhagic stroke OR – 2.33
- Cocaine hydrochloride
  - More often hemorrhagic events
- Crack cocaine
  - Both ischemic strokes and hemorrhagic strokes

Brust et al, Stroke 1993; Fonseca C& Ferro JM, 2013; *Rummala K et al, 2016
Cocaine - Ischemic stroke

- Of all cocaine-associated strokes, 25–60% are ischemic
- Any location (hemispheric, subcortical, cerebellar, brain stem, retinal, spinal) but majority (50-80%) MCA
- 4th decade of life, male
- Classic risk factors for ischemic stroke usually absent and fewer in case control-studies*, except smoking
- Most ischemic strokes related to cocaine occur in the first few hours after consumption, but there may be a delay of up to several hours between cocaine intake and onset of stroke

Cocaine – ischemic stroke types and mechanisms

• Large-artery, small-artery, and cardioembolic strokes in equal %

• Acute effects
  – Vasospam, sudden hypertension, myocardial infarction, cardiac arrhythmias

• Long-term effects & repeated use
  – Cardiomyopathy, endothelial dysfunction, accelerated atherosclerosis, increased platelet activation
  – Vasculitis (poorly documented and controversial)

Koch, 2008; Martin-Schild S et al, 2009; Sáez, 2011; Pereira, Platelets 2011; Ren, 2011; Fonseca C & Ferro JM, 2013
COCAINE INDUCED STROKE
Vasospasm – intracranial stenosis

28 year old male – visual field defect after smoking cocaine and ecstasy
COCAINE INDUCED STROKE
Artery-to artery embolism

43 year old female – aphasia and right hemiplegia after smoking crack
COCOAINE INDUCED STROKE
Artery-to artery embolism

Severe anemia; normal ECG, Holter and TE echo
Thrombolysis and Thrombectomy are safe in cocaine induced stroke

- IV thrombolysis - retrospective case-series
  - No complications in patients with cocaine-associated stroke
  - Similar stroke severity and safety outcomes than controls

- IA thrombolysis and thrombectomy
  - 4 case-reports
    - 2 thrombectomy
    - iv rtPA and thromboaspiration
  - Safe

Prognosis

• Contradictory results
  – Retrospective study*: disability from cocaine-related stroke is not significantly different from that of other strokes
  – **Retrospective and prospective study of ischemic stroke in the young: higher % of complications (33.3 % vs 15.2 %) and mortality (11.1 % vs 3.8 %) (p>0.05)
  – ***Case (crack users) – control study: more favorable outcome (NIHSS 3.3 v. 7; mRS 1.8 vs. 2.3)

• Long-term cocaine use causes dopamine and noradrenergic depletion
  – Post-stroke depression and deficits in attention and initiative

Tolat et al, Brain Inj 2000; *Bhattacharya et al, J Stroke Cereb Dis 2011; **Carcelén-Gadea, Rev Neurol 2012; Giraldo EA et al, Neurocrit Care 2012
Cocaine - Intracranial hemorrhage

• Cocaine users have a higher frequency of intracranial hemorrhages (ICHs) than non-cocaine users:
  – Intraparenchymal hemorrhage
  – Intraventricular hemorrhage
  – Subarachnoid hemorrhage (SAH)

• Headache following consumption of cocaine should alert the physician to the possibility of ICH
Mechanisms of ICH

• Sudden increase in blood pressure
  – Rupture of an underlying aneurysm or AVM (~40%)
• Hemorrhagic transformation of ischemic infarcts related to multifocal vasoconstriction
  (Reversible Cerebral Vasoconstriction Syndrome)
• Changes in cerebrovascular autoregulation
• Vasculitis (?)
Clinical features

• Cocaine-associated ICH patients have:
  - Higher admission blood pressures
  - More subcortical locations
  - Higher risk of intraventricular hemorrhage

• Poorer prognosis
  – Worse functional outcome
  – Fewer discharged home
  – Higher (3x) mortality during hospitalizations

Martin-Schild S et al, Stroke 2010
Subarachnoid hemorrhage

- Age: younger than controls: 45.1 years vs 54.1 years
- Risk factors: more likely to smoke tobacco and drink alcohol
- Aneurysms: smaller and rupture at a younger age
- Vasospasm: more intense (2 studies) or similar (1)
- Outcome: worse (1 study) or similar (1)

Amphetamines

- Psychomotor stimulant

- The systemic effects of amphetamines include sympathomimetic actions:
  - ↑ systolic and diastolic blood pressure
  - Tachycardia
  - Dysrhythmias
  - Hyperpyrexia.
Amphetamines

• All forms of use related to stroke (oral, intravenous, nasal, and smoking).
• Increases the odds of stroke by almost 4x
• Disproportionate rate of hemorrhagic stroke
• Associated with both ischemic and all types of hemorrhagic strokes (ICH and SAH)

Petitti et al, Epidemiology 1998
Ho et al; Neurocrit Care 2009; Fonseca C & Ferro JM, 2013
Mechanism

- Experimental and clinical evidence suggests methamphetamine has a direct toxic or immunological effect in the cerebral vessels.
- Cerebral vasculitis is a commonly described histologic and radiological finding with either hemorrhagic or ischemic stroke.
- Histology has shown necrotic lesions in small and large cerebral arteries, with moderate to extensive medical necrosis with minimal inflammatory cells.

McGee et al, Am J Forensic Med Pathol 2004
Brust, Neurol Clin 1997
Amphetamine-associated ICH

• Acute hypertension
• Cerebral necrotic vasculitis
• Has been described after a single dose
• Patients with ICH related to short-term use may present with fever and acute hypertension.
• Subcortical and lobar hematomas have been described
• Increased risk of death
• SAH: often have un underlying aneurysm

McGee et al, Am J Forensic Med Pathol, 2004; Ho et al; Neurocrit Care 2009; Westover et al, Arch Gen Psychiatry. 2007; Fonseca C & Ferro JM, 2013
ECTASY
3,4-methylenedioxyamphetamine

• Modifies brain serotonin concentration
• 5HT2 receptors – regulation of cerebral microvessels
• Several case reports of IS, ICH and SAH
• Ischemic stroke more frequent in occipital lobe and globus pallidus – areas of high expression of serotonin receptors
• Acute hypertension? Vasoconstriction? Vasculitis??
Opioids – Heroin

Few reports of stroke

• Heroin - acetylation of morphine
• Binds to endogenous opiate receptors (mu receptor) responsible for the actions on the CNS and cardiovascular system.
• Causes hypotension, bradycardia, respiratory depression and several ECG changes
• Stroke associated to heroin
  – Few cases, almost all ischemic
  – More frequent after intravenous use, but also after inhalation

Lipski, Am Heart J, 1973; Fonseca C & Ferro JM, 2013
Heroin associated stroke Mechanisms

• Cardioembolism
  – Infective endocarditis
  – Cardiac arrhythmias
  – Foreign substances, adulterants
  – Right-to-left shunt

• Severe intoxication
  – Global brain hypoperfusion and hypoxia
  – Carotid compression due to prolonged lateral neck flexion

• Vasculitis (?)
  – No pathological proof
DRUG EFFECT OR CONFOUNDER?

- 45 year old male
- Sudden onset of numbness and paresis of his right upper limb, left-sided hemicranial headache
- Smoked heroin some hours before
- Hypertension, diabetes mellitus type 2, hyperlipidemia, smoker (60 units), coronary heart disease
- Carotid duplex – irregular 50% stenosis on both IC bifurcations
CANNABIS
Increased risk of stroke

• Marijuana
  – Psychotropic effect
  – Systemic effects: changes in BP, tachycardia
• Large nº of exposed persons
• Increased risk of stroke
  – Case control study: 1.8 x risk of ischemic stroke
  – Nationwide Inpatient Sample 2004-11: 1.2 x risk of ischemic stroke
• Synthetic cannabinoids (spice, K2, bonzai)
  – Case reports, including hemorrhagic stroke

CANNABIS
Mechanisms of stroke

• Vasospasm
• Hypotension
• Cardiac
  – Cardiac arrhythmias
  – Myocardial infarction
• Contaminants, adulterants

Kaku DA & Lowenstein DH, 1990; Rumalla K et al, 2016
CANNABIS Vasospasm

- 159 young adult stroke patients
- Illicit drug exposure
  - Questionnaire
  - Urine screening
- Patients who used vasoactive substance (35) (cannabis 30)
  - High frequency of intracranial stenosis (23)
  - HR 5.98

Wolff V et al, 2014
CANNABIS
Ischemic stroke

28 year old female, smoker, heavy user of cannabis
Sudden onset of anomia, facial weakness and mild upper limb paresis
CANNABIS
Vasoconstriction

TCD & angio-MR - Narrowing of left ACA, MCA and PCA
Screening for illicit drugs in acute stroke

• Urine screening for all patients?
• 21.6 % of patients had a positive toxicology screen despite patients denying illicit drug use
• 10% of stroke/TIAs patients + for cocaine
• Screening consecutive 483 stroke patients
  – Cannabinoids 22 pt (4.6%), cocaine 5 pt (1.2%), amphetamine and phencyclidine 1 pt each (0.2%)
  – Highest yield for younger patients who were also smokers

Screening for illicit drugs in acute stroke

Kalani R et al, 2015
LIMITATIONS OF CURRENT EVIDENCE

- Exposure
  - Difficult to measure with accuracy, likely to be omitted or underreported
  - Quantification of exposure not reported
- Confounders
  - Multiple, including vascular risk factors (smoking)
  - Difficult to detect (e.g. mixed drug use, adulterants)
  - Use of illicit drugs: a marker of poorer health
- Association
  - Case-control studies – overestimation
- Temporal association
  - No case-crossover studies available
Conclusions

• All illicit drugs increase the risk of stroke, both ischemic and hemorrhagic. The risk is higher for amphetamines and cocaine
• The main stroke mechanisms are acute hypertension and vasoconstriction (cocaine, amphetamines, cannabis) and cardioembolism (IV heroin)
• Toxicology screening for illicit drugs should be performed in cases with a high pre-test probability
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