Propofol infusion syndrome

PRIS

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February 2017

The presentation based on Propofol infusion syndrome

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Risk factors

♦ Severe head injuries
♦ Sepsis
♦ High exogenous or endogenous catecholamine and glucocorticoid levels
♦ Low carbohydrate to high lipid intake
♦ Inborn errors of fatty acid oxidation
History of PRIS

♦ The first death associated with propofol infusion was reported in 1990-Danish medical committee issued a warning!

♦ 1992-BMJ highlighted the dangers of high doses of propofol infusions in children and urged caution in adults

♦ 1996-first adults case reports

♦ Firstly mentioned by Bray in 1998 to describe adverse effects associated with the use of propofol in paediatric population.
Initial definition of PRIS

Defined as acute refractory bradycardia leading to asystole in the presence of one or more of the following:

1. metabolic acidosis (base excess of $-10 \text{ mmol litre}^{-1}$)
2. rhabdomyolysis or myoglobinuria
3. lipaemic plasma
4. enlarged liver or fatty liver
Incidence

- 1.1% and to occur at a median of 3 days (range of 1–6 days) after the start of propofol
- Mortality rate-18%
- There is probably a concentration-dependant increase in 28 day mortality (8% mortality with 1% propofol and 11% with 2% propofol in paediatric population)
Clinical presentation

- new-onset metabolic acidosis (86%)
- cardiac dysfunction (88%)
- rhabdomyolysis (cardiac and skeletal muscle) (45%)
- renal failure (37%)
- hypertriglyceridaemia (15%)
- hepatomegaly
- hyperkalemia
- lipaemia
Cardiac dysfunction

- ECG changes as a first sign of impending instability
  1. Brugada like (coved type ST elevation in V1-V3)
  2. AF
  3. Ventricular and supraventricular tachycardia
  4. BBB
  5. Bradycardia
  6. asystole

ECG characteristics in Brugada Syndrome:
- a. Broad P wave with some PQ prolongation
- b. J point elevation
- c. Coved type ST segment elevation
- d. Inverted T wave
Lipaemia

- Due to increased sympathetic stimulation, high circulating cortisol and growth hormone levels
- Due to blockade of mitochondrial fatty acid oxidation impairing lipid metabolism
- High circulating levels of non-esterified fatty acids
- Raised serum triglyceride
Rhabdomyolysis

- Direct muscle necrosis of both skeletal and cardiac myocytes
- Release of creatinine kinase (CK) and myoglobin
- CK is often >10,000 units litre⁻¹
- Increasing CK levels after 24–48 h of propofol infusion should raise the suspicion of PRIS in the absence of any other muscular pathologies
- Renal failure related to myoglobinuria
Why?

- Imbalance between energy demand and utilization caused by:
  1. Impairment of mitochondrial oxidative phosphorylation
  2. Impairment of free fatty acid utilization

  **Result:** lactic acidosis and myocyte necrosis

- Propofol antagonizes β-adrenergic receptor and calcium channel binding
Biochemistry

- Uncoupling of intracellular oxidative phosphorylation and energy production in the mitochondria
- inhibition of electron flow through the electron transport chain in myocytes

Result:
- An imbalance between energy demand and utilization
- Malfunction of cardiac and peripheral muscle cell
Mitochondrial pathology

- Increased activity of malonyl CoA inhibits carnitine palmitoyl transferase I, decreased transfer of long chain fatty acids into the mitochondria.

- Uncoupling β-oxidation and the respiratory electron transport chain at complex I.

Neither medium- nor short chain free fatty acids, which freely cross the mitochondria membranes, can be utilized.
Pathophysiologica meaning

♦ Free fatty acids are essential fuel for myocardial and skeletal muscles under fasting or stress

♦ Oxydation of fatty acids is a main source of producing electrons transferred to the respiratory chain

♦ Prolonged process can lead to muscle necrosis
Propofol and cardiovascular system

- Inhibits cardiac β-adrenoceptor binding
- Inhibits cardiac calcium channel function
- Suppresses the activity of sympathetic nerves and the baroreceptor reflex
Management

- High index of suspicion in the risk groups
- Monitor CK and triglyceride levels daily, starting from 48 h of propofol infusion.
- Check CK levels
- Stop propofol and use alternative sedation agent
- Cardiovascular support including
  ① Electrical pacing (either via temporary wire or transcutaneously)
  ② Extracorporeal membrane oxygenation
- Renal replacement therapy to treat the ensuing lactic acidosis, clear propofol, and its metabolites
Prevention

- Maximal dose 4mg/kg/h

- Provide adequate carbohydrate intake with glucose infusions and minimizing lipid loads

- Consider risk factors:
  1. severe head injuries
  2. sepsis
  3. high exogenous or endogenous catecholamine and glucocorticoid levels
  4. low carbohydrate to high lipid intake
  5. inborn errors of fatty acid oxidation.
Summary

♦ Be vigilant!

♦ An average general ICU with admission rates of 300–400 a year

♦ Prevention is better than cure