Fentanyl can be mitochondrion -toxic depending on dosage and cell type

We read with interest the article by Thampi *et al*. about a 9-year-old female child with MELAS syndrome who successfully underwent laparoscopic gastrostomy after she had developed dysphagia and aspiration pneumonia.[1] The study raised the following comments and concerns.

We do not agree with the notion that fentanyl is nonhazardous in patients with a mitochondrial disorder (MID).[1] There are several data showing that fentanyl may disturb mitochondrial functions. In a recent study of human hepatoma (HepG2) cells, exposed to fentanyl or pretreated with naloxone or 5-hydroxydecanoate, an inhibitor of mitochondrial adenosine triphosphate (ATP)-sensitive potassium (mitoKATP) channels, fentanyl reduced the stimulated mitochondrial respiration of cultured hepatocytes through a mechanism which is blocked by mitoKATP channel antagonists.[2] In a study of the bioenergetic status of rat brain mitochondria, fentanyl dosages >4 μg/mL impaired respiratory chain function, resulting in a decrease in the respiratory control ratio and state 3 and uncoupled respiration.[3] In a study of human fibroblasts exposed to fentanyl for 30 min, 0.05% fentanyl reduced mitochondrial activity after 1 h, 24 h, and 7 days. Mitochondrial functions were also reduced by 0.025% fentanyl.[4] In a 21-year-old male with mitochondrial encephalomyopathy, administration of fentanyl during anesthesia for removal of a maxillary cyst resulted in prolonged respiratory depression.[5] Respiratory depression lasted for 120 min and could be antagonised with naloxone.[5] In a study of cultured blood lymphocytes, incubation with fentanyl for 90 and 120 min resulted in disruption of the mitochondrial membrane potential and increased the production of reactive oxygen species, respectively. In addition, the rate of apoptosis was increased. In a study of hepatocyte mitochondria, fentanyl inhibited oxygen consumption by 40%. The inhibition of oxygen consumption was increased by oligomycin. Inhibition of the mitochondrial respiratory chain became evident either as reduced substrate oxidation or as a thermogenic proton leak.

The effect of anesthetics on mitochondria of patients with an MID may strongly depend on the mtDNA heteroplasmy rate in a specific cell type. Thus, we should be informed about heteroplasmy rates of the culprit mtDNA mutation in the index case. Since heteroplasmy rates vary considerably between tissues, they should be provided not only for blood lymphocytes but also for hair follicles, buccal mucosa cells, urinary epithelial cells, fibroblasts, and myocytes.

Since MELAS is maternally transmitted in three quarters of the cases, we should be informed if the mother was clinically affected or carried the genetic defect causative for MELAS in her daughter.

Overall, the study could be more meaningful by providing heteroplasmy rates from various tissues, by providing serum and cerebral lactate concentrations, and by detailing the family history of the index case. There are indications that fentanyl can be harmful in patients with a MID.

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Conflicts of interest

There are no conflicts of interest.

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