Opioids depress pupillary unrest

Deaths from overdose of opioid drugs such as morphine, heroin, dilaudid and oxycodone are a major public health problem worldwide. It is estimated that over 40,000 opioid related deaths occur annually in the United States, roughly equal to those from traffic accidents or gun violence. Death is caused by an action on the brain but evaluation of this effect is difficult; death from respiratory depression can be rapid and insidious. Our study examined the effect of these drugs on the brain by measuring the movements of the pupil, a phenomenon often called hippus or pupillary unrest. We used a portable instrument, called an infrared pupillometer, to measure these pupillary fluctuations in patients prior to their surgical procedures.

The pupil is the black circle in the center of the colored part of eye and has been of interest to physicians for over 2000 years. The Greek physician Galen for example observed the dilation of the pupil when the opposite eye was covered and used this test to decide when to remove a cataract.

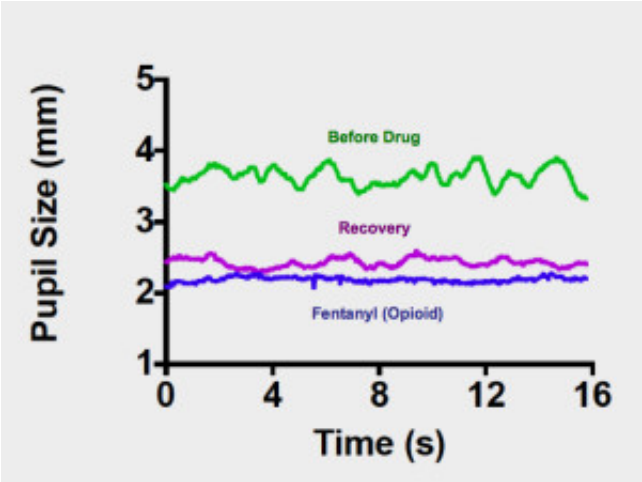

Fig. 1. Pupillary unrest before fentanyl (opioid), after fentanyl, and during recovery from the drug effect. Figure modified from Autonomic Neuroscience 189:68-74, 2015, with permission from the authors (Copyright may apply).

In 1747 Felice Fontana, a renaissance scientist from Florence, Italy, observed that ingestion of the opium poppy would make the pupil smaller (pupillary constriction). This effect was due to molecules of opioids, such as morphine, contained within the juice of the poppy seed capsule. The small pupil associated with ingestion of these drugs has provided physicians, paramedics and law enforcement personnel with a convenient "test" for opioid consumption. The so-called pinpoint pupil is thought to indicate prior opioid use but for a number of reasons this test is flawed.

Although the constriction of the pupil is used experimentally in normal human volunteers to assess the effect of opioids on the brain, it is not a practical tool to use in the general population. Some people have naturally small pupils even without ingestion of opioids. The small size of the pupil in these subjects limits the range of movement because the pupil cannot constrict below 2 mm in most subjects. Thus, the small pupil is an invalid test for prior opioid ingestion in a significant percentage of the population.

Based upon a number of previous animal studies we thought that the irregular motion of the pupil (pupillary unrest) would be depressed by opioids. We came upon this idea through a consideration that this irregular motion of the pupil might be generated by oscillating nerve cells that inhibit the brain center controlling pupil size. Opioids are known to depress inhibition in this part of the brain.

Our hypothesis was confirmed and to our surprise the action of the opioid fentanyl to reduce the oscillation of the pupil was brought about by a relatively small dose of the drug. Furthermore, the percentage change was much larger than the change in size of the pupil. We think this is a new method to detect the effect of opioids on the brain and will be of value to physicians who prescribe these drugs, and to law enforcement officers who might be interested in the detection of illegal opioid consumption.

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Publication

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