

## **Executive Summary**

The potential toxicity of ketamine had been studied in the monkeys and mice. The dosage used for the monkeys was 1mg/kg daily, a minimal dosage suggested to produce schizoid behaviour. This dosage is low when compared with the anesthetic dosage of children (about 10mg/kg). In the mice, the anesthetic dosage is at least 10 times higher because these animals have a very fast metabolism (Science 2011) (e.g. the heart rate of a mouse is 10 times that of a human). The anesthetic dose of the mice is therefore documented to be 100-150mg/kg, and our experiment showed that by 60mg/kg, the hind limbs of the mice would have incoordination. Therefore, we maintained our dose at half of 60mg/kg, i.e. 30mg/kg daily. This was calculated to be 1mg for each mice daily. Our preliminary evaluation from reports of addiction from the public security departments in the Southern China demonstrated that the addicts took an average dose of roughly 600mg per day.

From our experimental animals with the dosages used as mentioned above, we have documented the following changes:

- 1) Ketamine was able to kill neuronal cells in cell culture.
- 2) Ketamine injected daily to the animals will cause neuronal apoptosis, at a timing of 3 to 6 months.
- 3) Potentially, it was even more dangerous in that ketamine could cause phosphorylation of tau protein, a marker of Alzheimer degeneration in the brain of these animals.
- 4) fMRI indicated changes in the limbic system, corpus striatum, cerebellum, dorsomedial thalamus, prefrontal cortex (including basal forebrain). Some of these changes appeared as early as one month after ketamine treatment. The limbic system and the prefrontal cortex are important emotional and personality areas. The corpus striatum is an important area for regulation of movement, and any changes will result in deregulation of motion. The cerebellum is interestingly down regulated after ketamine intoxication, resulting in incoordination of muscles. The dorsomedial thalamus, in this case, is an important relay station between the hypothalamus and the prefrontal cortex, and any changes will therefore affect the endocrine and the brain.
- 5) The ketamine toxicity will also affect memory as was shown by our water maze study of the mice.
- 6) Molecular studies by this laboratory indicated the upregulation of GABA5 receptors in the brain after ketamine addiction.
- 7) Not only will the central nervous system be affected, but also other areas. In these

models, we have discovered that the kidneys and bladders are affected after 1 month of ketamine treatment. In both cases, infiltration of lymphocytes and monocytes were seen in the bladder and kidney. Further treatment would result in fibrosis and muscular degeneration of the urinary bladder so that the bladder became contracted. This is what happened in the clinical human situation. We further found that the sperm motility is affected as well by ketamine.

All the results above are either published or in manuscript forms ready to be submitted. There were, to this date, four published papers, one submitted paper and three manuscripts ready for submission. They represent de novo information for scientific studies in ketamine. We thank the Beat Drugs Fund Association for the grant (Ref. No.: BDF080048) awarded for this purpose.