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Title : CLINICAL STUDY OF THE OPTICAL ISOMERS OF KETAMINE  
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**Introduction:** Ketamine, a parenteral anesthetic, produces profound analgesia and lacks the cardiorespiratory depression seen with most other general anesthetics. Despite these important advantages, disturbing "emergence reactions" have precluded a widespread acceptance of ketamine. The ketamine molecule exists as two optical isomers, (+)ketamine (PK) and (-)ketamine (MK). All clinical studies to date have utilized a racemic mixture of the ketamine isomers, although optical isomers of other centrally active drugs are known to have different pharmacodynamic and pharmacokinetic properties. The concept that one of the isomers of ketamine might possess the beneficial effects without the disadvantages of the racemic mixture led us to compare the isomers with racemic ketamine (RK) as sole anesthetics for surgery.

**Methods:** Sixty, consenting ASA Class I adult surgical patients (approved by UCSF Committee on Human Research) were assigned in a random, double-blind fashion to one of three treatment groups. For induction, one group (N=20) received RK 2mg/kg IV, a second group (N=21) received PK 1mg/kg IV, and the third group (N=19) received MK 3mg/kg IV, based on the 3:1 isomer potency ratio obtained in animal studies.<sup>1,2</sup> Maintenance doses equalled to one-half the induction doses. Operating conditions were assessed by the surgeon and anesthesiologist and where adequate anesthesia could not be achieved with ketamine alone, adjunctive agents were used. During emergence patients were observed by a psychologist. We administered IPAT trait anxiety scales and profiles of mood states. 24 hrs after surgery, the patients completed a questionnaire assessing their perioperative experience. Plasma and urine specimens were assayed for ketamine and its major metabolites as described previously.<sup>3</sup>

**Results:** A potency ratio calculated from total dose, body weight and duration of anesthesia revealed that PK was 3.5X more potent than MK, with RK being of intermediate (1.8X) potency. At the termination of anesthesia, mean plasma levels of the parent compounds were 0.89µg/ml(RK) 0.46µg/ml(PK) and 1.68 µg/ml(MK). At equi-anesthetic doses, PK produced less cardiovascular stimulation and less spontaneous motor activity than either RK or MK. In terms of overall adequacy of anesthesia, PK was judged to produce more effective

anesthesia (95.2%) than either RK (75.0%) or MK (68.4%). Of patients receiving MK, 26.3% required adjunctive agents to complete surgery, while an inadequate anesthetic state was seen in only one case in the PK group. Verbal responses in the immediate post-anesthetic period suggested more psychic emergence reactions (e.g., vivid illusions, "wired trips", or delirium) after MK (36.8%) than either RK(15.0%) or PK(4.8%). Furthermore, MK produced more restlessness, thrashing and/or combative behavior (26.3%) than either RK(10.0%) or PK(0%). Pain, agitation and disorientation occurred more commonly in the RK and MK groups. Nausea, vomiting and dizziness were more frequent in patients who received either RK or PK. The overall incidence of "dreams" was 80.7% and did not differ significantly between groups. However, the dreams were usually pleasant experiences. Postoperative fear was reduced to a greater extent (relative to preoperative fear) in the PK group (42.9%) than either the RK(13.1%) or MK (19.6%) groups. Patients found PK (85.0%) more acceptable than either RK (65.0%) or MK (68.4%).

**Discussion:** Our study discloses several clinically important differences between the optical isomers of ketamine. These include differences in anesthetic potency, intraoperative effects, degree of analgesia, physical side-effects, and the incidence and type of post-anesthetic emergence phenomena. Parallelism of the plasma decay curves and similarities in the pattern of appearance and excretion of the ketamine metabolites for the three groups suggest that the differences in anesthetic potency were due to pharmacodynamic factors. These data would suggest that stereospecificity alters the pharmacodynamic effects of this anesthetic. Although PK is not a uniquely different anesthetic, it may offer distinctive clinical advantages over the currently used racemic mixture (Ketalar<sup>R</sup> or Ketaject<sup>R</sup>).

#### References:

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